Chapter 7. Carcinogenic Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and various cancers from the 1997 OEHHA report and this update are provided below in Table 7.0A. These findings are based on a weight of evidence approach. In summary, there is evidence that ETS exposure causes lung and nasal cancer. Epidemiologic studies, supported by animal data on carcinogenicity of ETS components, provide evidence consistent with a causal association between ETS exposure and breast cancer in younger primarily pre-menopausal women. In addition, there is evidence suggestive of an association between exposure to ETS and brain cancer and lymphomas in children.

Table 7.0A ETS and Cancer: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Findings OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
All cancers - Adult	5	1	Suggestive	Suggestive
All cancers - Childhood				
Mother (smoker)	7	6	Inconclusive	Inconclusive
Father (smoker)	1	6	Inconclusive	Suggestive
Lung	19	22 (7 meta)[a]	Conclusive	Conclusive (strengthened)
Breast	4	22 (4 meta)	Inconclusive	
Younger/pre-menopausal				Conclusive
Older/post-menopausal				Inconclusive
Head and Neck	0	2	Not reviewed	Inconclusive
Nasal sinus	3	0	Conclusive	Conclusive
Nasopharynx	0	4	No studies	Suggestive
Cervical	4	2	Suggestive	Suggestive
Lymphomas Children	6	6	Inconclusive	Suggestive*
Brain Children	10	12	Inconclusive	Suggestive*
Brain Adult	3	0	Inconclusive	Inconclusive
Bladder	2	1	Inconclusive	Inconclusive
Stomach	1	3	Inconclusive	Inconclusive
Leukemia Childhood	8	10	Inconclusive	Inconclusive

* May reflect an association with paternal pre-conceptional smoking rather than ETS exposure.

a. Meta = meta-analyses – not included in study counts

7.0. Introduction

Primary tobacco smoking is an established human carcinogen (IARC 2004a; U.S. DHHS 1989). Environmental tobacco smoke (ETS) has been established as a cause of lung cancer in nonsmokers (U.S. DHHS 1986e; NRC 1986e; U.S. EPA 1992a), most recently by IARC (2004a). This chapter updates the previous OEHHA review (Cal/EPA 1997) on the role of ETS in the etiology of cancers in nonsmokers.

One of the required elements in commonly used criteria for evaluating the possible causality of observed epidemiological associations is biological plausibility (see Chapter 1). In favorable cases, this may involve identification of a detailed mechanism by which a given exposure could produce the observed result. Even where this is not available, the observation of similar effects in other more closely controlled circumstances such as laboratory experiments may be regarded as evidence of biological plausibility. Thus, a carcinogenic effect in laboratory animals in the course of a well-designed bioassay (where other factors such as timing, dose level, consistency of subject groups and potential confounding exposures can be tightly controlled) is regarded as supporting the biological plausibility of an association between increased cancer incidence and exposure of humans seen in an epidemiological study.

In reviewing the case for a causal association between exposure to ETS and various cancers, OEHHA (Cal/EPA, 1997) noted the occurrence of a number of established carcinogens as ingredients of both direct and sidestream tobacco smoke. The list, presented as Table 2.2 in the 1997 document, includes 38 organic compounds and 5 inorganic elements or classes of compounds classified by IARC as 2B or higher, by U.S. EPA as B2 or higher, and/or listed as a carcinogen under Proposition 65. This probably under-represents the true number of carcinogenic components of tobacco smoke by a significant margin, both because tobacco smoke is a complex mixture, many components of which have not been conclusively identified, and also because many identified components have not been exhaustively tested for carcinogenicity. Since IARC monograph 38 (IARC 1986a), that agency has substantially increased the number of materials it has evaluated, and in some cases upgraded earlier evaluations in the light of new evidence or revised evaluation protocols. A further indication of the number and type of potentially carcinogenic components in tobacco smoke may be obtained from Table 7.0B below. This lists, as far as possible, those compounds present in tobacco smoke which have been evaluated by IARC. It is based on Appendix 2 of IARC (1986a), with some additions based on data on occurrence in tobacco smoke from U.S. EPA (1992g) and from IARC (2004a), Table 1.14. The evaluations were updated to reflect changes and additions listed in Supplement 6 (1987), Supplement 7 (1987), and in recent monographs up to and including Vol. 84

As with the previous OEHHA review (Cal/EPA, 1997), this chapter updates the data on the relationship between ETS and all cancers combined, in adults (Section 7.1.1) and in children (Section 7.1.2). Later sections present any additional published data on the role of ETS in the etiology of lung cancer (Section 7.2), cancer sites other than lung causally linked to active smoking (Section 7.3), and cancer sites which have been equivocally or suggestively linked to active smoking (Section 7.4). Section 7.4 also includes the evidence on ETS exposure and risk of specific childhood cancers. In addition, we discuss new studies on the impact of exposure misclassification on the results of epidemiological investigations into ETS exposure and human disease (Section 7.0).

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
1. Aliphatic hydrocarbons			
1,3-butadiene (20-40) (4)	Sufficient	Limited	Vol. 39, p.155-179; Suppl. 7, p. 136; Vol. 54, pp. 237-285; Vol. 71, pp. 109-225.
ethylene (200-400) (3)	Inadequate	Inadequate	Vol. 19, pp. 157-186, Suppl.7, p. 63, Vol. 60 pp. 45-71.
propylene (50-100) (3)	Inadequate	Inadequate	Vol. 19, pp. 213-230; Suppl.7, pp. 70-71, Vol. 60 pp. 161-180.
2. Aromatic hydrocarbons			
Monocyclic aromatic hydrocarbons			
benzene (12-50) (4)	Sufficient	Sufficient	Vol. 7, pp. 203-221; Vol. 29, pp. 93-148, 391-397; Suppl. 4, p. 56; Suppl. 6, pp. 91-95; Suppl. 7, pp.120-122.
styrene (14-19) (4)	Limited	Limited	Vol. 19, pp. 231-274; Suppl. 4, pp. 229-233; Suppl. 7, 345-347; Vol. 60, pp. 233-319; Vol. 82, 437-550.
Di- and polycyclic aromatic hydrocarbons			
anthanthrene (0.002-0.02) (2)	Limited	No data	Vol. 32, pp. 95-104; Suppl. 7, p. 57.
anthracene (0.023-0.23) (2)	Inadequate	No data	Vol. 32, pp. 105-121; Suppl. 7, p. 57.
benz[a]anthracene (0.02-0.07) (4)	Sufficient	No data	Vol. 3, pp. 45-48; Vol. 32, pp. 135-145; Suppl. 7, p. 58.
benzo[b]fluoranthene (0.004-022) (4)	Sufficient	No data	Vol. 3, pp. 69-81; Vol. 32, pp. 147-153; Suppl. 7, p. 58.
benzo[j]fluoranthene (0.006-021) (4)	Sufficient	No data	Vol. 3, pp. 82-90; Vol. 32, pp. 155-161; Suppl. 7, p. 58.
benzo[k]fluoranthene (0.006-0.012) (4)	Sufficient	No data	Vol. 32, pp. 163-170; Suppl. 7, p. 58.
benzo[ghi]fluoranthene (0.001-0.004) (2)	Inadequate	No data	Vol. 32, pp. 171-175; Suppl. 7, p. 58.
benzo[a]fluorene (0.049-0.18) (2)	Inadequate	No data	Vol. 32, pp. 177-182; Suppl. 7, p. 58.
benzo[b]fluorene (0.02) (2)	Inadequate	No data	Vol. 32, pp. 183-187; Suppl. 7, p. 58.
benzo[c]fluorene (2)	Inadequate	No data	Vol. 32, pp. 189-193; Suppl. 7, p. 58.
benzo[ghi]perylene (0.06) (1)	Inadequate (co-carcinogen)	No data	Vol. 32, pp. 195-204; Suppl. 7, p. 58.
benzo[c]phenanthrene (2)	Inadequate (initiator)	No data	Vol. 32, pp. 205-209; Suppl. 7, p. 58.
benzo[a]pyrene (0.0085-0.011) (4)	Sufficient	No data	Vol. 3, pp. 91-136; Vol. 32, pp. 211-224; Suppl. 4, pp. 227-228; Suppl. 7, p. 58.
benzo[e]pyrene (0.002-0.03) (2)	Inadequate (initiator?, promoter)	No data	Vol. 3, pp. 137-158; Vol. 32, pp. 225-237; Suppl. 7, p. 58.
chrysene (0.04-0.06) (1)	Limited (initiator, co-carcinogen)	Inadequate	Vol. 3, pp. 159-177; Vol. 32, pp. 247-261; Suppl. 7, p. 60.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
coronene (0.001) (2)	Inadequate (initiator)	No data	Vol. 32, pp. 263-268; Suppl. 7, p. 61.
dibenz[a,c]anthracene (present) (2)	Limited (initiator)	No data	Vol. 32, pp. 289-297; Suppl. 7, p. 61.
dibenz[a,h]anthracene (0.004) (4)	Sufficient	No data	Vol. 3, pp. 178-196; Vol. 32, pp. 299-308; Suppl. 7, p. 61.
dibenz[a,j]anthracene (0.01) (2)	Limited	No data	Vol. 32, pp. 309-313; Suppl. 7, p. 61.
dibenzo[a,e]fluoranthene (present) (4)	Limited (initiator)	No data	Vol. 32, pp. 321-325; Suppl. 7, p. 61.
dibenzo[a,e]pyrene (present) (4)	Sufficient	No data	Vol. 3, pp. 201-206; Vol. 32, pp. 327-330; Suppl. 7, p. 62.
dibenzo[a,h]pyrene (present) (2)	Sufficient	No data	Vol. 3, pp. 207-214; Vol. 32, pp. 331-335; Suppl. 7, p. 62.
dibenzo[a,i]pyrene (0.0017-0.0032) (4)	Sufficient	No data	Vol. 3, pp. 215-223; Vol. 32, pp. 337-342; Suppl. 7, p. 62.
dibenzo[a,l]pyrene (present) (2)	Sufficient	No data	Vol. 3, pp. 224-228; Vol. 32, pp. 343-347; Suppl. 7, p. 62.
1,4-dimethylphenanthrene (present) (2)	Inadequate (initiator)	No data	Vol. 32, pp. 349-353; Suppl. 7, p. 62.
fluoranthene (0.1-0.26) (1)	Inadequate (co-carcinogen)	No data	Vol. 32, pp. 355-364; Suppl. 7, p. 63.
fluorene (present) (2)	Inadequate	No data	Vol. 32, pp. 365-371; Suppl. 7, p. 63.
indeno[1,2,3-cd]pyrene (0.004-0.02) (2)	Sufficient	No data	Vol. 3, pp. 229-237; Vol. 32, pp. 373-379; Suppl. 7, p. 64.
1-methylchrysene (0.003) (2)	Inadequate (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
2-methylchrysene (0.001) (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
3-methylchrysene (0.006) (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
4-methylchrysene (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
5-methylchrysene (≤0.0006) (4)	Sufficient	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
6-methylchrysene (0.007) (2)	Limited (initiator)	No data	Vol. 32, pp. 379-397; Suppl. 7, p. 66.
2-methylfluoranthene (2)	Limited (initiator)	No data	Vol. 32, pp. 399-404; Suppl. 7, p. 66.
3-methylfluoranthene (2)	Inadequate	No data	Vol. 32, pp. 399-404; Suppl. 7, p. 66.
1-methylphenanthrene (0.03) (2)	Inadequate	No data	Vol. 32, pp. 405-409; Suppl. 7, p. 66.
naphthalene (53 – 177) (8)	Sufficient	Inadequate	Vol. 82, pp. 367-435.
perylene (0.003-0.005) (2)	Inadequate	No data	Vol. 32, pp. 411-418; Suppl. 7, p. 69.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
phenanthrene (0.09- 0.6) (2)	Inadequate	No data	Vol. 32, pp. 419-430; Suppl. 7, p. 69.
pyrene (0.05-0.2) (1)	Inadequate (co-carcinogen)	No data	Vol. 32, pp. 431-445; Suppl. 7, p. 71.
triphenylene (2)	Inadequate	No data	Vol. 32, pp. 447-451; Suppl. 7, p. 73.
3. Phenols and phenol ethers			
caffeic acid (<3) (4)	Sufficient	No data	Vol. 56, pp. 115-129
catechol (59-81) (4)	Sufficient	No data	Vol. 15, pp. 155-175; Suppl. 7, p. 59; Vol. 71, pp. 433-451.
eugenol (2-4) (2)	Limited	No data	Vol. 36, pp. 75-97; Suppl. 7, p. 63.
hydroquinone (88-155) (2)	Limited	Inadequate	Vol. 15, pp. 155-175; Suppl. 7, p. 64; Vol. 71, pp. 691-719.
resorcinol (8-80) (2)	Inadequate	No data	Vol. 15, pp. 155-175; Suppl. 7, p. 71; Vol. 71, pp. 1119-1131.
cholesterol (22) (2)	Inadequate	Inadequate	Vol. 10, pp. 99-111; vol. 31, pp. 95-132; Suppl. 7, 161-165
4. Aldehydes			
acetaldehyde (770-864) (4)	Sufficient	Inadequate	Vol. 36, pp. 101-132; Suppl. 7, 77-78; Vol. 71, p. 319-335.
acrolein (25-140) (4)	Inadequate	Inadequate	Vol. 19, pp. 479-494; Vol. 36, pp. 133-161; Suppl 6, pp.21-23; Suppl. 7, p. 78; Vol. 63, p. 337 -372 (correction Vol. 65, p.549).
crotonaldehyde (55-67) (4)	Inadequate	Inadequate	Vol. 63, pp. 373-391.
formaldehyde (10.3-25) (4)	Sufficient	Limited	Vol. 29, pp. 345-389; Suppl. 4, pp. 131-132; Suppl. 6, pp.321-324; Suppl. 7, pp. 211-216; Vol. 62, pp. 217-362 (corrections Vol. 65, p.549 and 66, p. 485).
5. Lactones, esters, epoxides, furans etc.			
benzofuran (present) (4)	Sufficient	No data	Vol. 63, pp. 431-441
γ-butyrolactone (10) (2)	Evidence suggesting lack of carcinogenicity	Inadequate	Vol. 11, pp. 231-240; Suppl. 7, p. 59; Vol. 71, pp. 367-382.
coumarin (3)	Limited	No data	Vol. 10, pp. 113-119; Suppl. 7, p. 61; Vol. 77, pp. 193-225.
ethylene oxide (7) (4)	Sufficient	Limited	Vol. 11, pp. 157-167; Vol 36, pp. 189-226; Suppl. 7, pp. 205-207; Vol. 60, pp. 73-159.
furan (20 - 40) (4)	Sufficient	No data	Vol. 63, pp. 393-407
propylene oxide (0 - 0.1) (4)	Sufficient	Inadequate	Vol. 11, pp. 191-199; Vol 36, pp. 227-243; Suppl. 7, pp. 328-329; Vol. 60, pp. 181-213
methyl acrylate (present) (2)	Inadequate	No data	Vol. 19, p. 52; Vol. 39 pp. 99-112; Suppl. 7, p. 66; Vol. 71, p. 1489-1496.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
6. Nitrogen compounds			
N-Nitroso compounds			
4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) (0.08-0.7) (2)	Sufficient	No data	Vol. 37, pp. 209-223; Suppl. 7, p. 68.
N'-nitrosoanabasine (0-0.2) (2)	Limited	No data	Vol. 37, pp. 225-231; Suppl. 7, p. 67.
N'-nitrosoanatabine (0-3.7) (1)	Inadequate	No data	Vol. 37, pp. 233-240; Suppl. 7, p. 67.
N'-nitrosodimethylamine (0.001-0.2) (1)	Sufficient	No data	Vol. 1, pp. 95-106; Vol. 17, pp. 125-175; Suppl. 7, p. 67.
N-nitrosodiethylamine (0-0.01) (1)	Sufficient	No data	Vol. 1, pp 107-124; Vol. 17, pp. 83-124; Suppl. 7, p. 67.
N-nitrosodi-n-propylamine (0-0.001) (2)	Sufficient	No data	Vol. 17, pp. 177-189; Suppl. 7, p. 68.
N-nitrosodi-n-butylamine (0-0.003) (1)	Sufficient	No data	Vol. 4, pp. 197-210; Vol. 17, pp. 51-75; Suppl. 7, p. 67.
N-Nitroso-N-methylethylamine (0.0001- 0.01) (1)	Sufficient	No data	Vol. 17, pp. 221-226; Suppl. 7, p. 68.
N'-nitrosonornicotine (0.13-0.25) (1)	Sufficient	No data	Vol. 17, pp. 281-286; Vol. 37, pp. 241-261; Suppl. 7, p. 68.
N-nitrosodiethanolamine (0-0.09) (2)	Sufficient	Inadequate	Vol. 17, pp. 77-82; Suppl. 7, p. 67; Vol. 77, pp. 403-438.
N-nitrosopyrrolidine (0.002-0.042) (1)	Sufficient	No data	Vol. 17, pp. 313-326; Suppl. 7, p. 68.
N-nitrosopiperidine (0-0.009) (1)	Sufficient	No data	Vol. 17, pp. 287-301; Suppl. 7, p. 68.
Polycyclic aza-arenes			
carbazole (1) (2)	Limited	No data	Vol. 32, pp. 239-245; Suppl. 7, p. 59; Vol. 71, pp.1319-1323.
dibenz[a,h]acridine (≤0.0001) (4)	Sufficient	No data	Vol. 3, pp. 247-253; Vol. 32, pp. 277-281; Suppl. 7, p. 61.
dibenz[a,j]acridine (≤0.010) (4)	Sufficient	No data	Vol. 3, pp. 254-259; Vol. 32, pp. 283-288; Suppl. 7, p. 61.
7H dibenzo[c,g]carbazole (≤0.0007) (4)	Sufficient	No data	Vol. 3, pp. 260-268; Vol. 32, pp. 315-319; Suppl. 7, p. 61.
benz[a]acridine (2)	Inadequate	No data	Vol. 32, pp. 123-127; Suppl. 7, p. 58.
benz[c]acridine (2)	Limited	No data	Vol. 3, pp. 241-246; Vol. 32, pp. 129-134; Suppl. 7, p. 58.
Amino acid pyrolysis products			
3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) (0.0003-0.0005) (4)	Sufficient	No data	Vol. 31, pp. 247-254; Suppl. 7, p. 73
2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) (0.00037-0.00089) (4)	Sufficient	No data	Vol. 40, pp. 223-233; Suppl. 7, p. 64

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
2-aminodipyrido[1,2-a:3',2'-d] imidazole (Glu-P-2) (0.00025-0.00088) (4)	Sufficient	No data	Vol. 40, pp. 235-243; Suppl. 7, p. 64
2-amino-3-methyl-3H-imidazo [4,5-f]quinoline (IQ) (0.00026) (4)	Sufficient	No data	Vol. 40, pp. 261-273; Suppl. 7, p. 64: Vol. 56, pp. 165-195
2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (0.011-0.023) (4)	Sufficient	No data	Vol. 56, pp. 229-242
2-amino-3-methyl-9H-pyrido [2,3-b]indole (MeA-α-C) (0.002-0.037) (4)	Sufficient	No data	Vol. 40, pp. 253-259
3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2) (0.0008-0.0011) (4)	Sufficient	No data	Vol. 31, pp. 255-263; Suppl. 7, p. 73
2-amino-9H-pyrido[2,3-b] indole (A-α-C) (0.025-0.26) (4)	Sufficient	No data	Vol. 40, pp. 245-252
Aromatic amines			
4-aminobiphenyl (0.002-0.005) (4)	Sufficient	Sufficient	Vol. 1, pp. 74-79; Suppl. 4, pp. 37-38; Suppl. 6, 60-63; Suppl. 7, 91-92.
ortho-anisidine (1-amino-2-methoxybenzene)	Sufficient	Inadequate	Vol. 27, pp. 63-80; Suppl. 7, p. 57; Vol. 73, pp. 49-58.
aniline (0.1-0.4) (2)	Limited	Inadequate	Vol. 4, pp. 27-39; Vol. 27, pp. 39-61; Suppl. 6, 68-70; Suppl. 7, 99-100.
2,6-dimethylaniline (4-50) (4)	Sufficient	No data	Vol. 57., pp. 323-335
1-naphthylamine (0.003-0.004) (1)	Inadequate	Inadequate	Vol. 4, pp. 87-96; Suppl. 4, pp. 164-165; Suppl. 6, 406-409; Suppl. 7, 260-261.
2-naphthylamine (0.001-0.022) (4)	Sufficient	Sufficient	Vol. 4, pp. 97-111; Suppl. 4, pp. 166-167; Suppl. 6, 410-414; Suppl. 7, 261-263.
N-phenyl-2-naphthylamine (2)	Limited	Inadequate	Vol. 16, pp. 325-341; Suppl. 4, pp. 213-215; Suppl. 6, 461-462; Suppl. 7, 318-319.
ortho-toluidine (2-methylaniline) (0.03-0.2) (4)	Sufficient	Limited	Vol. 16, pp. 349-366; Vol. 27, pp. 155-175; Suppl. 4, pp. 245-246; Suppl. 6, 523-527; Suppl. 7, 262-263; Vol. 77, pp. 267-322.
Miscellaneous nitrogen compounds			
acetamide (38-56) (4)	Sufficient	No data	Vol. 7, pp. 197-202; Suppl. 7, pp. 389-390; Vol. 71, pp. 1211-1221.
acrylamide (present) (4)	Inadequate	Sufficient	Suppl. 7, p. 62; Vol. 60, pp. 389-433:
acrylonitrile (3-15) (4)	Sufficient	Inadequate	Vol. 19, pp. 73-113; Suppl. 4, pp. 25-27 Suppl. 6, 27-31; Suppl. 7, 79-80; Vol. 71, pp. 43-108.

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
hydrazine (0.024-0.043) (4)	Sufficient	Inadequate	Vol. 4, pp. 127-136; Suppl. 4, pp. 136-138; Suppl. 6, 341-343; Suppl. 7, 223-224; Vol. 71, pp. 991-1013.
1,1-dimethylhydrazine (present) (4)	Sufficient	No data	Vol. 4, pp. 137-143; Suppl. 7, p. 62; Vol. 71, pp. 1425-1436.
nitrobenzene (25) (4)	Sufficient	Inadequate	Vol. 65, pp 381-408
nitromethane (0.5-0.6) (4)	Sufficient	Inadequate	Vol. 77, pp. 487-501
2-nitropropane (0.0.0007-0.0012) (4)	Sufficient	Inadequate	Vol. 29, pp. 331-343; Suppl. 7, p. 67; Vol. 71, p. 1079-1094.
urethane (0.020-0.038) (4)	Sufficient	No data	Vol. 7, pp. 111-140; Suppl. 7, p.73.
7. Agricultural chemicals and derivatives			
captan (0.4-34) (2)	Limited	No data	Vol. 30, pp. 295-318; Suppl. 7, p. 59.
DDT (0.7-1.2) (2)	Sufficient	Inadequate	Vol. 5, pp. 83-124; Suppl. 4, pp. 105-108; Suppl. 6, 212-215; Suppl. 7, 186-189; Vol. 53, p. 179-249.
endrin (2)	Inadequate	No data	Vol. 5, pp. 157-166; Suppl. 7, p.63.
malathion (2)	Inadequate	No data	Vol. 30, pp. 103-129; Suppl. 7, p.65.
maleic hydrazide (0.1-2.1) (2)	Inadequate	No data	Vol. 4, pp. 173-179; Suppl. 7, p.65.
succinic anhydride (2)	Limited	No data	Vol. 15, pp. 265-271; Suppl. 7, p.72.
8. Halogen compounds			
vinyl chloride (0.011-0.015) (4)	Sufficient	Sufficient	Vol. 7, pp. 291-318; Vol. 19, pp. 377-438; Suppl. 4, pp. 260-262; Suppl. 6, 566-569; Suppl. 7, 373-376.
9. Inorganic elements			
Arsenic (0.040-0.12) (4)	Sufficient	Sufficient	Vol. 1, p. 41; Vol. 2, pp. 48-73; Vol. 23, pp. 39-141; Suppl. 4, pp. 50-51, Suppl. 6, 71-76; Suppl. 7, 100-106, Volume 84 pp 39-267.
Cadmium (0.041-0.062) (4)	Sufficient	Sufficient	Vol. 2, pp. 74-99; Vol. 11, pp. 39-74; Suppl. 4, pp. 71-73; Suppl. 6, 132-135; Suppl. 7, 139-142; Vol. 58, pp. 119-237.
Chromium VI (0.004-0.07) (4)	Sufficient	Sufficient	Vol. 2, pp. 100-125; Vol. 23, pp. 205-323; Suppl. 4, pp. 91-93; Suppl. 6, 168-175; Suppl. 7, 165-168; Vol. 49, p. 49-256 (correction Vol. 51, p. 483).
Lead (0.034-0.085) (4) Inorganic Pb: Organic Pb:	 Sufficient Inadequate	 Limited Inadequate	Vol. 1, pp. 40-50; vol. 2, p. 52; vol. 23, pp. 40, 209, 325-415; Suppl. 4, pp. 149-150; Suppl. 6, 351-354; Suppl. 7, 230-232, Vol 87, in preparation.
Nickel (≤0.6) (4)	Sufficient	Sufficient	Vol. 2, pp. 126-149; Vol. 11, pp. 75-112; Suppl. 4, pp. 167-170; Suppl. 6, 417-420; Suppl. 7, 264-269; Vol. 49, p. 257-445 (correction Vol. 67, p. 395).

Table 7.0B. Chemical compounds identified in tobacco smoke that have been evaluated for carcinogenicity in the IARC Monographs series.

Compound[a]	Degree of evidence in animals	Degree of evidence in humans	Reference[b]
^{210}Polonium (0.03-1.0 pCi) (4)	Sufficient	Sufficient	Vol. 78, pp. 465-477. (Group 1 lisitng is of all internally deposited α-emitting radionuclides, considered as a group.
Selenium (≤0.012) (4)	Inadequate	Inadequate	Vol. 9, pp. 245-260; Suppl. 7, p.71.

Footnotes to Table 7.0B

[a] In parentheses: concentration expressed as µg in the mainstream smoke of one cigarette; exceptionally, as µg/g tobacco smoked. Second parentheses refer to the following references:
1. Wynder & Hoffmann (1982), Wynder & Hoffmann (1979)
2. Wynder & Hoffmann (1967)
3. IARC (1983c)
4. IARC (2004a)

[b] IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volumes 1-84 and Supplements 4, 6 and 7. See Table 7.6.1 for full citations.

7.0.1. Misclassification of Smoking Status

As discussed in Chapter 1, the accurate classification of an individual's smoke exposure is critical to the determination of the degree of association between ETS and disease. For example, the estimate of relative risk of disease from exposure to ETS will be overestimated if active smokers are misclassified as passive smokers. Similarly, if light or infrequent smokers or passive smokers are included in the control non-smoke-exposed group, the relative risks from exposure will be underestimated and biased toward the null.

7.0.1.1. Summary of Previous Findings on Misclassification of Smoking Status

Previously, OEHHA concluded that collective evidence from the two most recent studies examined (Riboli *et al.*, 1995; Nyberg *et al.*, 1997), as well as studies reviewed by the U.S. EPA (1992d), demonstrated that misclassification of smoking status, particularly the potential for identifying smokers as nonsmokers, remains low and does not explain the lung cancer risk associated with ETS exposure (Cal/EPA, 1997).

7.0.1.2. Recent Data on Misclassification of Smoking Status and of Exposure

The parameters utilized to define the referent population in epidemiological studies may have an important impact on the ability to uncover an association with ETS exposure. In many, particularly older studies, the referent (non-exposed) population is defined in ways that include many significantly ETS-exposed individuals. An example of this is utilizing a single question, "Does your spouse smoke?", to define the non-exposed referent group, ignoring other household, workplace or outside exposures. In many studies, exposure is identified for only a single point in time. Since carcinogenesis often involves a long latency period, the exposure periods of interest may include decades. Prior to the last decade, the prevalence of smoking and therefore ETS exposure was much higher, making it difficult to define a truly non-exposed referent group.

Failure to correct for this background exposure will bias results toward the null. The impact of such referent group "misclassification" has been examined within individual studies (Johnson *et al.* 2001; Morabia *et al.*, 1998) and shown to lead to an underestimation of the effect (see further discussion in Section 7.4.1.3).

In a study comparing self-reported smoking status and cotinine levels from seven studies of lung cancer in a U.S. EPA report (U.S. EPA, 1992) and three newer studies, Wells *et al.* (1998) noted differences in the smoking misclassification rates associated with majority/minority classification. Among females, the misclassification rate of regular smokers as never smokers was 0.8% for majority females and 2.8% for minority females, while misclassification of occasional smokers as nonsmokers was higher, 6.0% and 15.3%, respectively. The respective misclassification rates among males were generally higher (1.4%, 3.7%, 5.1% and 19.7%). These data suggest that the ethnic make-up of study subjects should be considered when adjusting for misclassification bias. They also confirm the conclusion in the EPA report that misclassification bias is small and unlikely to account for the increased risk of lung cancer associated with ETS exposure.

In a more recent review of exposure misclassification bias in studies of ETS and lung cancer, Wu (1999) found that the proportion of ever smokers reported as never-smokers, the proportion of nonsmokers misclassified as ever-smokers, and the risk of lung cancer among misclassified smokers were all low (≤ 5%). One of the studies reviewed by Wu (1999) was a case-control study of active and passive smoking in lung cancer (Nyberg *et al.* 1998b). This study compared subjects' self-reported smoke exposure with reports from next of kin and found a very low proportion (1.2%) of misclassified ever-regular smokers among reported never-smokers. They also estimated the misclassification associated with occasional smoking using an exclusion criterion of >400 cigarettes to be 2.6%. After exclusion of potentially misclassified subjects, very little change was found in the effect estimates associated with ETS exposure. These observations support the conclusion in the previous document that smoker misclassification cannot explain the ETS effect on lung cancer in never-smokers.

In a study of ETS exposure as assessed by salivary cotinine, measures of airborne nicotine and exposure self-classification, Jenkins and Counts (1999) report misclassification rates of subjects claiming to be lifetime never-smokers based on salivary cotinine cutoffs of 106, 35, 15, and 10 ng/ml ranged from 3.22% to 5.94%. The effect again is to bias toward the null.

7.1. All Cancers (Combined)

The following background information is reiterated from the earlier OEHHA report (Cal/EPA, 1997):

> "Overall death rates for smokers are about two times higher than for nonsmokers (U.S. DHEW 1979). Those nonsmokers who are exposed to tobacco smoke are exposed to the same toxic constituents of tobacco smoke as smokers (U.S. DHHS 1986f), although active smokers and those exposed to ETS may differ in the relative amounts of carcinogens to which they are exposed. Furthermore, the phase distributions of compounds differ between mainstream smoke and ETS. More of the constituents appear in the vapor phase (versus the particulate phases) in ETS compared to mainstream smoke, and particle sizes are smaller in ETS. Components also enter the vapor phase from the particulate phase as ETS ages. Therefore, the relative uptake and deposition of these components potentially differ between active and passive smokers (Guerin *et al.,* 1992) (See Chapter 2, Exposure Measurement and Prevalence). Because of these differences, it is not apparent which cancer sites may be most affected by ETS exposure. This section describes studies addressing the overall risk of cancer (all sites combined) from ETS exposure, in adults and in children."

7.1.1. All Cancers in Adults

Cancer risk in adult life may be due to a lifetime accumulation of exposures and resulting biological effects, including those due to exposures occurring transplacentally, during childhood and/or adulthood. Earlier studies examining the potential role of ETS exposure in the etiology of various cancers in adults have focused on the association between adult exposure to ETS and cancer risk (Hirayama, 1984; Sandler *et al.,* 1985a; Reynolds *et al.*, 1987; Sandler *et al.*, 1989), with more limited work on the role of childhood ETS exposure and subsequent adult onset cancers (Sandler *et al.*, 1985b). More recent epidemiological studies on adult cancers and ETS exposure have focused on individual anatomic sites, such as lung (Section 7.2) or breast (Section 7.4.1.2), with increasing focus on lifetime and/or multiple sources of ETS.

7.1.1.1. Overall Cancer Risk in Adults: Previous Findings

In 1997, OEHHA determined that the epidemiological evidence for a relationship between ETS and overall cancer risk in adults was limited (Cal/EPA, 1997). Three of the five studies summarized, including two based on cancer mortality, determined that exposure to spousal smoking may increase the overall cancer risk among women (Hirayama, 1984; Sandler *et al.* 1985a; Reynolds *et al.,* 1987). These studies lacked information on other sources of ETS exposure, were based on a limited number of smoking-related cancers, and often lacked data on other known cancer risk factors.

7.1.1.2. Overall Cancer Risk in Adults: Recent Epidemiological Findings

As described in section 7.2.3, Nishino *et al*. (2001) conducted a population-based prospective study on the effects of exposure to spousal smoking among 9,675 Japanese women between 1984 and 1992. After adjusting for age, alcohol use, intake of green and yellow vegetables, and

fruit intake, an RR of 1.1 (95% CI 0.91-1.4) was reported for cancer at all sites in association with ETS exposure. For smoking-related cancers, the adjusted RR was 1.7 (95% CI 0.94-3.1).

7.1.1.3. Summary on Overall Cancer Risk in Adults

In 1997, OEHHA concluded:

> "In summary, there is limited evidence from two cohort studies (Hirayama, 1984; Reynolds *et al.*, 1987) and one case-control study (Sandler *et al.*, 1985a) that exposure to spouses' smoking may increase overall risk of cancer in nonsmoking women. In one study, the increase is explained primarily by an elevated risk observed for lung cancer (Hirayama, 1984). However, in two studies, elevated risks were observed for sites not typically related to active smoking as well as sites related to smoking (Reynolds *et al.*, 1987; Sandler *et al.*, 1985a). In the study by Reynolds *et al.* (1987), the strong association between husbands' smoking and smoking-related tumors was based on very few cases, accounting for only 6% of all cancers. In the study by Sandler *et al.* (1985a), increased risks were observed for both smoking-related (lung, cervix), and non-smoking-related sites (breast and endocrine gland) after adjustment for age and education. Although the results on nonsmoking-related cancers are intriguing, they are difficult to interpret given that known risk factors for the specific cancers under study were not adjusted for (Sandler *et al.*, 1985a). Possible effects of potential confounders are a concern and in further studies should be more carefully researched. For example, sexual activity is a risk factor for cervical cancer and exposure to ETS may be associated with sexual activity. Alcohol intake is a risk factor for breast cancer and exposure to ETS may be positively associated with alcohol use."

While the study by Nishino *et al*. (2001) suggests a weak association between ETS exposure and all cancers, no other additional studies were found that reported on overall adult cancer risk associated with ETS exposure. Thus, no compelling evidence exists for modifying the above conclusions regarding the potential role of ETS of increasing adult onset cancer risk for all malignancies combined.

7.1.2. All Cancers in Children

As outlined in the previous OEHHA report (Cal/EPA, 1997), as well as more recently published quantitative and qualitative reviews (Thornton and Lee, 1998b; Sasco and Vainio, 1999; Boffetta *et al.*, 2000), ETS exposure has been investigated as a risk factor for all childhood cancers combined and for specific childhood tumors (see Sections 7.1.2 to 7.1.2.5). However, difficulties exist in distinguishing the effects of ETS on children, both prior to and after birth, by various exposures routes, including preconceptional, transplacental prenatal, and postnatal exposure from a variety of sources, i.e., mothers' smoking, fathers' smoking, other ETS sources. As with many studies on childhood cancer and ETS exposure, the previous OEHHA report also considered parental smoking during pregnancy as a surrogate measure of postnatal parental smoking, and thereby childhood ETS exposure. Limited data exist to support the assumption that smoking habits during pregnancy represent an unbiased estimate of smoking habits after pregnancy (Cal/EPA, 1997).

Historically, most studies only reported on ever-maternal active smoking, ever-paternal active smoking, or maternal active smoking during the pregnancy. More recent studies have attempted to analyze maternal smoking prior to or at conception (Filippini *et al.*, 1994; Shu *et al.*, 1996; Sorahan *et al.*, 1995; Sorahan *et al.*, 2001), maternal active smoking during pregnancy (Bunin *et al.*, 1994; Brondum *et al.*, 1999; Cordier *et al.*, 1994; Filippini *et al.*, 1994; Infante-Rivard *et al.*, 2000; Klebanoff *et al.*, 1996; Norman *et al.*, 1996; Schuz *et al.*, 1999; Sorahan *et al.*, 1995; Sorahan *et al.*, 2001) or postnatal exposures (Cordier *et al.*, 1994; Infante-Rivard *et al.*, 2000), and to a more limited extent, pre- or postnatal paternal ETS exposure (Ji *et al.*, 1997). Other studies on childhood cancers obtained information on both maternal and paternal smoking habits during various time periods relative to the pregnancy (Bunin *et al.*, 1994; Brondum *et al.*, 1999; Filippini *et al.*, 1994; Infante-Rivard *et al.*, 2000; Shu *et al.*, 1996; Schuz *et al.* 1999; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a; b; Sorahan *et al.*, 2001). As with earlier studies, the relatively rare nature of childhood cancer and the overwhelming reliance on case-control study design led to the majority of data on parental smoking habits being ascertained retrospectively, after cancer diagnosis or cancer-related death.

Studies also varied substantially in the age range of cases; the majority included children under age 15, while others were restricted to infants (Shu *et al.*, 1996), children under age six or eight or ten years of age (Klebanoff *et al.*, 1996; Infante-Rivard *et al.*, 2000; Bunin *et al.*, 1994), or adolescents up to age 15 (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.* 1997a;b; Sorahan *et al.* 2001; Brondum *et al.*, 1999; Cordier *et al.*, 1994; Filippini *et al.*, 1994; Schuz *et al.*, 1999) or 19 (Linet *et al.*, 1996; Norman *et al.*, 1996). Patterns of cancer occurrence, with respect to overall incidence, anatomic site, or specific histology, vary substantially by age. Age-specific incidence rates for all cancer sites combined peak by age 5, decline until age 14, prior to rising again during adolescence continuing through adulthood (Campleman *et al.*, 1999; Ries *et al.*, 1999). Therefore, making any comparison between these individual studies analyzing for excess in overall cancer risk in different age groups at varying risk for individual cancer types remains difficult.

7.1.2.1. Biomarker Studies of Exposure to Tobacco Smoke Constituents *In Utero* and Postnatally: Previous Findings.

Several studies, described previously in Cal/EPA (1997), investigated the availability of biological markers of tobacco smoke exposure in newborns (Eliopoulos *et al.*, 1994), fetal blood samples (Coghlin *et al.*, 1991; Hammond *et al.*, 1993), or young, pre-school age children (Crawford *et al.*, 1994). Nicotine and cotinine levels in newborns (obtained from hair shaft samples) were highest among smokers, followed by those exposed to passive smoke and non-smokers (Eliopoulos *et al.*, 1994). In another cross-sectional study, levels of 4-amino-biphenyl (4-ABP) hemoglobin adducts were identified in the maternal-fetal paired blood samples of both smoking and non-smoking mothers. 4-ABP hemoglobin adduct levels in the blood of nonsmoking women and their fetuses were 12% and 9%, respectively, of the levels found in smokers (Hammond *et al.*, 1993). In the third study, Crawford *et al.* (1994) evaluated levels of serum cotinine and polycyclic aromatic hydrocarbon (PAH)-albumin adducts in preschool children and their mothers. Maternal mean serum cotinine, childhood mean serum cotinine, and PAH-albumin adducts levels all demonstrated a decreasing gradient by active smoking, passive smoking and nonsmokers with no ETS exposures. Comparisons between the three groups of mothers and of preschool children demonstrated statistically significant differences in levels of

cotinine and PAH-albumin adducts. Adduct levels were higher in smokers (or their children) than in passive smokers and nonsmokers not exposed to ETS (or their children). Another recent study measured BaP-DNA adducts and cotinine levels in paired maternal and fetal blood (Perera *et al*., 2004). They found higher BaP-DNA adducts in the newborns than in the mothers despite an estimated 10 fold higher dose to the mother as well as significantly higher level of maternal cotinine. These results are indicative of both a reduced ability to clear ETS constituents and an increased susceptibility to DNA damage in the fetus.

These studies provide evidence that constituents of tobacco smoke are present in the biological fluids of nonsmokers exposed to ETS, that such chemicals readily cross the human placenta in both nonsmoking and smoking mothers, and that young children may carry a biological burden from exposure to ETS that exceeds that of the parent.

7.1.2.2. Biomarker Studies of Exposure to Tobacco Smoke Constituents *In Utero* and Postnatally: Recent Data.

Two additional studies have reported on the levels of two different biomarkers of tobacco smoke exposure in pregnant women and their offspring, one in the fetus (Pinorini-Godly and Myers, 1996), and the other in newborns (Whyatt *et al.*, 1998b), while a third study reported on the uptake of a tobacco-related carcinogen by school age children exposed to ETS (Hecht *et al.*, 2001). These studies, in particular Pinorini-Godley and Myers (1996) and Hecht *et al.* (2001), further demonstrate transplacental transfer of tobacco-related constituents, and carcinogen uptake by children exposed to ETS.

Table 7.1A. 4-Aminobiphenyl hemoglobin adduct concentrations in pregnant women and fetuses by exposure to tobacco smoke[1]

	HPLC[2] (pg ABP/g Hb)[3] Mean ± Standard Deviation	GC/MS[2] (pg ABP/g Hb)[3] Mean ± Standard Deviation
Maternal Blood		
nonsmokers (n = 21)	24 ± 14	30 ± 16
smokers (n = 21)	423 ± 154	488 ± 174
Fetal Blood		
nonsmokers (n = 21)	10 ± 5	14 ± 7
smokers (n = 21)	197 ± 77	244 ± 91

[1] Source: Pinorini-Godly and Myers (1996). [2] Data analyzed by two methods, high pressure liquid chromatography and gas chromatographic/mass spectrometry [3] ABP = 4-aminobiphenyl hemoglobin adducts; Hb = hemoglobin; pg ABP/g HB = picograms ABP adduct per gram hemoglobin

Pinorini-Godly and Myers, 1996. Maternal-fetal exchange of the tobacco-related carcinogen, 4-aminobiphenyl (4-ABP), was analyzed in a small group of women (21 smokers, 21 nonsmokers) and their corresponding fetuses during pregnancy. Maternal smoking status was determined via questionnaire and through immunoassay of serum cotinine in maternal/fetal blood samples. The mean level of 4-ABP in smoking women was significantly higher than nonsmoking women, 488 (± 174 pg 4-ABP/g Hb) versus 29.6 (± 16.2 pg 4-ABP/g Hb), respectively. A similar result was found among fetal samples, 244 (± 91 pg 4-ABP/g Hb) versus 14.0 (± 6.5 pg 4-ABP/g Hb), among fetuses of smokers and nonsmokers, respectively (Table 7.1A). Maternal and fetal

exposures were significantly correlated (GC/MS, R^2=0.95). This study confirmed that 4-ABP readily crosses the human placenta and binds to fetal hemoglobin in significantly larger amounts in smoking versus nonsmoking women.

Whyatt et al., 1998b. As part of a larger study investigating the relationship between ambient air pollution and DNA damage in Polish mothers and newborns, DNA adducts of polycyclic aromatic hydrocarbons (PAHs) were measured in maternal and umbilical white blood cells. This cohort included 70 mothers and newborns in Krakow, Poland. Smoking status (active and passive) was quantified via questionnaire with plasma cotinine used to verify questionnaire data. Maternal smoking (active and passive) significantly increased maternal adduct levels among current smokers compared to both nonsmokers and ex-smokers, including those who quit smoking during pregnancy. DNA adduct levels in newborns also increased with maternal exposure to active or passive smoking, but after adjusting for dietary PAHs, use of coal in the home, and home or occupational exposure to PAHs, the association became non-significant. In nonsmokers, maternal DNA-PAH adducts were significantly higher in women reporting exposure to ETS. However, no association was reported between maternal white blood cell DNA adduct levels and maternal plasma cotinine levels. Additionally, the study analyzed for the potential modulation of DNA-PAH adducts by two polymorphic metabolic enzymes, genotyping for glutathione S-transferase M1 (GSTM1) and cytochrome P4501A1 (CYP1A1) MspI. Neither polymorphism was associated with maternal adduct levels. However, in newborns the CYP1A1 RFLP was positively associated with higher adduct levels (heterozygotes and homozygotes), possibly due to low or absent levels of the conjugating enzyme, GSTM1, in the fetus. Thus, although this study did not find a statistically significant association between maternal ETS exposure and DNA adduct formation in newborns, any effect may have been masked by the effects of the ambient pollution, as suggested by a study by Vork *et al.* (2002), as well as limitations of the measurement techniques employed.

Hecht et al., 2001. A U.S. study utilized a series of biomarkers to investigate the uptake of the tobacco-related carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in elementary aged children. Urinary analysis assayed levels of two NNK metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide (NNAL-Gluc), as well as total cotinine (cotinine and cotinine glucuronide). Seventy of the 204 children assayed (34%) had a total cotinine level ≥ 5 ng/mL, and among these children NNAL and NNAL-Gluc metabolites were identified in the majority of samples analyzed (96%). Additionally, partial analysis for NNAL/NNAL-Gluc among children with < 5 ng/mL total urinary cotinine found half the samples (10/20) also positive for the carcinogenic metabolites, indicating the potential widespread distribution of this tobacco-specific carcinogen in elementary-school-aged children. Children identified as "ever exposed to ETS" via interviewer questionnaire had significantly higher mean urinary levels of NNAL (0.032 ± 0.039 vs 0.010 ± 0.020 pmol/ml), NNAL plus NNAL-Gluc (0.095 ± 0.088 vs 0.035 ± 0.058 pmol/ml), and total cotinine (24.5 ± 22.4 vs 5.0 ± 8.7 µg/ml), relative to "unexposed" children. Levels detected in this study were comparable with levels previously identified in the urine of women with spousal ETS exposure (Anderson *et al.* 2001).

7.1.2.3. Overall cancer risk in children/adolescents: previous findings

In the 1997 report, OEHHA reviewed a total of 21 published studies examining the potential relationship between ETS exposure and the risk of developing childhood cancer, both for all cancer types combined and for specific childhood tumors (Cal/EPA, 1997). In summary, the previous report found only inconclusive evidence for an association between parental smoking and childhood cancers (all cancer sites combined). One of the two cohort studies reviewed found an elevated, but statistically non-significant association between maternal smoking and all cancer sites combined (Neutel and Buck, 1971), while the second cohort found no association between maternal smoking and the risk of all cancers combined (Pershagen *et al.*, 1992). Two of the five case-control studies reviewed reported significant associations between mother's smoking during pregnancy and risk of childhood cancers (Stjernfeldt *et al.*, 1986b; Golding *et al.*, 1990). A third case-control study (John *et al.*, 1991), the only to assess paternal smoking independently from maternal smoking, found no association with maternal smoking but a statistically non-significant increased risk with paternal smoking.

7.1.2.4. Overall cancer risk in children/adolescents: recent epidemiological findings

Seven newer studies not previously reviewed in Cal/EPA (1997) are described below. The six studies with data on smoking during the index pregnancy are summarized in Table 7.1C.

Klebanoff et al., 1996. This United States study was based on a prospective, multi-center cohort, the Collaborative Perinatal Project. The cohort, 44,621 pregnant women enrolled from 1959 to 1966 at 12 university-affiliated medical centers, was initially selected to study risk factors for neurodevelopmental disorders, not cancer. All 54,795 live born children were eligible for enrollment. Maternal smoking data available for 54,306 births indicated that 52% of the mothers smoked during pregnancy (smoking determined at each prenatal visit). No data on paternal or other passive smoking exposure were available. Follow up was limited, with children followed to either age 7 (80%) or 8 years (36%). Fifty-one cancer cases were reported (17 leukemia cases). No overall association (RR 0.67, 95% CI 0.38-1.17) (Table 7.1C) or dose-response gradient (0, 1-10, >10) was found for all cancers combined. Limited covariate analysis was presented, but did not alter the risk estimates to any substantial degree.

Ji et al. 1997. A population based case control study in Shanghai, People's Republic of China, studied the association between parental smoking and childhood cancer incidence diagnosed between 1981 through 1991 (1985-1991 only for acute leukemia). Cases were ascertained from a population based cancer registry for children under the age of 15 at diagnosis. A total of 680 cases were eligible with 642 participating. Population controls were matched to cases based on age, sex and local governmental sampling unit. Only paternal smoking was analyzed in this study. Three mothers that reported ever smoking were excluded, all other mothers were considered nonsmokers.

Paternal smoking status (ever versus never) was positively associated with increased risk for all childhood cancers combined [adjusted RR 1.3 (95% C.I. 1.0-.7)]. Adjusted risk estimates were highest among fathers that started smoking under age 20 [RR 1.9 (95% C.I. 1.3-2.7)], smoked 15 or more years, [RR 1.7 (95% C.I. 1.2-2.5)], or smoked more than 10 pack years [RR 1.6 (95% C.I. 1.1-2.4)]. Additional analysis examining the cancer risk among children according to

exposure period, either before conception or after birth, found the greatest risk associated with preconception smoking (adjusted for birth weight, income, paternal age, education and alcohol consumption). Among offspring of fathers smoking more than 5 pack-years before conception, an elevated risk of 1.7 (95% C.I. 1.2-2.5) was observed (Table 7.1C). When childhood cancers were analyzed by age of diagnosis, there was a highly significant association between paternal preconception smoking and incidence of childhood cancer (all sites) in children diagnosed before 5 years of age (see Table 7.1B). The greatest risk was noted with fathers smoking ≥ 5 pack-years preconception [RR = 3.5 (CI 1.8-6.6)]. This association shows a strong dose-response with a p-value of 0.0002 for trend. No significant associations were noted between paternal preconception smoking and age of cancer diagnosis at older ages (5-14 years). These findings suggest prezygotic genetic damage. See further discussion of Ji *et al.* (1997) in Section 7.4.3.4.

Table 7.1B. Age-specific odds ratios (adjusted for birth weight, income, paternal age, education, and alcohol drinking) and 95% confidence intervals for childhood cancers (all sites combined) in relation to paternal smoking before conception[1].

Pack-years	Age at diagnosis of cancer		
	0-4 years OR (95%CI)	5-9 years OR (95%CI)	10-14 years OR (95%CI)
≤ 2	1.6 (1.0-2.7)	0.7 (0.3-1.7)	0.8 (0.1-4.2)
> 2 and < 5	1.8 (1.8-3.1)	1.0 (0.5-2.1)	0.8 (0.2-2.8)
≥ 5	3.5 (1.8-6.6)	0.7 (0.3-1.6)	0.9 (0.4-2.4)
(p for trend)	0.0002	0.71	0.77

[1]Source: Table 5 of Ji *et al.* (1997)

Sorahan et al. 1995; 1997a; 1997b. Three United Kingdom case-control studies of childhood cancer deaths in relation to reported parental tobacco consumption have been published from the Oxford Survey of Childhood Cancers (OSCC) (Sorahan *et al.*, 1995; Sorahan *et al.* 1997a;b). The survey was initiated in 1956 with interviews conducted with the parents of any child dying of cancer prior to age 16. Controls were selected from the birth register in the same local authority matched on sex and date of birth.

In the 1995 report, a subset of cases was utilized. There were 3,364 childhood cancer deaths which occurred between 1977 and 1981, with 1,816 case parents interviewed (60.5% all cases) however, only 1,641 matched pairs were available (48.8% of all cases). Case and control interview data were reviewed to abstract data on parental alcohol consumption and tobacco consumption (prior to pregnancy) for reanalysis. Maternal consumption of cigarettes before pregnancy was not associated with an increased risk of childhood cancer death. However, paternal smoking was significantly associated with overall cancer death, with a positive trend of association between risk and daily cigarette consumption (p = 0.003), and risk estimates ranging from 1.17 to 1.39. Analysis combining maternal and paternal smoking habits, with and without adjustment for social class and maternal age, was the same for paternal only [RR 1.37 (95% C.I. 1.12-1.68) and both parents combined [RR 1.37 (95% C.I. 1.13-1.67)] (Table 7.1C).

The two 1997 publications analyzed childhood cancer deaths from two other periods, 1953 to 1955 (Sorahan *et al.*, 1997a) and 1971 to 1976 (Sorahan *et al.*, 1997b). The study focusing on 1953 to 1955 included 1,549 childhood cases from the 3,364 period deaths with controls matched on child age, residence and sex. Exposure consisted of maternal and paternal postnatal smoking.

No significant association was seen for maternal smoking either alone, in combination with paternal smoking, or adjusted for other factors including maternal/paternal age, parity, social class and obstetric x-ray. Positive associations with childhood cancer were seen for paternal smoking alone [1.30 (95% CI 1.10-1.53)], or in combination with maternal smoking [1.70 (95% CI 1.32-2.18)]. There was a statistically significant dose-response trend between paternal daily cigarette consumption (current habit at interview) and the overall risk of childhood cancer ($p<0.001$) after adjustment for several factors including social class, maternal smoking, parental age, birth order and obstetric radiography (Sorahan *et al.*, 1997a).

The later analysis (Sorahan *et al.*, 1997b) incorporated data on 2,587 matched pairs (from 5,111 total number of period deaths). As with the previous study (Sorahan *et al.*, 1997a), smoking questions were on current habits at time of interview. However, reliability of the smoking data was examined by comparing birth weight to reported smoking habits. Among both case and control groups, mean birth weight was significantly associated with reported daily maternal cigarette consumption (negative trend $p<0.001$). Relative risks for death due to all types of childhood cancer combined were analyzed by maternal smoking alone, paternal smoking alone, and combined parental smoking, with and without adjustment for other factors (parental ages, social class, parity and obstetric radiography). As with the previous OSCC analyses, maternal cigarette consumption was not significantly associated with risk of childhood cancer [adjusted RR 0.94 (95% C.I. 0.78-1.12)] and the study found no significant trend with increasing daily maternal smoking. Paternal cigarette smoking was again statistically significantly associated with risk of childhood cancer when analyzed alone [RR 1.29 (95% C.I. 1.10-1.51)] or combined with maternal smoking [RR 1.27 (95% C.I. 1.09-1.48)](Table 7.1C). Significantly elevated risk estimates were derived for four out of five paternal daily consumption categories (10-19, 20-29, 30-39, $\geq$ 40 cigarettes per day), whether analyzed alone, combined with maternal smoking, or adjusted for other factors. A positive significant trend for paternal smoking was observed in all three analyses ($p<0.001$).

All three OSCC studies found no association between maternal smoking and risk of childhood cancer deaths for the three time periods individually, 1953 to 1955 deaths, 1971 to 1976 deaths, and 1977 to 1981 deaths. However, the studies did find paternal smoking associated with childhood cancer death (all sites combined), including a statistically significant positive trend associated with daily cigarette consumption in the three separate analyses (Sorahan *et al.*, 1997b). Pooled estimates of risk comparing paternal smokers versus paternal nonsmokers also gave a significant estimate [RR 1.29 (95% C.I. 1.19-1.41)] for all cancer sites combined (Sorahan *et al.*, 1997b). The consistent parental results from the three OSCC analyses are unlikely due to chance, as each gave positive significant trends with parental smoking. The newer study adjusted for several important confounders, including social class and paternal age, with little effect on the risk estimates (Sorahan *et al.*, 1997b). The study related maternal smoking data to mean birth weights as a test of reliability, however no similar surrogate test was available for paternal smoking data. A concern for all three OSCC subsets remains the modest response rate in some subsets and the potential influence of non-responders on any true estimate of risk.

Seersholm et al., 1997. A cohort study from the Danish Cancer Registry investigated the incidence of childhood cancer in the offspring of lung cancer patients (under age 56), under the assumption that such children were likely exposed to ETS; no direct assessment of ETS exposure

was included. The study included 3,348 lung cancer cases and 6,417 children born between 1953 and 1991. Follow up continued until death, emigration, 35th birthday, or December 31, 1999. Total follow up was 135,333 person-years. In all, 26 malignancies were identified among the children, with no overall increased cancer risk for children of the lung cancer cases [SIR 0.9 (95% CI 0.6-1.2)]. A stratified analysis by sex of the lung cancer patients identified an elevated, but non-significant overall cancer risk, among children of female lung cancer patients [SIR 1.2 (95% CI 0.8-1.8)].

Sorahan et al., 2001. Another set of data from the United Kingdom, the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC), was reanalyzed for the association between parental smoking and childhood cancer (Birch *et al.*, 1985; McKinney and Stiller, 1986; Sorahan *et al.*, 2001). The authors report that some data overlap exists between this data set and one OSCC study (Sorahan *et al.*, 1995). Additionally, the previous OEHHA report (Cal/EPA 1997) details an earlier analysis from this study. IRESCC was designed to investigate etiological factors of childhood cancer. The original study included incident cases of childhood cancer. Study data were re-abstracted from the original interview data. Two controls were selected for each case, one hospital (same region, acute surgical/accident) and one general practitioner (same GP practice list as case, considered as a population based control). Participation rates were 97% for cases, 74% for GP controls and 64% for hospital controls. Maternal and paternal smoking habits were analyzed separately, combined, with and without adjustment for other factors (maternal/paternal age, socioeconomic status based on paternal occupation, and ethnicity).

Five hundred fifty-five incident childhood cancer cases diagnosed before their fifteenth birthday between January 1980 and January 1983 were included in the study (615 eligible). Two separate matched pair analyses were reported, one for each control group. Maternal smoking was not positively associated with increased risk of childhood cancer. In the GP control analysis, paternal smoking was significantly associated with overall risk of childhood cancer, with a positive significant trend (p=0.02) and significant point estimates for two daily consumption categories [10-19 cigarettes/day, RR 1.63 (CI 1.10-2.41); and 20-29 cigarettes/day, RR 1.46 (1.05-2.03)] (Table 7.1C). Adjustment for other potential confounding factors did not influence the estimates. Simultaneous analysis of parental smoking habits also gave a positive significant trend for childhood cancer risk and paternal smoking (p=0.003), again for GP control analysis.

The choice of control group substantially influenced analysis results. Comparing cases to hospital controls gave a statistically significant negative trend between the risk of childhood cancer and both maternal and parental smoking. The study authors admit that "confident interpretation of these data is difficult in that the two sets of controls produced very different findings: the analyses with GP controls supported the hypothesis under test, the analyses with hospital controls did not" (Sorahan *et al.*, 2001). However, the parents of hospital controls had an "unusually" high prevalence of smoking relative to national smoking surveys, and therefore may not have been as representative as the population at risk relative to the GP controls. Overall, the analysis with the population based GP controls supports an association between daily paternal cigarette smoking and increased overall risk of childhood cancer.

Table 7.1C. Parental smoking during index pregnancy and risk of all childhood cancers combined.

Cohort Study (Age of Subjects)	# Cases/ #Controls	Smoking Habits	RR (95% CI) Maternal Smoking	RR (95% CI) Paternal Smoking
Klebanoff *et al.*,1996	51	During pregnancy	0.67 (0.38-1.17)[a]	Not available
(Deaths, age < 8)		Daily cigarettes per day:		
		1-10 cpd	0.45[b]	Not available
		>10 cpd	0.83	Not available
Ji *et al.* (1997)	642/642	Never Active		1.0 (Referent)[c]
(Deaths, age <15)		Ever Active	Not available	1.3 (1.0-1.7)
		Cigarettes per day:		
		<10 cpd	Not available	1.5 (1.1-2.3)
		10-14cpd	Not available	1.1 (0.8-1.6)
		>15 cpd	Not available	1.5 (1.0-2.3)
				p trend=0.07
		Duration (years):		
		<10	Not available	1.2 (0.7-1.8)
		10-14	Not available	1.1 (0.8-1.7)
		>15	Not available	1.7 (1.2-2.5)
				p trend=0.007
		Pack-year prior conception:		
		≤2	Not available	1.2 (0.8-1.8)
		>2-<5	Not available	1.3 (0.9-2.0)
		≥5	Not available	1.7 (1.2-2.5)
				p trend=0.006
Sorahan *et al.*, 1995; 1997a; 1997b				
(Deaths, age < 15)		Current at interview (after death of child)		
1953-1955 (1997a)	1549/1549	Current Daily Use:		
		<1 cpd	1.0 (Referent) [d]	1.0 (Referent)
		1-9 cpd	0.99 (0.83-1.18)	1.03 (0.81-1.29)
		10-20 cpd	1.23 (0.98-1.54)	1.31 (1.06-1.62)
		>20 cpd	1.28 (0.71-2.32)	1.42 (1.08-1.87)
			p trend=0.092	p trend<0.001
		Unknown	0.65 (0.28-1.48)	1.89 (0.84-4.24)
		Moderate/Heavy Smokers		
		Both parents ever smoked	1.70 (1.32-2.18)	
		Father only ever smoked	1.30 (1.10-1.53)	
		Mother only ever smoked	1.21 (0.84-1.75)[d]	

[a] RR (Proportional hazards ratio) adjusted for maternal age, other factors adjusted one at a time also presented, Table 2 Klebanoff *et al.* (1996).
[b] 95% CI was not stated in the original paper.
[c] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).
[d] RRs adjusted for social class, paternal/maternal age, birth order, obstetric radiography; Tables 1 and 3, Sorahan *et al.* (1997a).

Table 7.1C. Parental smoking during index pregnancy and risk of all childhood cancers combined.

Cohort Study (Age of Subjects)	# Cases/ #Controls	Smoking Habits	RR (95% CI) Maternal Smoking	RR (95% CI) Paternal Smoking
Sorahan *et al.*, 1995; 1997a; 1997b (cont.)				
1971-1976 (1997b)	2128/2128	Current Daily Use:		
		1-9 cpd	0.92 (0.75-1.13)[e]	1.02 (0.78-1.34)[e]
		10-19 cpd	1.00 (0.85-1.19)	1.37 (1.13-1.65)
		20-29 cpd	1.03 (0.87-1.22)	1.33 (1.13-1.55)
		30-39 cpd	0.75 (0.52-1.09)	1.42 (1.09-1.84)
		>40 cpd	1.48 (0.89-2.44)	1.63 (1.23-2.15)
			p trend=0.909	p trend < 0.001
		Both parents ever smoked	1.27 (1.09-1.48)[e]	
		Father only ever smoked	1.29 (1.10-1.51)	
		Mother only ever smoked	0.94 (0.78-1.12)	
1977-1981 (1995)	1641/1641	Daily Prenatal Use:		
		<10 cpd	1.04 (0.78-1.38) [f]	1.23 (0.82-1.86)
		10-19 cpd	1.21 (0.98-1.49)	1.17 (0.92-1.49)
		20-29 cpd	1.01 (0.81-1.25)	1.24 (1.02-1.49)
		30-39 cpd	0.98 (0.60-1.60)	1.30 (0.98-1.73)
		>40 cpd	1.70 (0.91-3.20)	1.39 (1.00-1.92)
			p trend=0.796	p trend=0.003
		Both parents ever smoked	1.37 (1.13-1.67)[g]	
		Father only ever smoked	1.37 (1.12-1.68)	
		Mother only ever smoked	1.22 (0.95-1.56)	
Pooled Estimate: Three time-periods (1997b)	5640/5673 (M)[h] 5504/5572 (P)	Current at interview:	1.02 (0.94-1.10)[i]	1.29 (1.19-1.41)
Sorahan *et al.*, 2001 (Deaths, age < 15)		At conception:		
	549/549(M)	Non-smoker	1.0 (Referent)[j]	1.0 (Referent)[j]
	555/555 (P)	<10 cpd	1.77 (1.07-2.92)	0.94 (0.53-1.66)
		10-19	1.51 (1.08-2.13)	1.63 (1.10-2.41)
		20-29	1.22 (0.86-1.74)	1.46 (1.05-2.03)
		30-39	0.48 (0.17-1.37)	0.95 (0.52-1.73)
		> 40 cpd	(30+ max)	1.77 (0.94-3.34)
			p trend=0.53	p trend=0.02
	549/549	During pregnancy (5th month):		
		Non-smoker	1.0 (Referent)[j]	
		<10 cpd	1.49 (0.93-2.39)	Not available
		10-19	1.58 (1.09-2.30)	Not available
		20-29	1.02 (0.68-1.54)	Not available
		>30 cpd	0.74 (0.30-1.83)	Not available
			p trend=0.36	

[e] RRs adjusted for social class, paternal/maternal age, birth order, obstetric radiography; Tables 1 and 3, Sorahan *et al.* (1997b).
[f] RRs adjusted for alcohol consumption Table 2 Sorahan *et al.* (1995)
[g] RRs adjusted for daily alcohol/cigarette consumption, social class and maternal age Table 3 Sorahan *et al.* (1995).
[h] (M)=Maternal cases and/or controls, (P)=Paternal cases and/or controls.
[i] RRs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b).
[j] Unadjusted RRs presented in Tables 1 and 2 of Sorahan *et al.* (2001) for GP controls.

7.1.2.5. Summary of Overall Cancer Risk in Children/Adolescents

The risk of childhood cancer due to ETS exposure, via either maternal or paternal smoking, varied across studies, with the majority of studies finding an elevated, and frequently statistically significant increase associated with some measure of parental smoking (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001). In studies where maternal and paternal, or only paternal, smoking data were available, risk estimates usually appeared higher for paternal smoking and were often statistically significant (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001).

Additionally, several studies attempted to identify potential dose-response relationships between either duration or amount of parental smoking and overall cancer risk (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001), with some evidence for a trend in the association between estimated duration of paternal smoking, but not maternal smoking, either prior to (Ji *et al.*, 1997; Sorahan *et al.*, 2001) or during pregnancy (Sorahan *et al.*, 1995) and cancer risk. However, as with the earlier studies reviewed in the previous OEHHA report (Cal/EPA, 1997), several additional limitations still remain in more recent studies between ETS exposure and risk of childhood cancers.

Hospital-based or collaborative studies of childhood cancers may be prone to selection bias of cases if the childhood cancer patients admitted to, and enrolled from, academic institutions are unrepresentative of all childhood cancers in the population (*e.g.,* higher social class). However, this has not been a problem in the U.K. and, within at least the U.S., the likelihood of this bias has declined with time, as the majority of childhood cancer patients, particularly those diagnosed prior to adolescence (under age 15), receive treatment at tertiary or academic cancer centers regardless of social class (Ross *et al.*, 1996). One of the studies summarized above, Klebanoff *et al.* (1996), could be affected by such enrollment bias; however, it was not originally designed to study childhood cancer.

As with studies previously reviewed (Cal/EPA, 1997), parental recall of smoking habits may lead to substantial information bias, particularly if parents of cases were more likely to remember potentially hazardous exposure prior to or during pregnancy (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b; Sorahan *et al.*, 2001). However, the rare nature of childhood cancer, with age-adjusted U.S. incidence rates near 15 new cases per 100,000 children under age 15, inhibits the ability to conduct anything other than case-control studies (Campleman *et al.*, 1999; Ries *et al.*, 1999). In the one recent cohort study at which maternal smoking habits were assessed at each prenatal visit prior to cancer diagnosis, no association was found (Klebanoff *et al.*, 1996). However, this study varied substantially from the other recent studies in size (only 51 total cancers versus hundreds) and population age (only cancer diagnosis up to 8 years of age, compared to other recent studies addressing risk up to mid-adolescence, age 14.) As found previously (Cal/EPA, 1997), the limited exposure assessment, particularly reliance of "ever" or "never" active smoker, continues to inhibit the ability to separate and analyze for effects of ETS temporally (pre-conception, during pregnancy and during childhood); however, a few studies attempted to account for time-specific exposure (Ji *et al.*, 1997; Sorahan *et al.*, 1995; Sorahan *et al.*, 2001).

Although the majority of these recent publications reported the collection of data on other relevant risk factors, adjusted risk estimates were not always reported (Klebanoff *et al.*, 1996; Sorahan *et*

al., 2001) or reported for some but not all results (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a,b). However, in the three U.K.mortality reports, the adjusted risk estimates for paternal smoking and overall childhood cancer risk remained significantly elevated after adjustment for several factors including parental age and social class (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a,b).

In summary, the evidence for a role of parental smoking and all childhood cancers combined remains inconclusive for maternal smoking, as the majority of studies continue to find either no overall association (Klebanoff *et al.*, 1996) or a slightly elevated, but statistically non-significant risk (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a;b). Additionally, the studies continue to lack evidence for a dose-response between maternal smoking duration and/or amount smoked with childhood cancer risk.

Figure 7.1.1. Association between paternal smoking and an elevated risk of childhood cancer (all sites combined). These studies used a variety of exposure measures.

Several studies report statistically significant increases in overall cancer risk often with supporting dose-response data (Sorahan *et al.*, 1995; Sorahan *et al.*, 1997a,b; Sorahan *et al.*, 2001). Studies identifying positive associations between parental smoking and childhood cancer risk, specifically paternal smoking, usually reported increased risks between 10% and 20%, similar to estimates derived from recent meta-analyses (Thornton and Lee, 1998b; Boffetta *et al.*, 2000). It should be noted that since the increase is relatively small, it remains difficult to rule out bias and confounding as contributing to this overall risk of childhood cancer. However, as evident in Figure 7.1.1 above, there are a number of studies with adequate sample size that show statistically significant increases in cancer risk with paternal smoking. A pooled estimate indicates tight confidence limits. Thus, data provide evidence suggestive of a causal relationship between paternal smoking and overall childhood cancer. However, this may be the result of a potential heritable mutation in germ cells, as implied by data in Ji *et al.* (1997), rather than an effect of ETS exposure directly on the child. Thus, we consider the data suggestive of an association between ETS and childhood cancers, rather than conclusive.

7.2. ETS and Lung Cancer

Active smoking is firmly established as a causal factor for lung cancer. The Surgeon General (U.S. DHHSa, 1986), the National Research Council (NRC, 1986e), the U.S. EPA (U.S. EPA, 1992a), OEHHA (Cal/EPA, 1997), and most recently, the International Agency for Research on Cancer (IARC, 2004a) have reviewed epidemiological studies investigating the role of ETS exposure as a cause of lung cancer in nonsmokers. IARC (2004a) recently determined that ETS is a probable human lung carcinogen. This current review focuses on studies published since the previous OEHHA report (Cal/EPA, 1997), including a large Canadian population-based case-control study (Johnson *et al.*, 2001), a multi-center, pooled analysis from twelve European sites in seven countries (Boffetta *et al.*, 1998), and five individual European case-control studies (Jockel *et al.*, 1998; Nyberg *et al.*, 1998b; Zaridze *et al.*, 1998; Kreuzer *et al.*, 2000; Rachtan, 2002). Additionally, brief summaries are presented for six case-control (Du *et al.* 1995; Du *et al.*, 1996; Rapiti *et al.*, 1999; Zhong *et al.*, 1999; Lee *et al.*, 2000; Wang *et al.*, 2000), two population and four hospital-based, and two cohort studies (Jee *et al.*, 1999; Nishino *et al.*, 2001), from Asia. No recent primary U.S. studies on ETS exposure and lung cancer risk were identified.

7.2.1. ETS and Lung Cancer: Previous Findings

The previous OEHHA report reviewed in detail three large U.S. population-based case-control studies designed specifically to investigate the association between ETS exposure and lung cancer published since 1991 (Cal/EPA, 1997). These studies were conducted in Florida (Stockwell *et al.*, 1992), Missouri (Brownson *et al.*, 1992), and a multicenter study in five geographic areas of the U.S. (New Orleans, Louisiana; Atlanta, Georgia; Houston, Texas; Los Angeles County, California; and San Francisco Bay Area, California) (Fontham *et al.*, 1991; Fontham *et al.*, 1994). A smaller, hospital-based study (Kabat *et al.*, 1995), as well as several other smaller studies were also summarized (Liu *et al.*, 1993; Schwartz *et al.*, 1996; Ko *et al.*, 1997). The results of one U.S. cohort study were also discussed (Cardenas *et al.*, 1997).

OEHHA determined that these three population-based studies successfully addressed many of the weaknesses (*i.e.*, small sample size, possible selection bias, possible misclassification biases, inadequate adjustment for potential confounders) found in previous studies on ETS and lung cancer. All three case-control studies identified a statistically significant association between increased risk of lung cancer and long-term ETS exposures. Additionally, lung cancer risk increased with increasing ETS in all three studies. The cohort study reported an elevated, but statistically non-significant, risk for lung cancer associated with ETS exposure. All five studies reported about a 20% increased risk of lung cancer in nonsmokers due to ETS exposure, which is the same as the excess risk identified in the U.S. EPA pooled estimate (U.S. EPA, 1992c).

7.2.2. Recent Epidemiological Studies

7.2.2.1. Case-Control Studies on ETS and Lung Cancer

No new U.S. population-based case-control studies designed specifically to investigate the association between ETS exposure and lung cancer have been published since the previous OEHHA review (Cal/EPA, 1997). However, a large population-based Canadian study was

conducted in 8 of 10 provinces through the National Enhanced Cancer Surveillance System (Johnson *et al.*, 2001). Six published reports described results from case-control studies in Europe and Russia (Jockel *et al.*, 1998; Nyberg *et al.*, 1998a; Zaridze *et al.*, 1998; Kreuzer *et al.*, 2000; Kreuzer *et al.*, 2001), which overlap to varying degrees with the pooled multicenter International Agency for Research on Cancer (IARC) analysis (Boffetta *et al.*, 1998), and two additional hospital-based studies were available from Czechoslovakia (Kubik *et al.*, 2001) and Poland (Rachtan, 2002). Four reports based on two case-control studies, one population-based mortality study (Du *et al.*, 1995;1996) and two hospital-based incidence studies (Wang *et al.*, 1996a,b), were published prior to, but not reviewed in, the previous OEHHA report. More recent studies from China were population-based (Zhong *et al.*, 1999) and hospital-based (Wang *et al.*, 2000). Other studies briefly summarized below include hospital-based studies from Taiwan (Lee *et al.*, 2000) and India (Rapiti *et al.*, 1999).

For these recently published studies, the respective study designs and the main findings are summarized in Tables 7.2A-D. As in the previous OEHHA review, the evaluation of the methodological issues related to the study of ETS exposure will focus on the sources of cases and controls, the methods used to obtain information on the exposure, the verification of the exposure and of the diagnosis of lung cancer, and the consideration of potential confounding variables in the analysis of ETS exposure.

Brennan et al. (2004) conducted a pooled analysis of data from two large published case-control studies on the association of lung cancer with passive smoking. The data set analyzed included 1,263 lung cancer cases and 2,740 controls recruited in 1985-1994, and represented 5 metropolitan areas in the U.S. and 11 areas in 7 European countries. The analysis examined passive exposure at home (years a subject lived with a smoking spouse), at work (years working in an environment where others smoked), and years of exposure to ETS in other areas (at least 2 hrs per week in the US study). Nonsmokers were defined as having smoked less than 100 cigarettes in their lifetime.

For exposure to spousal smoking, the OR for lung cancer was 1.18 (95% CI 1.01-1.37). There was evidence of an exposure-response trend ($p = 0.07$) with the greatest risk in the highest tertile of exposure (>30.9 yr): OR 1.23 (95% CI 1.01-1.51). Exclusion of proxy data from the analysis gave similar results, while exclusion of data from hospital-based centers gave a higher risk in the upper tertile (OR 1.30, 95% CI 1.04-1.63) and a statistically significant exposure response trend ($p = 0.04$).

Ever exposure to ETS in the workplace resulted in elevated risk that did not achieve statistical significance (OR 1.13, 95% CI 0.97-1.31). However, the exposure-response trend from workplace exposure was significant ($p = 0.01$) with a risk in the highest tertile (≥ 21 yrs) of 1.25 (95% CI 1.03-1.51). Similarly, the risk associated with ever exposure in other settings was 1.17 (95% CI 1.00-1.36), with a significant exposure-response trend ($p = 0.02$), and an OR of 1.26 (95% CI 1.01-1.58) for > 20 yrs exposure.

The ORs presented above and in Table 7.2A were adjusted for age, center and gender. The authors report that analyses adjusted for employment in high risk occupations, education, and vegetable consumption gave similar results, suggesting little confounding from these variables. For example, the OR for lung cancer with any exposure from the three sources combined was

identical (1.22, 95% CI 0.99-1.51) with or without adjustment for these potential confounders. In addition, the exposure-response trend was significant (p = 0.01) with an OR of 1.32 (95% CI 1.04-1.66) for the greatest exposure (≥ 39 yrs). However, it is not clear why the adjusted data were not presented.

As with other interview-base studies, since the duration but not the intensity of ETS exposure was determined it is not known how the intensity of exposure may have affected risk estimates. The intensity of current exposures was reflected in the urinary cotinine levels determined in the U.S. study but used only to validate current nonsmoking status. In three European centers, validation of nonsmoking status was achieved through cross interviews with next of kin. Potential misclassification bias associated with the inclusion of proxy-based interviews, as well as bias associated with the use of hospital-based controls was examined and found to likely cause a slight attenuation of risk estimates.

The analyses were also stratified by histological type of cancer, and it was noted that ETS exposure from any sources increased risk in an exposure-dependent fashion for both adenocarcinomas and squamous/small cell carcinomas. Overall, this analysis found an association between ETS exposure from any source and lung cancer that was significant with the longest exposures, and that demonstrated a significant exposure-response trend.

Table 7.2A. Risk of Lung Cancer with ETS Exposure from Three Sources

Exposure	Duration	Cases/Ctrls	OR (95% CI)
Spousal	Ever	764/1,458	1.18 (1.01-1.37)
	<16 yr	246/457	1.18 (0.97-1.44)
	16-30.9	224/480	1.05 (0.86-1.29)
	≥ 31	264/491	1.23 (1.01-1.51)
		Trend	p = 0.07
Work	Ever	729/1,560	1.13 (0.97-1.31)
	< 8.0 yr	198/472	0.94 (0.76-1.15)
	8-20.9	267/544	1.17 (0.97-1.42)
	≥ 21	262/543	1.25 (1.03-1.51)
		Trend	p = 0.01
Other	Ever	407/904	1.17 (1.00-1.36)
	< 8.0 yr	123/287	1.04 (0.84-1.32)
	8-19.9	128/290	1.20 (0.95-1.52)
	≥ 20	154/320	1.26 (1.01-1.58)
		Trend	p = 0.02
Any	Ever	1,102/2,351	1.22 (0.99-1.51)
	< 20.0	329/752	1.09 (0.86-1.39)
	20.0-38.9	348/768	1.21 (0.96-1.54)
	≥39.0	413/817	1.32 (1.04-1.66)
		Trend	p = 0.01

Boffetta et al., 1998. The International Agency for Research on Cancer coordinated a multicenter case-control study of lung cancer among nonsmokers. Twelve centers from seven European countries participated in the study, contributing a total of 650 nonsmoking cases and 1,542 nonsmoking controls. Cases were enrolled from 1988 to 1994 varying by study center. Study design did vary by site, particularly selection of controls - four sites utilized hospital controls, and one site used hospital and community controls, with the remaining seven centers relied only on community controls. The majority of cases (96.5%) were microscopically confirmed. Again control matching varied by site, with some centers conducting individual matching based on age and sex, while other study sites used frequency matching. Response rate varied by site from <50% to 95%.

Data on ETS exposure in childhood and adulthood, including residential, occupational, and other settings were obtained via interview with a common questionnaire based on data from a previous urinary cotinine/ETS study (Riboli *et al.*, 1990). A subset of study centers also collected dietary data on the consumption of vegetables, fruits and related nutrients (Boffetta *et al.*, 1998).

Individuals were considered eligible for study enrollment (e.g., were "nonsmokers") if lifetime cigarette consumption did not exceed 400 cigarettes. Additionally, three centers conducted validation of never-smoking status through secondary confirmation interviews with next of kin for comparison with subject responses. Childhood ETS exposure (up to age 18 years) variables were either binomial ("ever" versus "never") or based on number of household smokers and years exposed weighted by identity of smoker (mother 1.0 > father 0.75 > other adults 0.25). Weighting was based on urinary cotinine concentrations previously found in children (Jarvis *et al.*, 1991). Spousal/cohabitant ETS exposure variables included duration in years, duration as hours/day x year, average daily cigarette consumption, and/or pack-years. Workplace ETS variables were duration in total years and duration in years weighted by hours of daily exposure and subjective index of "smokiness" (Boffetta *et al.*, 1998). Categorical ETS exposure variables were based on the distribution among controls, specifically defined by the 75th and 90th percentiles (<75th, 75th-90th, >90th), based on previous work in Germany and Poland (Becher *et al.*, 1992). For example cumulative exposure (in weighted smoker years) is divided into "nonexposed", 0.1-14 (< 75th percentile), 14.1-18.0 (75th-90th percentile), and ≥ 18.1 (>90th percentile) categories.

No association between childhood exposure to ETS and lung cancer was observed in Boffetta *et al.* (1998). The overall risk estimate for "ever" exposed to childhood ETS was below unity [adjusted OR 0.78 (95% CI 0.64-0.96) after adjustment for age, and sex-study center interaction]. Risk estimates for paternal specific and maternal specific ETS exposure were similar [adjusted ORs 0.76 (95% CI 0.61-0.94) and 0.92 (95% CI 0.57-1.49), respectively]. No evidence for trend in risk by number of household smokers was evident. Additionally, lung cancer risk decreased with increasing cumulative exposure (weighted smoker-years), p for trend 0.02 (see Table 7.2C). Additional analysis found similar results for subjects also reporting adulthood ETS exposure (data not shown). Stratifying childhood ETS exposure by age of exposure, birth to 10 years and 11 to 18 years, produced estimates similar to those for overall childhood exposure (data not shown).

In the case of spousal ETS exposure, risk estimates for individuals ever married to a smoker were elevated [adjusted OR 1.27 (95% CI 1.00-1.62)], slightly lower in women [adjusted OR

1.11 (95% CI 0.88-1.39)], and higher in men [adjusted OR 1.65 (95% CI 0.85-3.18)]. Heterogeneity across study centers existed (one center OR was below 0.7 and three ORs were above 1.5); however, the tests of heterogeneity were not significant (p=0.42). Evidence of a dose-response was noted for increasing lung cancer risk with increasing duration of exposure (hours/day × years), but not so with duration of exposure in years alone or average daily intake (cigarettes/day; Table 7.2B). The lung cancer risk was statistically significantly elevated for the maximum exposure category based on duration of exposure (hours/day × years) [adjusted OR for all subjects 1.80 (95% CI 1.12-2.90); adjusted OR for women only 1.70 (95% CI 1.05-2.75)], and on cumulative exposure (pack-years), [adjusted OR for all subjects 1.64 (95% CI 1.04-2.59)].

The overall association between lung cancer and spousal ETS may vary by histology, being weakest for adenocarcinoma compared to squamous cell carcinoma or small-cell carcinoma [adjusted ORs were 1.08 (95% CI 0.82-1.42), 1.21 (95% CI 0.77-1.91) and 1.39 (95% CI 0.79-2.45), respectively], but these differences were not statistically significant. While none of these results are statistically significant, they are consistent with point estimates of the meta-analysis of Taylor *et al.* (2001) (Figure 7.2.1).

ETS exposure in the workplace was associated with a slightly elevated, yet statistically non-significant risk of lung cancer [adjusted OR 1.17 (95% CI 0.94-1.45)]. Risk estimates were above unity in eight of twelve study centers, with no statistically significant heterogeneity (p = 0.23). Trend analysis for weighted duration of exposure (total years weighted by hours of daily exposure and subjective "smokiness" scale) demonstrated a statistically significant association with increasing lung cancer risk [0.1-46.1: adjusted OR 0.97 (95% CI 0.76-1.25); 46.2-88.9: adjusted OR 1.41 (95% CI 0.93-2.12); ≥ 89.0: adjusted OR 2.07 (95% CI 1.33-3.21)] (see Table 7.2D). The adjusted OR for "ever" occupational exposure to ETS was highest for squamous cell carcinoma [adjusted OR 1.27 (95% CI 0.82-1.97)] compared to adenocarcinoma [adjusted OR 1.06 (95% CI 0.81-1.40)] or small-cell carcinoma [adjusted OR 1.17 (95% CI 0.67-2.04)]. The authors report that adjustment for additional confounders (education, urban residence, occupational carcinogens, dietary vegetable intake) did not affect the estimated ORs (data not shown).

Adult exposure to spousal and/or workplace ETS was also associated with a slightly elevated but not statistically significant risk of lung cancer [adjusted OR 1.14 (95% CI 0.88-1.47)]; risks were similar for men and women [adjusted ORs 1.13 and 1.15, respectively]. A significant trend between lung cancer risk and duration of either major ETS source was evident in one variable (hours/day × year) but not the other (years) (see Table 7.2E). Duration of exposure to ETS was associated with a higher risk of squamous cell carcinoma [adjusted OR 1.57 (95% CI 0.89-2.76)] and small-cell carcinoma [adjusted OR 1.19 (95% CI 0.62-2.30)] relative to adenocarcinoma [adjusted OR 1.01 (95% CI 0.73-1.40)]; however, the differences were not statistically significant.

Additional estimates for lung cancer risk associated with ETS exposure in vehicles [adjusted OR 1.14 (95% CI 0.88-1.48)] or other public indoor settings [adjusted OR 1.03 (95% CI 0.82-1.29)] were presented.

Jockel et al. 1998. As a subsequent analysis to an occupational study of risk factors for lung cancer, Jockel *et al.* (1998) examined ETS exposure and lung cancer risk among nonsmokers. The original study included 1,004 lung cancer cases and population-based controls in northwestern Germany, with this sub-analysis restricted to subjects who never smoked regularly (71 cases and 236 controls). Occasional smokers were included (at least one cigarette/day, or five cigarettes/week, or one pack/month for at least six months); however, risk estimates were provided for nonsmokers (including occasional) and never smokers separately. All cases were histologically or cytologically confirmed primary malignancies. Additional covariate data collected via interviewer-administered questionnaire included occupational, dietary, active smoking history and demographic characteristics. Several sources of ETS exposure were categorized based on percentile – during childhood (cumulative hours), spousal (cumulative hours), workplace, public transportation, and other public places (weighted duration) – into low or no exposure (<75th), intermediate exposure (75th-90th), or high exposure (>90th) (as with Boffetta *et al.*, 1998). This no/low exposure group (38 cases, 143 controls with occasional smokers) was used as a referent category. Risk estimates were adjusted for sex, age, region and smoking status (for occasional smokers in the total "nonsmoker" analysis).

In lifetime never-smokers (55 cases, 160 controls), an elevated, statistically significant increase in risk was reported in the "high" total (childhood and adult) ETS exposure group [adjusted OR 3.24 (95% C.I. 1.44-7.32)](Table 7.2B) with no increases in risk for the "intermediate" total ETS exposure group [adjusted OR 0.87 (95% C.I. 0.36-2.07)]. If occasional smokers were included the ORs for "high" and "intermediate" total ETS exposure were 2.09 (95% CI 1.02-4.28) and 1.05 (95% CI 0.52-2.12), respectively. Restricting analysis to never-smokers, there was a slightly increased, but statistically non-significant risk with "ever-exposed" to spousal ETS [adjusted OR 1.12 (95% CI 0.54-2.32)] and "high" spousal ETS [adjusted OR 1.87 (95% CI 0.45-7.74)] (Table 7.2B). In this same never-smoker group, ORs for other adult ETS exposures (workplace, public transit, and other public places) were significantly elevated in the "high" category [adjusted OR 3.10 (95% CI 1.12-8.60)]. Few cases reported childhood exposure to ETS (10 cases, 24 controls among never-smokers); nonetheless, the reported adjusted ORs were elevated [2.02 (95% CI 0.60-6.75) and 1.07 (95% CI 0.35-3.30), "high" and "intermediate" exposure, respectively] (Table 7.2C).

Also, although case numbers were limited, the authors analyzed lung cancer risk in the nonsmokers (including occasional smokers) for total ETS exposure and spousal ETS exposure controlling for dietary intake of fruit and salad. After including education and dietary intake of fruit and salad in the full model, the "high" ETS exposed group (with occasional smokers) had an increased effect estimate that was statistically significant [adjusted OR 2.33 (95% CI 1.11-4.91)]. The "intermediate" ETS exposed group had a statistically non-significant increase in risk [1.08 (95% CI 0.53-2.21)].

Nyberg et al. (1998a) investigated the relationship between ETS exposure and lung cancer among never-smokers in Sweden; these cases were also included in Boffetta *et al.* (1998). Cases were enrolled from Stockholm County and its three hospitals between 1989 and 1995. Cases were either microscopically confirmed or presented with an unambiguous chest radiograph with typical clinical course. In addition, histological or cytological slides were retrieved and underwent pathologic review. Population-based controls were frequency matched by sex, age and hospital catchment area. Smokers were defined as ever having smoked 1 cigarette/day, 10

cigarettes/week, 3 cigars/week, or 4 pipes/week for 1 year or longer. Data were obtained on occasional smoking, residential history, occupational history, and dietary habits. The study enrolled 124 never-smoking cases and 235 never-smoking controls (includes occasional smokers), that underwent either personal or telephone interview (response rate 85.5% and 82.9%).

Residential exposure to ETS with a binomial "ever" or "never" measure was not clearly associated with lung cancer risk for spousal smoking [adjusted RR 1.17 (95% CI 0.73-1.88)], paternal smoking [adjusted RR 1.02 (95% CI 0.63-1.66], or maternal smoking [adjusted RR 0.72 (95% CI 0.28-1.87)]. Risk estimates were adjusted for age, sex, catchment area, occasional smoking, vegetable consumption, urban residence, and years occupational exposure. Low and high exposure categories for spousal ETS exposure based on average daily exposure (cigarettes/day) or duration of exposure (years or hour-years) identified similar elevated, but statistically non-significant risks for the highest exposed group, adjusted RRs 1.16, 1.14 and 1.25 for ≥ 10 cigarettes/day, ≥ 30 years, and ≥ 90 hour-years, respectively (Table 7.2B). Lung cancer risk increased with the cumulative matrix ("pack-years smoked in subject's presence") for the highest exposure category [adjusted RR 1.53 (95% CI 0.76-3.09)].

Occupational ETS exposure ("ever" exposed at work) was associated with elevated, but not statistically significant, lung cancer risk for all subjects combined [adjusted ORs 1.61 (95% CI 0.91-2.85)] (Table 7.2D), increasing slightly in men [adjusted OR 1.89 (95% CI 0.53-6.67)]. Additionally, lung cancer risk increased with increasing duration of occupational ETS measured in either years [< 30 years: adjusted OR 1.40 (95% 0.76-2.56); ≥ 30 years: adjusted OR 2.21 (95% CI 1.08-4.52)], or hour-years, [<30 hour-years: adjusted OR 1.27 (95% 0.69-2.34); ≥ 30 hour-years: adjusted OR 2.51 (95% CI 1.28-4.93)] (Table 7.2D), with statistically significant elevated risk estimates for the high exposure category by either measure.

Additional risk estimates were presented for binomial exposure categories for ETS exposure in other indoor locations [adjusted OR 0.94 (95% CI 0.54-1.63)], or in vehicles (not occupational) [adjusted OR 0.98 (95% CI 0.41-2.37)]. However, risk estimates were higher among men "ever" exposed to either other indoor ETS [adjusted OR 1.31 (95% CI 0.50-3.38)] or vehicle related ETS [adjusted OR 1.71 (95% CI 0.49-5.98)].

As misclassification by individual ETS variable was potentially high when analyzed separately, Nyberg *et al.* (1998b) combined the two major ETS source estimates for each study subject, with major source being either spousal or occupational. In this combined analysis, lung cancer risk tended to be higher in the high exposure groups or with more recent ETS exposure. However, dose response relationships were not consistent (no trend tests reported). When accounting for time since last exposure (years) to either ETS source, spousal or occupational, risk was highest for individuals exposed more recently, ≤ 2 years [adjusted OR 2.12 (95% CI 0.91-4.92)]. In the highest duration ETS category for either spousal or occupational exposure, lung cancer risk was highest among those above the 90th percentile by years [adjusted ORs 1.84 (95% CI 0.77-4.37)] and statistically significant [2.52 (95% CI 1.08-5.85)] by hour-years.

Zaridze et al. 1998. This hospital-based case-control study was conducted in Moscow, Russia among lifetime nonsmoking women. One hundred eighty nine microscopically confirmed primary lung cancer cases and 358 oncology controls (restricted to cancers other than upper

respiratory tumors) underwent in-person interviews on demographic, residential, occupational history and ETS exposures (spousal, parental and occupational). Subjects from this study were included within the IARC multicenter study (Boffetta *et al.*, 1998).

A statistically elevated risk of lung cancer was associated with spousal smoking (yes/no) [adjusted OR 1.53 (95% CI 1.06-2.21)], after adjusting for age and education (Table 7.2B). Stratifying by histology gave a similar risk estimate for spousal ETS and adenocarcinoma [adjusted OR 1.52 (95% 0.96-2.39], increasing for squamous cell carcinoma [adjusted OR 1.94 (95% CI 0.99-3.81)]. No effect on lung cancer risk was observed for other cohabitant smoking or parental smoking.

Occupational ETS exposure, simply measured as yes or no, was not associated with an increased overall lung cancer risk [adjusted OR 0.88 (95% CI 0.55-1.41)] (Table 7.2D), or with adenocarcinoma [adjusted OR 0.99 (95% CI 0.56-1.73)]; a slightly higher, but still statistically non-significant risk was observed for squamous cell carcinoma [adjusted OR 1.20 (95% CI 0.54-2.63)].

Kreuzer et al. 2000, 2001. The study population consisted of 292 lung cancer patients and 1,338 controls, a subset derived from a larger study on lung cancer risk and radon exposure in Germany (Kreuzer *et al.*, 2000; Kreuzer *et al.*, 2001). Incident cases of histologically or cytologically confirmed primary lung cancer cases, diagnosed between 1990 and 1996, were recruited from fifteen medical clinics. The response rate among eligible cases was 76%. Population-based controls were obtained from either random digit dialing or mandatory registries at a 41% response rate. Some overlap exists with the multicenter IARC study (Boffetta *et al.*, 1998), which shared 173 cases and 215 controls. Data on basic demographics, residential history, active/passive smoking history, dietary habits, occupational and medical history were obtained via personal interview. Individuals were classified as "nonsmokers" if they never smoked more than one cigarette/day, four cigarillos/week, three cigars/week, or three pipes/week for longer than 6 months. Occasional smokers were also included if they had not smoked more than 400 cigarettes during a lifetime. The publications presented data for all nonsmoking subjects and nonsmoking women (Kreuzer *et al.*, 2000), and for nonsmoking men separately (Kreuzer *et al.*, 2001).

Several sources of ETS exposure were categorized based on percentile – during childhood, during adulthood at home (spousal or other cohabitants), at the workplace, in public transportation, and other public places. Categories of ETS exposure were derived from quantitative variables for cumulative duration hours (childhood), cumulative hours and duration in pack-years, duration hours and cumulative hours weighted by qualitative smokiness (workplace, other public places, vehicles). Similar to Jockel *et al.* (1998), 75th and 90th percentiles were utilized to create categories, low or no exposure (< 75th), medium exposure (75th-90th), or high exposure (> 90th). These other categories were combined to derive summary indicators for total ETS exposure. Risk estimates were adjusted for sex, age, region, occupational exposure, and diet. Previous lung disease and social class were entered into the statistical models, but reportedly did not influence the risk estimates.

Childhood exposure to ETS was not associated with increased lung cancer risk [adjusted OR 0.84 (95% CI 0.63-1.11)] for "ever" exposed (up to age 18). Similar risk estimates were

obtained for paternal or maternal exposure [adjusted ORs 0.83 (95% CI 0.62-1.11) and 0.62 (95% CI 0.27-1.44), respectively]. No evidence for a dose-response with childhood duration of exposure (cumulative hours) was observed. Restricting the analysis to either women or men gave similar results (Kreuzer *et al.*, 2000).

Spousal exposure to ETS also gave no indication of an association between "ever" exposed to spousal smoke and lung cancer [adjusted OR 0.99 (95% CI 0.73-1.34)]. No trend was observed between either cumulative exposure in pack-years or duration in hours. The authors indicate that the "high" exposure group for duration among women, cumulative hours > 67,900, had a statistically non-significant increased risk of lung cancer [adjusted OR 1.69 (95% CI 0.94-3.03)], as did the "high" exposure group based on pack-years, > 23 [adjusted OR 1.03 (95% CI 0.48-2.24)] (see Table 7.2B). Risk estimates for "ever" spousal exposure were similar by histopathological type (categorized by adenocarcinoma and other). Also, restricting the analysis to women or men only did not substantially alter the findings (Kreuzer *et al.*, 2000; Kreuzer *et al.*, 2001).

Analysis of workplace exposure to ETS gave some evidence of increased lung cancer risk among nonsmokers with increased exposure, particularly women subjects categorized into the "high" exposure group. For the binomial "ever" exposed in the workplace no increased risk was found for all subjects [adjusted OR 1.03 (95% CI 0.78-1.36)] (Table 7.2D). A slightly elevated but non-significant lung cancer risk was found among women [adjusted OR 1.14 (95% CI 0.83-1.57)]. Some evidence for increasing lung cancer risk by increasing duration of exposure was presented, particularly among women. When cumulative exposure was estimated in total hours, risk estimates for the "medium" category (> 29,000-61,000 hours) and "high" category (>61,000 hours) were elevated [adjusted ORs 1.85 (95% CI 0.96-3.54) and 2.70 (95% CI 1.01-7.18), respectively, with p for trend 0.01]; the highest category OR showed statistical significance. Additionally, a similar dose-response was observed for women with the ETS weighted duration measure (hours x degree of "smokiness") "high" category [adjusted OR 2.52 (95% CI 1.12-5.71), P for trend 0.04] (Kreuzer *et al.*, 2000) (Table 7.2D).

ETS exposures in other settings, e.g. in vehicles or other indoor public settings (bars, restaurants), were estimated both binomially, "ever" or "never", and weighted duration cumulative exposure (hours × level of "smokiness"); however, only a small subset of cases and controls reported "ever" exposure within vehicles, 35 cases and 167 controls, or other public settings, 82 cases and 454 controls (Kreuzer *et al.*, 2000). Slightly elevated, non-significant risk estimates were associated with "ever" exposure in vehicles [adjusted OR 1.15 (95% CI 0.76-1.75)] for all subjects combined but not for women only [adjusted OR 0.96 (95% CI 0.57-1.60)]. In the highest weighted duration of exposure category (hours × level of smokiness, >10,950), risk estimates were significantly increased for all subjects and in women only [adjusted ORs 2.64 (95% CI 1.30-5.36) and 2.63 (95% CI 1.04-6.68), respectively]. Lung cancer risk due to ETS exposure in other indoor public settings was not elevated except in the highest weighted duration of exposure group (hours × level of smokiness, >19,710), for all subjects combined [adjusted OR 1.48 (95% CI 0.65-3.36)] (Kreuzer *et al.*, 2000).

Kreuzer *et al.* (2000, 2001) estimated ETS exposure from all sources and all outside the home sources (workplace, vehicles, and other public settings) during adulthood. Risk estimates adjusted for age, sex and region were presented by exposure category "no/low" (referent group),

"medium", and "high". Risk estimates for those from all adulthood ETS sources were elevated, but not significantly, in the highest exposure group for all subjects combined and for women only [adjusted ORs 1.39 (95% CI 0.96-2.01) and 1.51 (95% CI 0.97-2.33)]. Estimates were similar when stratified by histology, adenocarcinoma or other carcinomas, again in the highest exposure category. Restricting the summary ETS adulthood exposure to nonresidential sources gave higher risk estimates which were statistically significant for the high exposure group [adjusted OR 1.29 (95% CI 0.79-2.09) and 1.78 (95% CI 1.05-3.04), medium and high exposure groups for all subjects]. Again, risk estimates were similar between the two histology groups, adenocarcinoma and other carcinomas, except among women with cancer other than adenocarcinoma [adjusted OR 2.22 (95% CI 1.03-4.80) and 2.35 (95% CI 0.88-6.80), medium and high exposure groups].

Johnson et al. 2001. This case-control study utilized female cases obtained from the population-based Canadian National Enhanced Cancer Surveillance System diagnosed between 1994 and 1997. 61.6% of cases contacted by the registry responded. Controls were obtained via publicly funded health insurance plans (5 of 8 provinces), provincial property assessment files (1 province) or random-digit dialing (2 provinces). The response rate for controls was 70.2%. Demographic, dietary, lifetime passive smoking, residential and occupational history data were collected via mailed questionnaire from a total of 1,558 cases and 2,531 controls. The final analysis utilized 71 never active smoking cases and 761 never active smoking controls with relatively complete residential lifetime passive smoking exposure history (90% complete). The study created two summary passive smoking variables each for residential and occupational ETS exposures: duration total years (total years × number of regular smokers in residence) and smoker-years (total years × number of regular smokers at work). An additional summary ETS variable combined residential and occupational exposure.

Never-smoking women exposed to passive smoke as both a child and an adult had an elevated lung cancer risk [adjusted OR 1.63 (95% CI 0.8-3.5)] compared to adult only exposure [adjusted OR 1.20 (95% CI 0.5-3.0)]; however, neither risk estimate was statistically significant (adjusted for age, province, education and dietary fruit and vegetable consumption) (Table 7.2B).

The risk estimate for lifetime residential ETS exposure was elevated, but not significantly, across the exposure categories in years, with no statistical evidence of trend [1-20 years: adjusted OR 1.10 (95% CI 0.4-2.8); 21-38 years: adjusted OR 1.52 (95% CI 0.6-3.6); ≥ 39 years: adjusted OR 1.29 (95% CI 0.5-3.2)] (Table 7.2B). Similar results were observed for the smoker-years variable. Although longer residential ETS exposure generally had higher risk estimates, no statistical evidence of a dose-response was demonstrated. Similarly, occupational years of ETS exposure also gave non-significantly elevated adjusted risk estimates with no evidence of trend [1-7 years: adjusted OR 1.24 (95% CI 0.5-3.3); 8-19 years: adjusted OR 1.71 (95% CI 0.7-4.3); ≥ 20 years: adjusted OR 1.71 (95% CI 0.7-4.3)]; with the smoker-years occupational variable, the two highest exposure categories gave similar risk estimates [adjusted ORs 1.98 (95% CI 0.8-4.9) and 1.58 (95% CI 0.6-4.0), respectively] (Table 7.2D). Combined smoker-years of residential and occupational exposure did demonstrate a statistically significant trend (p=0.05) [1-36 smoker-years: adjusted OR 0.83 (95% CI 0.3-2.1); 37-77 smoker-years: adjusted OR 1.54 (95% CI 0.7-3.5); ≥ 78 smoker-years: adjusted OR 1.82 (95% CI 0.8-4.2)] (Table 7.2E).

Rachtan 2002. This hospital-based case-control study consisted of 242 Polish women with newly diagnosed lung cancer (March 1991 through December 1997) and 352 healthy controls. Controls were a convenience sample derived from the next-of-kin of other hospital patients diagnosed without tobacco-related cancers. Cancer diagnosis was based on surgical resection/staging or histology samples. Data on demographics, residential and health histories, family history of cancer, occupational exposures, diet, alcohol use, and active and passive smoking were obtained through interviewer-administered questionnaires. Smokers were defined as ever smoking one or more cigarettes per day for at least seven months.

ETS exposure was defined as residential/domestic exposure during childhood (before age 18). The majority of ETS-related analyses presented used women "never-exposed" to passive smoking prior to age 18, regardless of active smoking or other ETS exposure after age 18. After adjusting for age and pack-years of active smoking, women exposed to ETS prior to age 18 had a significantly higher lung cancer risk (all cell types combined) [RR 2.31 (95% CI 1.47-3.63)], relative to women unexposed to ETS during childhood. A multivariate analysis identified a similar risk estimate [RR 2.49 (1.36-4.54)] after adjusting for age, alcohol consumption, dietary components, family history, occupational exposures, and pack-years smoking. In a smaller subset analysis, restricted to lifetime non-smokers (54 cases/251 controls), the age-adjusted lung cancer risk for childhood ETS exposure was also elevated [RR 2.53 (95% CI 1.45-4.41)]. After including the other potential risk factors in a multivariate analysis, the estimated lung cancer risk (all histological types combined) associated with childhood ETS exposure increased to RR 3.31 (95% CI 1.26-8.69) (Table 7.2C).

7.2.2.2. Other Case-Control Studies Conducted in Asia and India

Five reports based on three case-control studies, one population-based mortality (Du *et al.*, 1995, 1996) and two hospital-based incidence studies (Wang *et al.*, 1996a; Wang *et al.*, 1996b), were published prior to, but not reviewed in, the previous OEHHA report (Cal/EPA, 1997). More recent reviewed studies from China were population-based (Zhong *et al.*, 1999; Wang *et al.*, 2000). Other studies summarized below include smaller hospital studies from Taiwan (Lee *et al.*, 2000) and India (Rapiti *et al.*, 1999).

The series of registry-based case-control lung cancer mortality analyses by Du *et al.* (1995) included either 120 cases among nonsmoking residents, or 75 lung cancer cases among nonsmoking women married to smokers, all in Guangzhou, China during 1985-1986. Controls were deaths due to either non-respiratory disease or other non-respiratory cancer-related deaths. In the first analysis, no effect of ETS exposure on lung cancer death was reported (no risk estimates presented). In the second study, spousal ETS exposure was associated with an elevated, statistically non-significant increase in the risk of death due to lung cancer among nonsmoking women [OR 1.19 (95% CI 0.66-2.16)] with risk increasing as the number of cigarettes smoked/day by the spouse increased [ORs 0.72 and 1.62, <20 and ≥ 20 cigarettes/day, respectively (using non-tumor related death controls)]. Point estimates were not statistically significant (Table 7.2B).

A more recently published population-based case-control study among nonsmoking women in Shanghai, China included 504 women diagnosed between 1992 and 1994 (Zhong *et al.*, 1999). Controls were obtained from a residential registry (n = 601). Data on lifetime residential and

occupational exposure to ETS were obtained via interview. Risk estimates were adjusted for age, income, vitamin C intake, smokiness during cooking, family history of lung cancer and high-risk occupations. ETS exposure during childhood (up to age 23) was not associated with an elevated risk of lung cancer [adjusted OR 0.9 (95% CI 0.5-1.6)] (Table 7.2C). There was evidence of a significant dose-response effect from ETS exposure when analyzed by both number of hours exposed per day (p for trend = 0.001) and number of co-workers who smoked (p for trend < 0.001) (see Table 7.2D). Lung cancer risk was not statistically significantly associated with adult residential ETS exposure [adjusted OR 1.2 (95% CI 0.8-1.8)] (Table 7.2C) or occupational ETS exposure alone [adjusted OR 1.9 (95% CI 0.9-3.7)] (Table 7.2D). However, the risk due to adult ETS exposure at work and at home combined was significantly elevated [adjusted OR 1.9 (95% CI 1.1-3.5)] (Table 7.2E).

Another recent report by Wang *et al.* (2000) identified 233 lung cancer cases among never-smokers from hospitals and clinics throughout Gansu Province in 1995; the authors' considered their case-ascertainment as population-based. The lung cancer risk for "ever" exposure to ETS was slightly elevated, but not statistically significantly [adjusted for age and place of residence OR 1.19 (95% CI 0.7-2.0)] (Table 7.2C). Risk estimates were similar for men and women. ETS exposure in childhood was associated with a significantly elevated lung cancer risk [adjusted OR 1.52 (95% CI 1.1-2.2)], with evidence for a trend (p<0.01) with increasing exposure duration (expressed as pack-years) [adjusted ORs 1.43, 1.81, and 2.95] (Table7.2C). No elevated risk was observed for ETS exposure exclusively in adulthood [adjusted OR 0.90 (95% CI 0.6-1.4)].

Two smaller hospital-based studies conducted in China, one in Guangzhou, between 1990 and 1993 (Wang *et al.*, 1996a) and another in Shenyang, between 1992 and 1994 (Wang *et al.* 1996b), found contrasting results. The first study reported that spousal ETS exposure was significantly related to elevated lung cancer risk among nonsmoking women, while the second study did not find a significant association (Table 7.2B). Additionally, a small hospital study from Chandigarh, India, based on 58 nonsmoking lung cancer patients (microscopically confirmed), found a strong association between childhood ETS exposure [adjusted OR 3.9 (95% CI 1.9-8.2)], with risk highest for cigarette smoke [adjusted OR 12 (95% CI 4.2-34)] after adjustment for sex, age, residence and religion (Rapiti *et al.*, 1999) (Table 7.2C). Increased risk due to exposure to a smoking spouse was significantly elevated for individuals exposed to cigarette smoke [OR 5.1 (95% CI 1.5-17)] .

A hospital-based study in Taiwan based on 268 cases and 445 controls evaluated the risk of lung cancer in nonsmoking women due to lifetime ETS exposure (Lee *et al.*, 2000). Risk estimates were adjusted for residential area, education, occupation, tuberculosis, and cooking related variables (cooking fuels and fume extractor). Childhood exposure (≤ 19 years) to ETS was associated with a statistically elevated lung cancer risk [adjusted OR 1.7 (95% CI 1.1-2.6)]. Cumulative childhood exposure gave evidence of trend [1-20 smoker-years: adjusted OR 1.8 (95% CI 0.9-3.6); > 20 smoker-years: adjusted OR 2.2 (95% CI 1.4-3.4), p for trend 0.001] (Table 7.2C). Adult exposure to spousal ETS was also significantly associated with increased lung cancer risk [adjusted OR 2.2 (95% CI 1.5-3.3)], however, workplace exposure was not [adjusted OR 1.2 (95% CI 0.5-2.4)] (Table 7.2D). Among women with husbands that smoked in their presence, the risk of lung cancer increased with increasing pack-years [1-20: adjusted OR 1.5 (95% CI 0.9-2.4); 21-40: adjusted OR 2.5 (95% CI 1.5-4.2); > 40: adjusted OR 3.3 (95% CI 1.7-6.2)] (Table 7.2B). Combined adult life exposure (home and workplace) demonstrated a

trend for increasing cancer risk with increasing smoker-years [1-20 smoker-years: adjusted OR 1.3 (95% CI 0.7-2.5); 21-40 smoker-years: adjusted OR 1.5 (95% CI 0.9-2.4); ≥ 40 smoker-years: adjusted OR 2.6 (95% CI 1.6-4.2), p for trend 0.001] (Table 7.2E). Cumulative lifetime exposure to ETS (childhood and adulthood) demonstrated a similar trend [1-20 smoker-years: adjusted OR 1.3 (95% CI 0.6-2.6); 21-40 smoker-years: adjusted OR 1.6 (95% CI 0.9-2.6); 41-60: adjusted OR 2.0 (95% CI 1.2-3.5); > 60 smoker-years: adjusted OR 2.8 (95% CI 1.6-4.8), p for trend 0.001] (Table 7.2E).

7.2.3. Recent Cohort Studies of ETS and Lung Cancer

Since the prior review by OEHHA, only three reports from cohort studies examining ETS exposure and lung cancer risk were available for review, two investigating cancer incidence among non-smoking women married to smokers, the third involving both genders with smoking spouses. The Korean study addressed the effects of spousal smoking on lung cancer risk in a group of health plan enrollees (Jee *et al.*, 1999), while the population-based Japanese study enrolled women from three cities (Nishino *et al.*, 2001). The third study utilized data from the American Cancer Society's CPS-I study (Enstrom and Kabat, 2003).

Jee et al. (1999) investigated the effects of spousal smoking in Korean women receiving health benefits through the Korea Medical Insurance Corporation (KMIC). Approximately 11% of the population of Korea was eligible for KMIC in 1992. This study enrolled 160,130 non-working spouses; among these 157,436 women were non-smokers. KMIC enrollees (husbands) and dependents (wives) received questionnaires on smoking, dietary, and health habits. Lung cancer cases were ascertained through hospital discharge summaries through a unique personal identification number from July 1994 through December 1997. A total of 79 lung cancer cases were identified during the 3.5 years of follow-up. The adjusted relative risk of lung cancer among women married to current smokers was statistically elevated [RR 1.9 (95% CI 1.0-3.5)] after adjustment for age, socioeconomic status, residency, vegetable consumption, and husband's occupation (Table 7.2B). Lung cancer risk increased among women with increasing years of spousal smoking [adjusted RRs 1.6 (95% CI 0.8-3.0) and 3.1 (95% CI 1.4-6.6), 1-29 and ≥ 30 years among current smokers, respectively ($p < 0.01$)]. Although the follow up period was limited, less than four years, the high follow up rates, large sample size, and repeated measures of smoking habits (1992 and 1994) increase the reliability of the risk estimates.

Nishino et al. (2001) investigated the effects of spousal smoking among 9,675 women completing mailed questionnaires (total response rate of 96% for men and women). Individuals were followed for 9 years with cancer cases identified through record linkage with a population cancer registry. ETS exposure was based on spousal smoking at time of initial survey.

Twenty-four lung cancers were identified within the cohort, eleven in women reporting spousal exposure. The age-adjusted relative risk for lung cancer associated with having a smoking husband was elevated, but not significantly [RR 1.9 (95% CI 0.81-4.4)]. A similar, non-significantly elevated lung cancer risk was reported after additional adjustment for alcohol, dietary factors, past history of lung disease and residential area [RR 1.8 (95% CI 0.67-4.6)] (Table 7.2B).

This study identified an elevated, but statistically non-significant lung cancer risk, based on only 24 lung cancer cases. Although the study adjusted for several potentially important confounding factors, including dietary intake of vegetables, it was limited by a single ETS exposure indicator (spousal smoking) at baseline.

Enstrom and Kabat (2003) examined ETS exposure and long-term mortality from CHD, lung cancer and chronic obstructive pulmonary disease (COPD) in a prospective cohort study of the adult Californians enrolled in 1959 in the American Cancer Society's Cancer Prevention Study (CPS-I). Never smokers married to current or former smokers were compared to never smokers married to never smokers, with the former group subdivided based on the smoking status of the spouse (1-9, 10-19, 20, 21-39, ≥ 40 cigarettes per day). Former smokers were considered in a separate category. The relative risk of death was calculated as a function of the spouse's smoking status and adjusted for age and seven potential confounders at baseline: race, education, exercise, BMI, urbanization, fruit or fruit juice intake, and health status (good, fair, poor, sick).

The adjusted RR for lung cancer death among all men married to a formerly smoking spouse was 0.82 (95% CI 0.29-2.26). With a currently smoking spouse, the RR was 0.57 (95% CI 0.26-1.26), while with an ever-smoking spouse the RR was 0.63 (95% CI 0.33-1.22). In never-smoking women, there was a slight but non-significant risk associated with previous exposure from a formerly smoking spouse (1.04, 95% CI 0.69-1.57), but not with exposure to a currently or ever-smoking spouse (0.88, 95% CI 0.60-1.28 and 0.94, 95% CI 0.66-1.33, respectively) (see Table 7.2E).

There are several concerns with this study. It is based on data from which it is not possible to distinguish ETS-exposed from truly non-exposed individuals. At the start of CPS-I, the only information regarding potential ETS exposure was the smoking habits of the spouse. At that time, cigarette smoking was more prevalent, and ETS much more pervasive than it is now. As a result, the control group, defined as non-ETS-exposed based on the absence of spousal smoking, would include individuals with extensive ETS exposure outside the home, at work and elsewhere. As noted by Thun (2003), the potential misclassification of smoke exposure was enhanced by the absence of spousal smoking data after 1972 (an additional 26 years of study follow-up, representing two-thirds of the study length). A re-survey of 681 subjects in 1999 comprised only 7% of the original 9,619 life-long nonsmokers at enrollment, lending little assurance about the validity of exposure measurements. Thus, individuals no longer married to a smoking spouse, married to a spouse who had quit smoking, or whose spouse had died, were still classified as ETS-exposed. As both duration of exposure and total dose measurements are important factors, the resulting misclassification would be a major liability to this study. Similarly, analyses were adjusted for the factors listed above at baseline and while exercise, weight, height, and fruit intake reportedly changed little over time, changes in health status or in other lifestyle factors that could affect survival were not included in the adjustment. There was, for example, a large increase between 1959 and 1999 in the proportion of the population using vitamin pills (38.3% and 81.2%, respectively), which may have partly mitigated the effects of smoke exposure. In addition, the category of current smokers may include intermittent smokers and those who started smoking relatively recently, potentially leading to wide variations in the duration of ETS exposure among never smokers, and a dilution of effects. The problems noted above result in a study that is uninformative with respect to the health outcomes related to ETS exposure.

7.2.4. ETS Exposure from Spouses

7.2.4.1. Spousal ETS and Lung cancer: Previous Findings

In the previous OEHHA report (Cal/EPA, 1997), the population-based case-control studies reported that risks for lung cancer associated with ETS exposure from spousal smoking ranged from 1.0 to 1.6 for "ever" exposed or cumulative exposure estimates (Brownson *et al.*, 1992; Stockwell *et al.*, 1992; Fontham *et al.*, 1991; Kabat *et al*., 1995), which were comparable with the pooled estimate of the U.S. EPA report (U.S. EPA, 1992c). Statistical significance was achieved in the overall estimate only in the largest study [OR 1.29, (95% CI 1.04-1.60)] (Fontham *et al.*, 1994) and for the highest exposure categories [OR 2.4, (95% CI 1.1-5.3) (Stockwell *et al.*, 1992) and OR 1.3 (95% CI 1.0-1.7) (Brownson *et al.*, 1992)]. Odds ratios from the hospital-based study were elevated but not statistically significantly, OR 1.60 and 1.08, males and females, respectively (Kabat *et al.*, 1995). The U.S. cohort study showed a similar, statistically non-significant increased risk of lung cancer associated with spousal smoking [RR 1.2 (95% CI 0.8-1.6)] (Cardenas *et al.*, 1997).

Additionally, the OEHHA report supported that either individually, or as a group, the studies reviewed, particularly the population based studies, addressed criticisms directed at earlier, smaller case-control studies including: diminishing selection bias by being population based; diminishing misclassification bias of smokers as non-smokers by improving smoking definition criteria; utilizing corroborative or multiple measures of smoking; diminishing misclassification of cases by improving diagnostic review; and improving adjustment for potential confounders.

The previous OEHHA report found that the concordance in the studies' results, in combination with improvements in study design and analysis, was indicative of a causal association between spousal ETS exposure and the risk of lung cancer (Cal/EPA, 1997).

7.2.4.2. Spousal ETS and Lung Cancer: Recent Primary Epidemiological Studies

Table 7.2B summarizes recent studies addressing spousal ETS exposure and lung cancer. These studies are improved over the earliest studies by having larger sample sizes and/or better case definition, and less misclassification bias, although the latter is still somewhat problematic. The newer reviewed studies provide additional evidence that exposure to ETS is causally related to development of lung cancer.

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Du *et al.* (1995,1996)	Residential exposure	OR[a]	Spouse cigarettes/day	OR
Mortality	Spousal smoking		0 (28/53)	1.0 (Referent)
Case-control	No (28/53)	1.0 (Referent)	< 20 (13/34)	0.72
China	Yes (47/75)	1.19 (0.66-2.16)	≥ 20 (30/35)	1.62 (0.83-3.15)
Population			Residential years	
			< 30	1.39 (0.61-3.16)
			≥ 30 (29/47)	1.17 (0.60-2.29)
Wang *et al.* (1996a)	Home and/or work (99/99)	2.5 (1.3; 5.1)		
Case-control- China				
Wang *et al.* (1996b)	Spousal smoking	OR (Crude)[b]	Years lived with smoking spouse	OR (Crude)
Case-control	No (NA)	1.0 (Referent)	< 20 (NA)	1.0 (Referent)
China	Yes (92/89)	1.11 (0.65-1.88)	20-29 (21/16)	1.41 (0.68-1.94)
Hospital Based			30-39 (32/32)	1.08 (0.58-2.00)
			≥ 40 (17/17)	1.08 (0.37-3.14)
Boffetta *et al.* (1998)	Spousal smoking	OR[c]	Duration exposure years	OR
Pooled case-control	Ever exposed (Women Only)		1-34	0.99 (0.77-1.27)
Multiple country	No (187/376)	1.00 (Referent)	35-42	1.57 (1.06-2.31)
	Yes (321/632)	1.11 (0.88-1.39)	≥ 43	1.05 (0.66-1.68)
			Duration hours/day × yrs	p trend=0.19
			1-135	0.80 (0.61-1.06)
			136-223	1.12 (0.72-1.74)
			≥ 224	1.70 (1.05-2.75)
				p trend=0.03

[a] Crude odds ratio; ORs from Table 2 Du *et al.* (1995) and Table 13 Du *et al.* (1996).
[b] Unadjusted ORs from Table 1 and 2 Wang *et al.* (1996b).
[c] ORs adjusted age and sex-study center interaction from Table 3 Boffetta *et al.* (1998).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Boffetta *et al.* (1998) (continued)			Average exposure (cig/day)	OR[c]
			Unexposed	1.00 (Referent)
			0.1-10.0	1.00 (0.77-1.31)
			10.1-18.0	0.57 (0.34-0.93)
			≥ 18.1	1.34 (0.83-2.17)
				p trend=0.97
			Cumulative exposure (pack-yrs)	
			0.1-13.0	0.91 (0.70-1.19)
			13.1-23.0	0.83 (0.52-1.30)
			≥ 23.1	1.54 (0.97-2.44)
				p trend=0.15
Jockel *et al.* (1998)	Spousal exposure	OR[d]	Spousal exposure	OR
Case-control	Never (99/25)	1.00 (Referent)	No/low (142/49)	1.00 (Referent)
Germany[*]	Ever/smoking spouse (61/30)	1.12 (0.54-2.32)	Intermediate (13/2)	0.22 (0.05-1.07)
	All other sources		High (5/4)	1.87 (0.45-7.74)
	High (11/9)	3.10 (1.12-8.60)	Total exposure	
			High (21/17)	3.24 (1.44-7.32)
Nyberg *et al.* (1998a)	Spouse ever smoker	OR[e]	Average daily spousal exposure	OR[f]
Case-control	Women		Unexposed (66/127)	1.0 (Referent)
Sweden	Never (39/71)	1.0 (Referent)	< 10 cpd (40/83)	0.96 (0.57-1.61)
	Ever (50/92)	1.05 (0.60-1.86)	≥ 10 cpd (15/24)	1.16 (0.55-2.45)

[c] ORs adjusted age and sex-study center interaction from Table 3 Boffetta *et al.* (1998).
[*] Included in Boffetta *et al.* (1998).
[d] ORs adjusted for sex, age and region; Table 3 Jockel *et al.* (1998); estimated for both sexes.
[e] ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 2 Nyberg *et al.* (1998a); OR for men 1.96 (0.72-5.36).
[f] Both genders combined; ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 3 Nyberg *et al.* (1998a).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)		Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)		Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Nyberg *et al.* (1998a) (continued)	Both Genders		1.17 (0.73-1.88)	Total duration spousal exposure		OR[f]
				< 30 years	(39/74)	1.01 (0.60-1.70)
				≥ 30 years	(19/34)	1.14 (0.56-2.29)
				Total weighted duration spousal Exposure ("hours-years")		
				< 90 HY	(36/84)	0.85 (0.50-1.44)
				≥ 90 HY	(16/23)	1.25 (0.59-2.66)
				Cumulative exposure to spousal ETS (pack-years in presence)		
				< 9 PY	(35/82)	0.84 (0.49-1.43)
				≥ 9 PY	(20/25)	1.53 (0.76-3.09)
Zaridze *et al.* (1998)	Spousal smoking		OR[g]	Husband's smoking duration (yrs)		OR[g]
Case-control	No	(195/80)	1.0 (Referent)	None	(195/80)	1.0 (Referent)
Russia[*]	Yes	(163/109)	1.53 (1.06-2.21)	1-15	(39/31)	1.86 (1.07-3.22)
				> 15	(124/78)	1.42 (0.95-2.12)
				Husband's smoking quantity		
				None	(195/80)	1.0 (Referent)
				1-10 cpd	(90/66)	1.66 (1.09-2.52)
				> 10 cpd	(73/43)	1.35 (0.84-2.18)

[f] Both genders combined; ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 3 Nyberg *et al.* (1998a).

[*] Included in Boffetta *et al.* (1998).

[g] OR adjusted for age and education; Table 3 Zaridze *et al.* (1998).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Jee *et al.* (1999)	Spousal smoking:	RR[i]	Spouse cigarettes/day (current):	RR[j]
Cohort Study	Non-smoker (12/36,109)[h]	1.0 (Referent)	Non-smoker (12/36,109)	(Referent)
Korea	Ex-smoker (16/36,802)	1.3 (0.6-2.7)	1-19 (35/72,254)	2.0 (1.1-3.9)
Health Insurance	Current smoker (51/84,525)[h]	1.9 (1.0-3.5)	≥ 20 (16/12,271)	1.5 (0.7-3.3) p < *0.1*
			Residential years (current):	
			1-29 (36/53,881)[e]	1.6 (0.8-3.0)
			≥ 30 (15/30,644)[e]	3.1 (1.4-6.6) p< *0.01*
Rapiti *et al.* (1999)	Spousal smoking	OR[k]		
Case-control	Husband non-smoker (28/46)	1.0 (Referent)		
India	Husband smoker (13/21)	1.2 (0.5-2.9)		
Hospital Based	Cigarettes only (11/5)	5.3 (1.6-18)		
Zhong *et al.* (1999)	Spousal smoking:	OR[l]	Years lived with smoking spouse:	OR[l]
Case-control	Women only spousal	1.1 (0.7-1.7)	None (114/85)	1.0 (Referent)
China	exposure		1-20 (86/82)	1.1 (0.7-1.8)
Population	(116/89)		21-35 (102/74)	1.0 (0.6-1.6)
			> 35 (108/83)	1.1 (0.7-1.8)
			Cigarettes per day:	
			1-10 (90/88)	1.4 (0.9-2.2)
			11-20 (174/123)	0.9 (0.6-1.4)
			> 20 (32/28)	1.4 (0.7-2.6)

[h] ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations; Table 2 Nyberg *et al.* (1998a); OR for men 1.96 (0.72-5.36).
[i] Cases of lung cancer and size cohort.
[j] RR from Table 1 Jee *et al.* (1999); RR = rate ratio; adjusted for age husband, age wife, socioeconomic status, residency, husband's vegetable consumption and occupation.
[k] ORs from Table 3 Rapiti *et al.* (1999); adjusted for age, residence and religion.
[l] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history lung cancer, and high-risk occupations; from Tables 2 and 4, Zhong *et al.* (1999).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Lee *et al* (2000)[m]	Spousal smoking[n]:	OR[o]	Spousal pack-years	OR
Case-control	Husband non-smoker	(Referent)	0	(Referent)
Taiwan	(82/192)		1-20 (55/89)	1.5 (0.9-2.4)
Hospital Based	Husband smoker		21-40 (53/51)	2.5 (1.5-4.2)
	"absence" (40/89)	1.2 (0.7-2.0)	> 40 (38/25)	3.3 (1.7-6.2)
	"presence" (146/164)	2.2 (1.5-3.3)		
Wang *et al.* (2000)	Spousal smoking[p]	OR	Spousal smoking pack-years[q]	OR
Case-control	No (31/70)	1.0 (Referent)	1-9 (52/122)	0.81 (0.5-1.4)
China	Yes (169/337)	1.03 (0.6-1.7)	10-19 (Wells *et al.* 1998)	1.00 (0.6-1.8)
Hospital Based			≥ 20 (58/102)	1.03 (0.6-1.8)
Kreuzer *et al.* (2000; 2001)	Spousal smoking:		Duration exposure (hours)	OR[r]
	Ever exposed (Women only)	OR[q]	0-49,400	1.00 (Referent)
Case-control	No (95/219)	1.00 (Referent)	> 49,400-67,900	0.98 (0.53-1.81)
Germany*	Yes (139/316)	0.96 (0.70-1.33)	≥ 67,900	1.69 (0.94-3.03)
				p trend=0.16
			Cumulative (pack-yrs)	
			1-10.0	1.00 (Referent)
			10.1-23.0	0.85 (0.46-1.57)
			≥ 23	1.03 (0.48-2.24)
				p trend=0.85

[m] Appears some case overlap with Ko *et al.* (1997).
[n] Smoker in the presence of passive smokers were classified as "presence", otherwise reported as "absence"; Lee *et al.* (2000).
[o] ORs from Table 3 Lee *et al.* (2000); adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor.
[p] ORs from Table II Wang *et al.* (2000); adjusted for childhood exposure, age, residence and socioeconomic factors. Adult residential exposure based after age 18 exposure to smoking cohabitants (spouse or others). Estimate presented for non-smoking women. Estimate for non-smoking men OR=0.56 (0.2-1.4) and non-smoking men/women combined OR=0.90 (0.6-1.4).
[q] Exposure included cigarettes and pipe exposure divided by 20 times duration of exposure in adulthood.
[r] ORs adjusted for sex, age, and region; Table 3, Kreuzer *et al.* (2000) * Included in Boffetta *et al.* (1998).

Table 7.2B. Association between risk of lung cancer in lifetime nonsmoking females and exposure to spousal smoking

Study	Exposure Status (#Cases or Deaths / #Controls)	Adjusted Odds Ratio (95% CI) for exposed	Years exposed / Amount smoked by spouse (#Cases / #Controls)	Adjusted Odds Ratio (95% CI) by duration or quantity smoked by spouse
Johnson *et al.* (2001)	Residential exposure	OR[s]	Residential years	OR[t]
	Never Exposed (10/135)	1.0 Referent)	Never exposed(10/135)	1.0 (Referent)
Case-control	Child Only (2/56)	0.54 (0.1-2.7)	1-20 (13/171)	1.10 (0.4-2.8)
Canada	Adult Only (13/159)	1.20 (0.5-3.0)	21-38 (21/189)	1.52 (0.6-3.6)
Population	Child and Adult (46/411)	1.63 (0.8-3.5)	≥ 39 (20/183)	1.29 (0.5-3.2)
			Residential smoker-years	
			Never exposed(10/135)	1.0 (Referent)
			1-23 (16/176)	1.33 (0.4-4.0)
			24-47 (13/182)	0.93 (0.4-2.4)
			≥ 48 (25/185)	1.64 (0.7-3.9)
Nishino *et al.* (2001)	Spousal smoking	RR[u]		
	Husband smoker at baseline	1.8 (0.67-4.6)		

[s] ORs adjusted for age, province, education and total fruit/vegetable consumption. Childhood defined as age 0-19. ORs are from Table II of Johnson *et al.* (2001).
[t] Sum over subject's lifetime of residential exposure (i.e. number of regular smokers living in the subject's home multiplied by the number of years in that home; ORs from Table III of Johnson *et al.* (2001); ORs adjusted for age, province, education and total fruit/vegetable consumption
[u] Relative risk adjusted for age, alcohol, fruit and vegetable intake, age at first birth, parity, age at menarche and BMI.

Results from these recent Canadian and European studies are comparable to the previous pooled estimate of the U.S. EPA (U.S. EPA, 1992c) report, summary OR of 1.19 (90% CI 1.04-1.35) for "ever" exposed to ETS from spouses (for U.S. studies). In the population-based case-control study of Johnson *et al.* (2001), the OR for adult exposure to residential ETS was 1.20 (95% CI 0.5-3.0) after adjustment for age, province, education and total fruit/vegetable consumption. Combining adult and childhood residential exposure increased this adjusted risk estimate [OR 1.63 (95% CI 0.8-3.5)], but the point estimate remained non-significant. Among the individual European population based case-control studies, risk estimates (range 0.96 to 1.17) were somewhat lower and usually non-significant (Jockel *et al.*, 1998; Kreuzer *et al.*, 1998; Kreuzer *et al.* 2000; Nyberg *et al.*, 1998a), similar to the pooled estimate from the multicenter study [OR 1.11 (95% CI 0.88-1.39)] (Boffetta *et al.*, 1998). The one Russian study did find a significant elevation of risk [OR 1.53 (95% CI 1.06-2.21)] (Zaridze *et al.*, 1998). Case-control studies from Asia varied more substantially, with hospital-base studies ORs ranging from 1.0 to 1.2 without statistical significance (Rapiti *et al.*, 1999; Wang *et al.*, 1996b; Wang *et al.*, 2000), to a statistically significant OR of 2.2 (95% CI 1.5-3.3) in Lee *et al.* (2000). Population-based estimates also gave similar non-significant risk estimates (range ORs 1.1 to 1.2) (Du *et al.*, 1995, 1996; Zhong *et al.*, 1999). Both cohort studies from Asia identified increased risks for lung cancer, with one being statistically significant; both estimates [adjusted RR 1.9 (95% CI 1.0-3.5) (Jee *et al.*, 1999) and adjusted RR 1.8 (95% CI 0.67-4.6) (Nishino *et al.*, 2001)] were higher than that reported in the earlier U.S. cohort study by Cardenas *et al.* (1997) [RR 1.2 (95% CI 0.8-1.6)].

In addition, several of these recent studies, including the prospective cohort (Jee *et al.*, 1999), provided evidence of positive increasing trends in lung cancer risk in nonsmokers with increasing ETS exposure, with some but not all exposure indices of duration, daily amount, or cumulative dose (7.2B). The large multicenter IARC study (Boffetta *et al.* 1998) did not find a trend with ETS exposure for three of four matrices: duration (years), average exposure (cigarettes/day), or cumulative exposure (pack-years). However, ETS exposure duration estimated in hours/day × years exposed was suggestive of a dose-response relationship (p for trend 0.03). Furthermore, the "non-exposed" referent group by definition contained people exposed to ETS.

The concordance in these study results gives further credibility to the finding of a causal association between spousal ETS exposure and risk of lung cancer described in the U.S. EPA (U.S. EPA, 1992a) and previous Cal/EPA (1997) reports.

As with the studies previously reviewed in the Cal/EPA (1997) report, these more recently published studies continue to improve on criticisms of earlier studies, particularly those published prior to 1991, including larger sample sizes, more attention to defining and improving on selection bias, confirmation of primary lung cancers, and adjustment for potential confounders. The individual population-based case-control studies conducted in Canada and Europe attempted to minimize selection bias associated with hospital-based cases and controls (Jockel *et al.*, 1998; Nyberg *et al.*, 1998a; Zaridze *et al.*, 1998; Kreuzer *et al.*, 2000; Johnson *et al.*, 2001). These studies also attempted to address bias due to the misclassification of nonsmokers as smokers by defining lifetime smokers; however, concerns continue to be raised regarding this issue (Boffetta *et al.*, 1998). The majority of studies also continue to address the

issue of microscopic confirmation of primary lung cancer by requiring microscopic confirmation or additional tissue review.

Additionally, several studies attempted to adjust for potential confounding factors, including dietary consumption of fruits, vegetables or other estimates of micronutrient intake (Nyberg *et al.*, 1998a; Jee *et al.*, 1999; Zhong *et al.*, 1999; Johnson *et al.*, 2001; Nishino *et al.*, 2001), education (Zhong *et al.*, 1999; Lee *et al.*, 2000; Johnson *et al.*, 2001), occupation (Nyberg *et al.*, 1998a; Jee *et al.*, 1999; Zhong *et al.* 1999; Lee *et al.*, 2000), socioeconomic status or income (Jee *et al.*, 1999; Zhong *et al.*, 1999), urban residence or region (Nyberg *et al.*, 1998a; Jee *et al.*, 1999; Lee *et al.*, 2000; Johnson *et al.*, 2001; Nishino *et al.*, 2001), or history of lung disease or family history of lung cancer (Zhong *et al.*, 1999; Lee *et al.*, 2000; Nishino *et al.*, 2001). Although the individual European studies tended to adjust for several factors, the multicenter IARC pooled study reported estimates adjusted for only age and sex-study center interaction as sites did vary in the type of data collected and methods of control assignment (Boffetta *et al.*, 1998).

The previous OEHHA report (Cal/EPA, 1997) summary states that there is a causal association between spousal ETS exposure and lung cancer, and "that either individually, or as a group, the studies reviewed, particularly the population based studies addressed criticisms directed at earlier, smaller case-control studies including diminishing selection bias by being population based; misclassification bias of smokers as non-smokers by improving smoking definition criteria, utilizing corroborative or multiple measures of smoking; misclassification of cases by improving diagnostic review; improved adjustment for potential confounders." No compelling evidence exists for modifying the above conclusion that there is a causal association between spousal ETS exposure and lung cancer risk.

7.2.4.3. Spousal ETS and Lung Cancer: Recent Meta-Analyses

Several meta-analyses of lung cancer risk among female spouses (or cohabitants) of male smokers have been published in the peer-reviewed literature subsequent to the Cal/EPA review in 1997 (Mengersen, 1995; Law and Hackshaw, 1996; Rundle *et al.*, 2002; Hackshaw *et al.*, 1997; Hackshaw, 1998; Boffetta *et al.*, 1998; Taylor *et al.*, 2001). Each publication included all studies available at the time of meta-analyses, thus the most recent meta-analysis (Taylor *et al.*, 2001) is the most comprehensive. The investigators analyzed a total of 43 epidemiological studies (4 cohort and 39 case-control) published between 1981 and 1999 of cancer risk among nonsmoking female spouses of male smokers. They estimated the overall rate ratio to be 1.29 (95% CI 1.17 – 1.43), which was consistent with, but a little higher than, summary rate ratios estimated by the other recent meta-analyses mentioned above (rate ratios ranged from1.14 to 1.26).

Male spouses of female smokers were the subject of a meta-analysis by Mengersen *et al.* (1995), who estimated the overall rate ratio for lung cancer to be 1.42 (95% CI 1.01-1.99), based on eight case-control and two cohort studies.

The sensitivity of the association found in meta-analyses between ETS and lung cancer to methods and potential biases were quantified in several papers. Mengersen *et al.* (1995) found small differences in the overall rate ratio estimate for 31 studies as a result of choosing fixed or

random effect models, use of exact or approximate confidence intervals for the primary studies, taking study quality into account, inclusion of unadjusted primary data, and adjustment for potential publication bias. They found some evidence of publication bias (large relative risks were favored for studies with small sample size), but they estimated that 80 additional negative studies would be required to reduce the summary risk to below statistical significance. Tweedie *et al.* (1996) compared the traditional methods of meta-analyses to Bayesian methods in a statistical paper that found very similar results. For 38 studies of female spouses of male smokers they estimated the overall rate ratio to be 1.20 (95% CI 1.07-1.34) with traditional methods and 1.22 (95% CI 1.08-1.37) with Bayesian methods. Hackshaw *et al.* (1997) found that adjustment for the potential effects of exposure misclassification and dietary confounding changed the rate ratio very little (from 1.24 to 1.26) in a meta-analysis of 37 studies of lung cancer among female spouses of male smokers. These recent meta-analyses strengthen the case for a causal association between exposure to spousal ETS and elevated lung cancer risk.

7.2.5. Other Sources of ETS Exposure

7.2.5.1. Other Sources of ETS and Lung Cancer: Previous Findings

Although the majority of studies published prior to 1991 addressing the potential associations between ETS and lung cancer focused on the risks associated with spousal smoking, comprehensive measures of lifetime ETS exposure also include assessment of other home (lifetime spousal, parental and other household sources), workplace and social exposures (Cummings *et al.*, 1989; Cal/EPA, 1997).

As reviewed in Cal/EPA (1997), ETS exposure from parents and/or other household members has not been consistently associated with an increased risk of lung cancer. However, among the four post-1991 U.S. case-control studies previously summarized, parental smoking was statistically associated with increased lung cancer risk in women in two studies, with 22 years childhood/adolescent exposure [OR 2.4 (95% CI 1.1-5.4)] (Stockwell *et al.*, 1992), and with combined childhood/adult exposure (48 years or more) [OR 3.25 (95% CI 1.42-7.46)] (Fontham *et al.*, 1994). The quality of data, particularly quantitative aspects of parental smoking, varied substantially by how exposure was ascertained, particularly declining with the use of surrogate respondents versus the lung cancer cases themselves. Such decreasing reliability of exposure data regarding household sources, compared to the more reliable data obtained regarding spousal smoking, was considered to limit the ability to identify strong or consistent associations (Cal/EPA, 1997).

Similar difficulties and limitations in assessing lifetime ETS work exposures exist, particularly when utilizing surrogate respondents. Often studies utilized indicators for most recent job, last job, or lacked information on the temporal relationship between exposure and diagnosis (Cal/EPA, 1997). However, in three studies reviewed, lifetime occupational history and assignment of workplace exposure were obtained (Wu *et al.*, 1985; Wu-Williams and Samet, 1990; Fontham *et al.*, 1994). OEHHA determined that the assessment of ETS workplace exposure in these studies was complete, and that the studies supported the association between workplace ETS exposure and an elevated risk of lung cancer (Cal/EPA, 1997).

More limited data were available to assess the potential association between ETS exposure in social settings with an elevated risk of lung cancer (Cal/EPA, 1997). One population-based case control study found an increased risk of lung cancer among women with increasing years of ETS exposure, 1-15, 16-30, and >30 years exposure, in social settings, ORs of 1.45, 1.59 and 1.54, respectively (p for trend 0.0002) (Fontham *et al.*, 1994). Also, one hospital-based case control study reported a non-significant elevated lung cancer risk associated with ETS in social settings, for males and females analyzed separately (Kabat *et al.*, 1995). However, OEHHA reported that this risk was significant for both sexes combined [calculated crude OR 1.73 (95% CI 1.03-2.29)]. This study also addressed ETS exposure in "other modes of transportation" among women (no men reported this exposure); associated lung cancer risk was significantly elevated [OR 5.17 (95% CI 1.46-18.24)] (Kabat *et al.*, 1995).

Overall, OEHHA found the evidence for an association between other, non-spousal, sources of ETS exposure and elevated lung cancer risk was supportive for workplace exposure and other household exposures, specifically when cumulative lifetime measures were analyzed. Data on ETS from social settings were also limited, but again, indicative of an elevated risk, particularly for cumulative exposures (Cal/EPA, 1997).

7.2.5.2. ETS Exposure from Parents and Other Household Members

Table 7.2C summarizes studies that included analysis of residential ETS exposure during childhood. Among the recent case-control studies, several of the population-based (Jockel *et al.*, 1998; Kreuzer *et al.* 1998; Nyberg *et al.* 1998a; Zhong *et al.*, 1999; Kreuzer *et al.*, 2000; Johnson *et al.*, 2001) and hospital-based studies (Wang *et al.*, 1996b; Lee *et al.*, 2000; Wang *et al.*, 2000; Rachtan 2002) attempted to evaluate the lung cancer risk associated with childhood exposure to ETS, including in combination with adult residential ETS exposure (Zhong *et al.*, 1999; Wang *et al.*, 2000; Johnson *et al.*, 2001). Most studies reported non-significant risk estimates of childhood ETS exposure as "ever" versus "never" for at least one parent, with ORs near 1, range 0.5 to 1.14 (Wang *et al.* 1996b; Kreuzer *et al.* 1998; Nyberg *et al.* 1998a; Zhong *et al.*, 1999; Lee *et al.*, 2000; Johnson *et al.*, 2001). Three studies reported elevated statistically significant risk estimates for childhood ETS exposure, OR 1.52 (95% CI 1.1-2.2) (Wang *et al.*, 2000), OR 1.7 (95% CI 1.1-2.6) (Lee *et al.*, 2000), and RR 3.31 (95% CI 1.26-8.69) (Rachtan, 2002). The European pooled analysis found an elevated non-significant risk for both sexes, OR 1.17 (95% 0.64-1.96), and a lowered, statistically significant risk for women only [OR 0.77 (95% CI 0.61-0.98)] (Boffetta *et al.*, 1998)

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Table 7.2C. Association between risk of lung cancer and ETS exposures from parents and other household members

Study	ETS Exposure	#Cases/ #Controls	OR (95% CI) for exposed
Johnson *et al.* (2001)	Period passive exposure[a]		OR
Case-control	Never exposed	10/135	(Referent)
Canada	Child only	2/56	0.54 (0.1-2.7)
Population	Adult only	13/159	1.20 (0.5-3.0)
	Child and Adult	46/411	1.63 (0.8-3.5)
Wang *et al.* (1996a)	Passive smoking in home		OR (Crude OR) [b]
Case-control	Total	Not presented.	1.91 (p<0.01)
China	Male		1.02 (p>0.05)
Hospital Based	Females		2.54 (p<0.05)
Wang *et al.* (1996b)	Childhood exposure ETS		OR (Crude) [cc]
Case-control	Non-smoking women	80/83	0.91(0.55-1.49)
China	(Prior to marriage)		
Hospital Based			
Zhong *et al.* (1999)	Childhood residential		OR[d]
Case-control	Childhood exposure only	64/44	0.9 (0.5-1.6)
China	Years childhood ETS		
Population	None	114/85	1.0 (Referent)
	1-19	33/20	0.9 (0.5-1.8)
	20-23	31/24	0.9 (0.5-1.9)
	Residential Total ETS		
	Adult only	162/132	1.2 (0.8-1.8)
	Childhood and Adult	134/107	1.0 (0.7-1.6)
Lee et al (2000)[e]	Childhood exposure home[f]		OR[f]
Case-control	Father		
Taiwan	Non-smoker	136/245	1.0 (Referent)
Hospital Based	Absence	36/96	0.8 (0.5-1.3)
Non-smoking women	Presence	96/104	1.7 (1.1-2.6)
	Mother		
	Non-smoker	260/436	1.0 (Referent)
	Absence	2/2	0.9 (0.1-7.8)
	Presence	6/7	0.9 (0.3-3.1)
	1-20 smoker years	27/33	1.8 (0.9-3.6)
	> 20 smoker years	90/94	2.2 (1.4-3.4)

[a] ORs adjusted for age, province, education and total fruit/vegetable consumption. Childhood defined as age 0-19. ORs are from Table II of Johnson *et al.* (2001).
[b] Unadjusted OR from Table 2, Wang *et al.* (1996a).
[c] Unadjusted OR from Table 1, Wang *et al.* (1996b).
[d] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history of lung cancer, and high-risk occupations, from Tables 2 and 3 Zhong *et al.* (1999). Childhood <23 years old.
[e] Appears some case overlap with Ko *et al.* (1997).
[f] ORs from Table 3 Lee *et al.* (2000). Adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor. Smoker in the presence of passive smokers were classified as "presence", otherwise reported as "absence", Lee *et al.* (2000).

Table 7.2C. Association between risk of lung cancer and ETS exposures from parents and other household members

Study	ETS Exposure	#Cases/ #Controls	OR (95% CI) for exposed
Wang *et al.* (2000)	Childhood ETS[g]		OR
Case-control	No	12/58	1.0 (Referent)
China;	Yes	20/56	1.52 (1.1-2.2)
Hospital Based	Childhood ETS pack-yrs[h]		
	1-9	91/203	1.43 (1.0-2.1)
	10-19	28/44	1.81 (1.0-3.3)
	> 20	8/8	2.95 (1.0-8.9)
			p trend < 0.01
	Lifetime ETS [i]		OR
	No	28/85	1.0 (Referent)
	Yes	200/436	1.19 (0.7-2.0)
	Lifetime ETS pack-yrs		
	1-9	50/130	1.04 (0.6-1.8)
	10-19	45/110	1.13 (0.6-2.2)
	≥ 20	76/141	1.51 (0.9-2.7)
			p trend < 0.05
Boffetta *et al.* (1998)	Childhood (<19 yrs) Ever		OR[j]
Pooled Case-control;	No	252/496	1.00 (Referent)
Multiple Countries in	Yes	389/1021	0.78 (0.64-0.96)
Europe	Women Only		
	No	187/295	1.00 (Referent)
	Yes	314/700	0.77 (0.61-0.98)
	Cumulative (smoker-yrs)		
	0	252/496	1.00 (Referent)
	0.1-14.0	248/582	0.83 (0.66-1.04)
	14.1-18.0	104/332	0.68 (0.51-0.92)
	≥ 18.0	37/107	0.80 (0.51-1.24)
			p trend=0.02
Jockel *et al.* (1998)	Childhood exposure		OR[k]
Case-control	No/low	136/45	1.00 (Referent)
Germany[*]	Intermediate	14/5	1.07 (0.35-3.30)
	High	10/5	2.02 (0.60-6.75)

[g] ORs from Table 2 Wang *et al.* (2000). Adjusted for adult exposure, age, residence and socioeconomic factors. Residential exposure based on exposure to smoking cohabitants (parents or others) prior to age 19. Estimates presented for both sexes combined. Estimate for non-smoking men OR=1.46 (0.6-3.7) and non-smoking women OR=1.51 (1.0-2.2).

[h] Exposure included cigarettes and pipe exposure divided by 20 times duration of exposure during childhood (or adulthood).

[i] ORs adjusted as above (plus childhood exposure) estimates presented for both sexes combined.

[j] ORs adjusted for age and sex-study center interaction from Table 2 Boffetta *et al.* (1998).

[*] Included in Boffetta *et al.* (1998)

[k] ORs adjusted for sex, age and region Table 3 Jockel *et al.* (1998).

Table 7.2C. Association between risk of lung cancer and ETS exposures from parents and other household members

Study	ETS Exposure	#Cases/ #Controls	OR (95% CI) for exposed
Nyberg *et al.* (1998a)	Childhood exposure to		OR[l]
Case-control	smoking father		1.00 (Referent)
Sweden[*]	Never	55/106	1.02 (0.63-1.66)
	Ever	59/107	
	Childhood exposure to		
	smoking mother		1.00 (Referent)
	Never	55/106	0.72 (0.28-1.87)
	Ever	10/21	
Rapiti *et al.* (1999)	Childhood exposure ever	31/30	3.9 (1.9-8.2)
Case-control	Cigarettes	20/9	12 (4.2-34)
India			
Rachtan (2002)	Lifetime non-smokers		RR
Case-control			3.31 (1.26-8.69)
Poland			
Kreuzer *et al.* (2000;1998)	Childhood Ever exposed		OR[m]
	No	110/476	1.00 (Referent)
Case-control	Yes	182/862	0.84 (0.63-1.11)
Germany	Women only		
	No	88/171	1.00 (Referent)
	Yes	148/364	0.78 (0.56-1.08)
	Duration exposure (hours)		
	Childhood Total		
	0-12,000	235/1,124	1.00 (Referent)
	> 12,000-22,500	22/103	1.06 (0.63-1.76)
	> 22,500	16/85	0.92 (0.51-1.65)
	Childhood Women		p trend=0.89
	0-12,000	188/452	1.00 (Referent)
	> 12,000-22,500	16/39	0.94 (0.51-1.73)
	> 22,500	13/33	0.97 (0.49-1.90)
			p trend=0.86

[*] Included in Boffetta *et al.* (1998)

[l] Both genders combined, ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations Table 2 Nyberg *et al.* (1998a).

[m] ORs adjusted for sex, age and region Table 2 Kreuzer *et al.* (1998).

The three individual population-based studies (Jockel *et al.*, 1998; Kreuzer *et al.*, 1998; Zhong *et al.*, 1999), as well as the pooled analysis (Boffetta *et al.*, 1998), did not find evidence of a dose-response between cancer risk and cumulative exposure (years, cumulative hours, combination). One hospital-based case-control study from China did report a significant trend between risk of lung cancer and childhood years of ETS exposure [1-9 pack-years: adjusted OR 1.43 (95% CI 1.0-2.1); 10-19 pack-years: adjusted OR 1.81 (95% CI 1.0-3.3); >20 years: adjusted OR 2.95 (95% CI 1.0-8.9), p for trend <0.01] (Wang *et al.*, 2000).

Three studies, two population-based and one hospital-based, reported lung cancer risk estimates for residential ETS exposure for childhood and adulthood combined (Zhong *et al.*, 1999; Wang *et al.*, 2000; Johnson *et al.*, 2001). In the Canadian population study of women, the combined risk estimate was elevated but statistically non-significant [adjusted OR 1.63 (95% 0.8-3.5)], as well as larger than the adult only point estimate [adjusted OR 1.20 (95% CI 0.5-3.0)] (Johnson *et al.*, 2001). The two case-control studies from China identified null [adjusted OR 1.0 (95% 0.7-1.6)], or elevated, but again statistically non-significant risk [adjusted OR 1.19 (95% CI 0.7-2.0)] (Zhong *et al.*, 1999; Wang *et al.*, 2000).

In summary, the majority of individual studies reported null or slightly elevated, but non-significant, risk estimates for "ever" exposure to ETS during childhood, including the large pooled European study (Boffetta *et al.*, 1998). A similar null result [RR 0.91 (95% CI 0.80-1.05)] was reported in a meta-analysis of eleven studies on lung cancer in nonsmokers and childhood ETS exposure (Boffetta *et al.*, 2000). As discussed previously in Cal/EPA (1997), the difficulty in accurately assessing childhood ETS exposure among adult lung cancer cases (and controls) may help explain this inconsistency in risk estimates, and potentially the failure to observe any stronger associations that may exist. However, in several instances, significantly elevated risks were noted for childhood exposure (Rapiti *et al.*, 1999; Rachtan, 2002; Lee *et al.*, 2000; Wang *et al.*, 2000). These studies are suggestive of an association between childhood ETS exposure and later development of lung cancer.

7.2.5.3. Workplace ETS Exposure

Table 7.2D summarizes results from studies reporting risk estimates for lung cancer associated with workplace exposure to ETS. Five population-based and three hospital-based case-control studies reported risk estimates for workplace ETS exposure at least as "ever" or "never" exposed (Wang *et al.* 1996a;b; Kreuzer *et al.*, 1998; Nyberg *et al.*, 1998a; Zaridze *et al.*, 1998; Zhong *et al.*, 1999; Lee *et al.*, 2000; Wang *et al.*, 2000; Johnson *et al.*, 2001). The pooled European estimate found elevated, non-significant risk, similar to the spousal risk estimates, for "ever" exposed [adjusted OR 1.17 (95% CI 0.94-1.45)] for both sexes or among women only [adjusted OR 1.19 (95% CI 0.94-1.51)] (Boffetta *et al.*, 1998). Among the three individual European case-control studies reporting "ever" workplace exposure estimates, one was non-significantly below null [adjusted OR 0.88 (95% CI 0.55-1.41)](Zaridze *et al.*, 1998), one was slightly elevated, particularly among women [adjusted OR 1.14 (0.83-1.57)] (Kreuzer *et al.*, 1998), and the third study was non-significantly elevated for both genders [adjusted OR 1.61 (95% CI 0.91-2.85)] (Nyberg *et al.*, 1998a). One population-based case-control study from China reported a statistically elevated lung cancer risk with workplace exposure ("ever") [adjusted OR 1.7 (95% CI 1.3-2.3)]. The hospital-based binomial risk variable estimates from China ranged from 0.89

to 1.90 (Wang *et al.*, 1996a,b; Lee *et al.*, 2000), with only the crude unadjusted estimate from Wang *et al.* (1996a) being statistically significant ($p<0.05$).

Limited evidence for a dose-response trend for increasing lung cancer risk with increasing duration of workplace exposure (by various indices) was observed in the Canadian population study (Johnson *et al.*, 2001), two European population studies (Nyberg *et al.*, 1998a; Kreuzer *et al.*, 1998), and the pooled European study (Boffetta *et al.*, 1998). Johnson *et al.* (2001) found increasing lung cancer risk estimates after eight years of workplace exposure measured in years [1-7: adjusted OR 1.24 (95% CI 0.5-2.8); 8-19: adjusted OR 1.71 (95% CI 0.7-4.3); ≥20: adjusted OR 1.71 (95% CI 0.7-4.3)] or smoker-years [1-23: adjusted OR 1.16 (95% CI 0.4-3.1); 24-47: adjusted OR 1.98 (95% CI 0.8-4.9); ≥48: adjusted OR 1.58 (95% CI 0.6-4.0)]. Using duration of exposure indices of total exposure in both hours and hours weighted by subjective ordinal of "smokiness", Kreuzer *et al.* (1998) reported that risk increased significantly, particularly for nonsmoking women (versus estimates for both sexes combined). Among women categorized in the intermediate and high exposure groups (>29,000-61,000 total hours, >61,000 total hours), lung cancer risk increased significantly with increasing hours relative to the no/low exposure group (p for trend 0.01) [adjusted ORs 1.85 (95% CI 0.96-3.54) and 2.70 (95% CI 1.01-7.18), respectively]. Finally, the study of Nyberg *et al.* (1998a) also reported increasing risk estimates with total ETS years at work [<30 years: adjusted OR 1.40 (95% CI 0.76-2.56); ≥30 years: adjusted OR 2.21 (95% CI 1.08-4.52)] and total weight duration ("hour-years") [<30 HY: adjusted OR 1.27 (95% CI 0.69-2.34); ≥30 HY: adjusted OR 2.51 (95% CI 1.28-4.93)].

Two meta-analyses of lung cancer risk from workplace ETS that were published subsequent to the Cal/EPA review in 1997 yielded similar non-significantly elevated overall rate ratios. Tweedie *et al.* (1996), using innovative Bayesian meta-analysis methods, estimated the rate ratio to be 1.12 (95% CI 0.93-1.28), based on 10 epidemiological studies. Merletti *et al.* (1998) estimated the rate ratio to be 1.14, 95% CI 0.98-1.33, using traditional meta-analysis methods (Tweedie *et al.*, 1996; Boffetta *et al.*, 1998). There was considerable overlap in studies included in the two meta-analyses of workplace exposure.

As with earlier studies, indicators of workplace ETS exposure may have varied substantially across studies, with often limited information provided on the specific occupational data obtained (Cal/EPA, 1997). However, studies generally identified elevated, non-significant risks, increasing with estimates for cumulative years of occupational ETS exposure (Boffetta *et al.*, 1998; Nyberg *et al.*, 1998a; Kreuzer *et al.*, 2000; Johnson *et al.*, 2001). Some of the earlier non-positive meta-analyses were affected by exposure estimation inconsistencies and errors in reporting the underlying studies, or inappropriate weighting factors applied in the meta-analyses, as described in detail by Wells and Henley (1997) and Wells (1998b). Several published meta-analyses on workplace ETS and lung cancer have reported pooled risk estimates between 1.0 and 1.6, varying substantially by the inclusion criteria and extracted risk estimates utilized (summarized in Wells, 1998b). Previously OEHHA concluded that workplace ETS exposure also increases the risk of lung cancer (Cal/EPA, 1997). More recent primary studies also support this conclusion despite difficulties in obtaining estimates of lifetime occupational exposure.

Table 7.2D Studies on ETS exposure at the workplace and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Johnson *et al.* (2001)				OR
Case-control	Occupational	Never exposed	10/135	1.0 (Referent)
Canada	years[a]:	Residential only	23/253	1.21 (0.5-2.8)
Population		1-7	10/131	1.24 (0.5-3.3)
		8-19	14/125	1.71 (0.7-4.3)
		≥ 20	14/117	1.71 (0.7-4.3)
				OR[b]
	Occupational	Never exposed	10/135	1.0 (Referent)
	smoker-	Residential only	23/253	1.21 (0.5-2.8)
	years:	1-23	10/126	1.16 (0.4-3.1)
		24-47	14/120	1.98 (0.8-4.9)
		≥ 48	14/127	1.58 (0.6-4.0)
Wang *et al.* (1996a)				OR (Crude)[c]
Case-control, China	Passive smoking	Total	Not presented	1.90 (p<0.05)
Hospital Based	at work:	Male		2.10 (p>0.05)
Wang *et al.* (1996b)	Workplace exposure ETS			OR (Crude)[d]
Case-control, China	Non-smoking women		113/115	0.89 (0.45-1.77)
Hospital Based				
Zhong *et al.* (1999)				OR[e]
Case-control	Workplace ETS:	Adult only	22/24	1.9 (0.9-3.7)
China		Childhood and Adult	24/29	1.7 (0.9-3.4)
Population Non-smoking women.	Exposed at work:	No	474/368	1.0 (Referent)
		Yes	127/136	1.7 (1.3-2.3)
	Number hours per day:	1-2	48/30	1.0 (0.6-1.7)
		3-4	49/45	1.6 (1.0-2.5)
		> 4	30/61	2.9 (1.8-4.7)
				p trend<0.001
	Number of years	1-12	35/43	2.0 (1.2-3.3)
		13-24	49/48	1.4 (0.9-2.3)
		> 24	43/45	1.8 (1.1-2.8)
				p trend=0.50
	Number co-workers	1-2	56/37	1.0 (0.6-1.6)
	Smoked:	3-4	41/42	1.7 (1.1-2.8)
		> 4	30/57	3.0 (1.8-4.9)
				p trend<0.001

[a] ORs adjusted for age, province, education and total fruit/vegetable consumption. ORs are from Table III of Johnson *et al.* (2001).
[b] Sum over the subject's lifetime of occupational exposure (i.e. number of employees smoked regularly in immediate work multiplied by the number of years in that job. ORs from Table III of Johnson *et al.* (2001), adjusted for age, province, education and total fruit/vegetable consumption.
[c] Unadjusted OR from Table 2, Wang *et al.* (1996a).
[d] Unadjusted OR from Table 1, Wang *et al.* (1996b)
[e] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history lung cancer, high-risk occupations, and residential ETS, from Tables 2 and 5 Zhong *et al.* (1999).

Table 7.2D Studies on ETS exposure at the workplace and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Lee *et al* (2000)[f]	Workplace exposure			
Case-control	Co-workers:	Non-smoker	236/400	(Referent)
Taiwan, Hospital Based		Absence	12/24	0.7 (0.3-1.5)
		Presence	21/12	1.2 (0.5-2.4)
Boffetta *et al.* (1998)				OR[g]
Pooled Case-control	Workplace Ever:	No	276/687	1.00 (Referent)
Multiple Country		Yes	374/855	1.17 (0.94-1.45)
	Women Only:	No	240/535	1.00 (Referent)
		Yes	269/476	1.19 (0.94-1.51)
	Exposure duration (years):	1-29	278/634	1.15 (0.91-1.44)
		30-38	55/129	1.26 (0.85-1.85)
		≥ 39	39/91	1.19 (0.76-1.86)
				p trend=0.21
	Women Only:	1-29	211/399	1.14 (0.89-1.47)
		30-38	37/47	1.50 (0.93-2.43)
		≥ 39	20/29	1.24 (0.67-2.28)
				p trend=0.10
	Exposure duration (index level × hr/day × yrs)	0.1-46.1	196/525	0.97 (0.76-1.25)
		46.2-88.9	47/105	1.41 (0.93-2.12)
		≥ 89.0	48/71	2.07 (1.33-3.21)
				p trend<0.01
Nyberg *et al.* (1998a)				OR[h]
Case-control	Exposed at work:	Never	27/69	1.00 (Referent)
Sweden[*]		Ever	97/166	1.61 (0.91-2.85)
	Total duration ETS at work:	Unexposed	27/69	1.00 (Referent)
		< 30 years	66/130	1.40 (0.76-2.56)
		≥ 30 years	31/36	2.21 (1.08-4.52)
	Total weighted duration ETS at work("hour-years")	Unexposed	27/69	1.00 (Referent)
		< 30 HY	57/120	1.27 (0.69-2.34)
		≥ 30 HY	40/45	2.51 (1.28-4.93)
Zaridze *et al.* (1998)	Colleagues' smoking			OR[i]
Case-control	No		291/153	1.00 (Referent)
Russia	Yes		67/36	0.88 (0.55-1.41)

[f] Appears some case overlap with Ko *et al.* (1997); ORs from Table 3 Lee *et al.* (2000); adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor. Smoker in the presence of passive smokers were classified as "presence", otherwise reported as "absence", Lee *et al.* (2000).

[g] ORs adjusted for age and sex-study center interaction from Table 4 Boffetta *et al.* (1998).

[*] Included in Boffetta *et al.* (1998).

[h] Both genders combined, ORs adjusted for sex, age, occasional smoking, vegetable consumption, urban residence and years exposure to risk occupations Tables 2 and 3 Nyberg *et al.* (1998a).

[i] ORs adjusted for age and education Table 3 Zardize *et al.* (1998a).

Table 7.2D Studies on ETS exposure at the workplace and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Kreuzer *et al.* (2000;1998)				OR[k]
Case-control	Ever exposed:	No	131/491	1.00 (Referent)
Germany[*]		Yes	161/847	1.03 (0.78-1.36)
	Women only	No	111/258	1.00 (Referent)
		Yes	123/277	1.14 (0.83-1.57)
	Exposure duration (hours):	0-29,000	247/1,101	1.00 (Referent)
		> 29,000-61,000	26/127	1.57 (0.97-2.54)
		> 61,000	13/87	1.36 (0.71-2.61)
				p trend=0.10
	Women only	0-29,000	203/497	1.00 (Referent)
		> 29,000-61,000	17/26	1.85 (0.96-3.54)
		> 61,000	9/8	2.70 (1.01-7.18)
				p trend=0.01
	Weighted duration[kj]:	0-56,200	199/873	1.00 (Referent)
		> 56,200-100,600	11/77	1.09 (0.55-2.19)
		> 100,600	17/55	1.93 (1.04-3.58)
				p trend=0.06
	Women only	0-56,200	162/385	1.00 (Referent)
		> 56,200-100,600	6/15	1.09 (0.41-2.91)
		> 100,600	13/12	2.52 (1.12-5.71)
				p trend=0.04

[*] Included in Boffetta *et al.* (1998)
[j] Weighted duration of exposure (hours × level of smokiness)
[k] ORs adjusted for sex, age and region Table 2 Kreuzer *et al.* (1998).

7.2.5.4. ETS Exposure in Other Settings

Table 7.2E summarizes data on ETS exposure from multiple settings available from seven studies. Among these more recent studies, few estimated exposure and/or lung cancer from other settings, such as public transit or other social settings (Jockel *et al.*, 1998). However, two did combine residential and occupational exposure (Boffetta *et al.*, 1998; Johnson *et al.*, 2001) or also combined these with other sources (Jockel *et al.*, 1998; Kreuzer *et al.*, 1998). In the pooled analysis (Boffetta *et al.*, 1998), the simple binomial combined variable was not substantially different from the spousal estimate [adjusted OR 1.14 (95% CI 0.88-1.47)]. However, the exposure duration variable for spousal/workplace combined (in hours/day × years) gave evidence of a trend in increasing risk with increasing exposure (p=0.01). The Canadian case-control study observed a similar trend for residential plus occupational years or smokers-years (p=0.05) (Johnson *et al.*, 2001).

In Jockel *et al.* (1998), the risk estimate for other ETS sources, a combination of workplace, transit and other, increased with increasing exposure [no/low: OR 1.0 (referent); intermediate: adjusted OR 1.44 (95% CI 0.47-4.45); high: 3.10 (95% CI 0.89-5.89)]. A similar increase in risk with estimated ETS dose was also observed with total ETS exposure, including spousal and childhood [intermediate: adjusted OR 0.87 (95% CI 0.36-2.07); high: 3.24 (95% CI 1.44-7.32)]. Note that the OR for 'high' exposure is statistically significant. Kreuzer *et al.* (1998) found a significant dose response trend with weighted exposure or weighted duration among women only, with statistically significant adjusted ORs in the highest exposed women at 2.70 (95% CI 1.01-7.18) and 2.52 (95% CI 1.12-5.71), respectively.

Table 7.2E. Studies on ETS exposure in multiple settings and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Johnson *et al.* (2001)	Residential plus	Never exposed	10/135	1.0 (Referent)
Case-control	occupational yrs[a]:	1-24	18/206	1.46 (0.6-3.5)
Canada		25-45	21/213	1.40 (0.6-3.3)
Population		≥ 46	22/207	1.35 (0.6-3.2)
	Residential plus	1-36	12/205	0.83 (0.3-2.1)
	occupational	37-77	24/214	1.54 (0.7-3.5)
	smoker-yrs[b]:	≥ 78	25/207	1.82 (0.8-4.2)
				p value 0.05
Zhong *et al.* (1999)	ETS at work and home			OR[c]
Case-control, China		Adulthood only	33/36	1.9 (1.1-3.5)
Non-smoking women.		Childhood and adulthood	48/47	1.6 (0.9-2.7)
Lee *et al.* (2000)[d]	Adult life exposure[e]	None	97/227	1.0 (Referent)
Case-control		1-20	22/42	1.3 (0.7-2.5)
Taiwan		21-40	64/100	1.5 (0.9-2.4)
Hospital Based		> 40	85/76	2.6 (1.6-4.2)
				p trend=0.001
	Lifetime exposure [f]	None	79/196	1.0 (Referent)
		1-20	16/33	1.3 (0.6-2.6)
		21-40	54/90	1.6 (0.9-2.6)
		41-60	43/59	2.0 (1.2-3.5)
		> 60	76/67	2.8 (1.6-4.8)
				p trend=0.001
Boffetta *et al.* (1998)	Spousal and Workplace			OR[g]
Pooled Case-control	Total	No	122/339	1.00 (Referent)
Multiple Country		Yes	527/1201	1.14 (0.88-1.47)
	Women Only	No	88/198	1.00 (Referent)
		Yes	420/811	1.15 (0.86-1.55)
	Exposure duration	None	122/339	1.00 (Referent)
	(hrs/day x yrs)	0-165	289/749	0.91 (0.69-1.20)
		166-253	63/151	1.31 (0.88-1.94)
		> 254	57/101	1.46 (0.96-2.22)
				p trend=0.01

[a] ORs adjusted for age, province, education and total fruit/vegetable consumption.
[b] Sum over the subject's lifetime of residential exposure (i.e. number of regular residential smokers multiplied by the number of years in that home). ORs from Table III of Johnson *et al.* (2001), adjusted for age, province, education and total fruit/vegetable consumption.
[c] ORs adjusted for age, income, intake vitamin C, kitchen cooking smoke, family history lung cancer, and high-risk occupations, from Tables 2 and 5 Zhong *et al.* (1999).
[d] Appears case overlap with Ko *et al.* (1997).
[e] Home and workplace adult exposure ORs from Table 4 Lee *et al.* (2000), adjusted for residential area, education, occupation, tuberculosis, cooking fuels and fume extractor.
[f] As above but included childhood exposure.
[g] ORs adjusted for age and sex-study center interaction from Table 5 Boffetta *et al.* (1998).

Table 7.2E. Studies on ETS exposure in multiple settings and lung cancer among lifetime nonsmoking subjects.

Study	Questions on ETS exposure		#Cases / #Controls	OR (95% CI) for exposed
Jockel *et al.* (1998)	All adult ETS exposure excluding			
Case-control	spousal (Workplace, transit, other):			OR[h]
Germany		No/low	131/41	1.00 (Referent)
		Intermediate	18/5	1.44 (0.47-4.45)
		High	11/9	3.10(1.12-8.60)
	Total exposure (child/adult,			
	spousal, work, other):	No/low	101/29	1.00 (Referent)
		Intermediate	38/9	0.87 (0.36-2.07)
		High	21/17	3.24 (1.44-7.32)
Kreuzer *et al.* (2000;1998)	ETS All Sources			OR[j]
Case-control	Exposure duration	0-29,000	247/1,101	1.00 (Referent)
Germany*	(hours):	> 29,000-61,000	26/127	1.57 (0.97-2.54)
		> 61,000	13/87	1.36 (0.71-2.61)
				p trend=0.10
	Women only:	0-29,000	203/497	1.00 (Referent)
		> 29,000-61,000	17/26	1.85 (0.96-3.54)
		> 61,000	9/8	2.70 (1.01-7.18)
				p trend=0.01
	Weighted duration[i]	0-56,200	199/873	1.00 (Referent)
		> 56,200-100,600	11/77	1.09 (0.55-2.19)
		> 100,600	17/55	1.93 (1.04-3.58)
				p trend=0.06
	Women only	0-56,200	162/385	1.00 (Referent)
		> 56,200-100,600	6/15	1.09 (0.41-2.91)
		> 100,600	13/12	2.52 (1.12-5.71)
				p trend=0.04
Enstrom and Kabat (2003)	Spousal smoking			RR[k] for death
United States	Men:	formerly smoking spouse		0.82 (0.29-2.26)
		currently smoking spouse		0.57 (0.26-1.26)
	Women:	formerly smoking spouse		1.04 (0.69-1.57)
		currently smoking spouse		0.88 (0.60-1.28)
		ever smoking spouse		0.94 (0.66-1.33)

[h] ORs adjusted for sex, age and region, Table 3 Jockel *et al.* (1998).
[i] Weighted duration of exposure (hours x level of smokiness).
[j] ORs adjusted for age, sex and region from Table 4 Kreuzer *et al.* (2000).
[k] Adjusted at baseline for age, race, education, exercise, BMI, urbanization, fruit or juice intake, health status.

7.2.6. Summary of ETS and Lung Cancer

Since the previous OEHHA review (Cal/EPA, 1997), numerous epidemiological studies and several meta-analyses (Mengersen, 1995; Law and Hackshaw, 1996; Rundle *et al.*, 2002; Hackshaw *et al.*, 1997; Hackshaw, 1998; Wells, 1998b; Boffetta *et al.*, 1998; Taylor *et al.*, 2001) have continued to examine the association between passive smoking and lung cancer. The rate ratio estimates from Taylor *et al* (2001) are presented in Figure 7.2.1. Unfortunately, only two additional U.S. based studies were available for review. In contrast to many earlier studies, the majority of recent primary studies, specifically the population-based studies on spousal ETS, addressed issues of small sample size, possible selection bias, misclassification biases, and inadequate adjustment for potential confounders, including adjustment for dietary factors.

Although arguments may still be made regarding the extent of the effect on cancer risk estimates due to the potential misclassification of smoking status (Hackshaw *et al.*, 1997; Hackshaw, 1998; Lee, 1998), in combination with studies described in the earlier OEHHA report (Cal/EPA, 1997), these recent studies provide additional evidence that ETS exposure is causally associated with lung cancer. They consistently report elevated and often significant risk estimates, particularly for women married to smokers. Results from the recent Canadian and European case-control studies are compatible not only with the previous pooled estimate of the U.S. EPA (1992c) report, summary RR of 1.19 (90% CI=1.04-1.35) for ever exposed to spousal ETS (for U.S. studies), but also with several recent meta-analyses, range RR 1.2-1.3 (Mengersen, 1995; Law and Hackshaw, 1996; Rundle *et al.*, 2002; Hackshaw *et al.*, 1997; Taylor *et al.*, 2001). In addition, several of the recent primary studies provided evidence of positive increasing trends in lung cancer risk in nonsmokers with increasing ETS exposure, with some but not all exposure indices of duration, daily amount, or cumulative dose, for both spousal and workplace exposures, as well as combined exposures.

Particularly in earlier studies, misclassification of exposure in the "unexposed" populations by not measuring lifetime exposure or exposure to sources other than spousal or residential would bias potential findings towards the null. Johnson *et al* (2001) developed a table of studies (Table IV, Johnson *et al.*, 2001) that evaluated lung cancer risk associated with spousal, occupational, and total passive smoking exposure in women who never smoked and included some form of quantitative adult lifetime residential and occupational assessment of ETS exposure. In Table 7.2F, we have taken the point estimates for the combined residential and occupational high exposure categories from these studies and created a weighting scheme by inverse variance (Rothman and Greenland, 1998). There was no difference in summary statistics found between a fixed or random effects models with both finding an OR of 1.8 (95% CI 1.5-2.2).

The conclusion that there is a causal association between ETS-exposure and lung cancer stated in the original OEHHA report (Cal EPA, 1997) is further strengthened by the new data.

Table 7.2F Lung cancer risk for high exposure categories, associated with total passive smoke exposure in never-smokers: Population-based studies that include quantitative adult lifetime residential and occupational assessment of ETS exposure.

Study	Weights fixed	Weights random	OR	Lower limit	Upper limit
Fontham *et al.*, 1994	20.72	20.02	1.74	1.14	2.65
Boffetta *et al.*, 1998	18.06	14.68	1.54	0.97	2.44
Nyberg *et al.*, 1998a	8.53	7.69	2.52	1.28	4.9
Jockel *et al.*, 1998	5.81	5.41	3.24	1.44	7.32
Zhong *et al.*, 1999	17.60	14.38	1.8	1.1	2.8
Kreuzer *et al.*, 2000	28.14	20.71	1.39	0.96	2.01
Lee *et al.*, 2000	12.73	10.95	2.8	1.6	4.8
Wang *et al.*, 2000	12.73	10.95	1.51	0.9	2.7
Johnson *et al.*, 2000	5.59	5.22	1.82	0.8	4.2
Summary fixed effects			1.79	1.49	2.16
Summary random effects			1.82	1.48	2.24

Test for heterogeneity: Q = 8.171 on 7 degrees of freedom (p = 0.318). Der Simonian and Laird estimate of between studies variance = 0.013. Summary estimates based on fixed and random effects models with 95% confidence intervals. Weighting by inverse variance. Based on table IV in Johnson *et al.* (2001)

7.2.6.1. Deaths and Incident Cases of Lung Cancer Attributable to ETS

The U.S. EPA (1992c) method of estimating attributable lung cancer deaths was applied to estimate lung cancer attributable risk using updated exposure and population-at-risk inputs. This method and the inputs to the model are described in Appendix B at the end of Chapter 7.

The calculation, based on the equations of U.S. EPA (1992c), apportions the overall number of lung cancer deaths into four categories: (1) deaths in mainstream smokers and former smokers, (2) ETS-attributable deaths in nonsmokers exposed to spousal smoking, (3) ETS-attributable deaths in non-smokers not exposed to spousal smoking, and (4) deaths not related to tobacco smoke.

The equations (described in Appendix B at the end of Chapter 7) use the assumption that risk is linear in dose, as specified in the NRC (1986f) model for relative risk in epidemiology studies:

$$R(d_E) = (1 + Z * ßd_N)/(1 + ßd_N)$$

where $R(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS). Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N. ß is the amount of increased risk per unit dose.

We estimate that for the nation in 2003, the number of ETS-attributable lung cancer deaths associated with spousal smoking for both genders combined is in the range of 3423 to 8866. In the summary table in the Executive Summary (Table ES-2), we only include the lower number as it is based on a relative risk estimate obtained in the best U.S. study which quantified exposure on the basis of cotinine levels (Fontham *et al*., 1994), and is also similar to the pooled estimate from the majority of the meta-analyses. The deaths among males are lower than among females reflecting the lower proportion of non-smoking males with spousal exposure. On the other hand, this analysis does not address ETS exposure at work or in other venues that may be generally higher for males than for females.

The number of ETS-attributable lung cancer deaths in Californian may be crudely estimated by taking California's population as 12% of the national population, and assuming the same rates of exposure to active and spousal smoking. This would result in estimates for females and males, respectively, of 307 and 104 deaths. The total ETS attributable lung cancer deaths in California would thus be expected to be in the range of 411-1064.

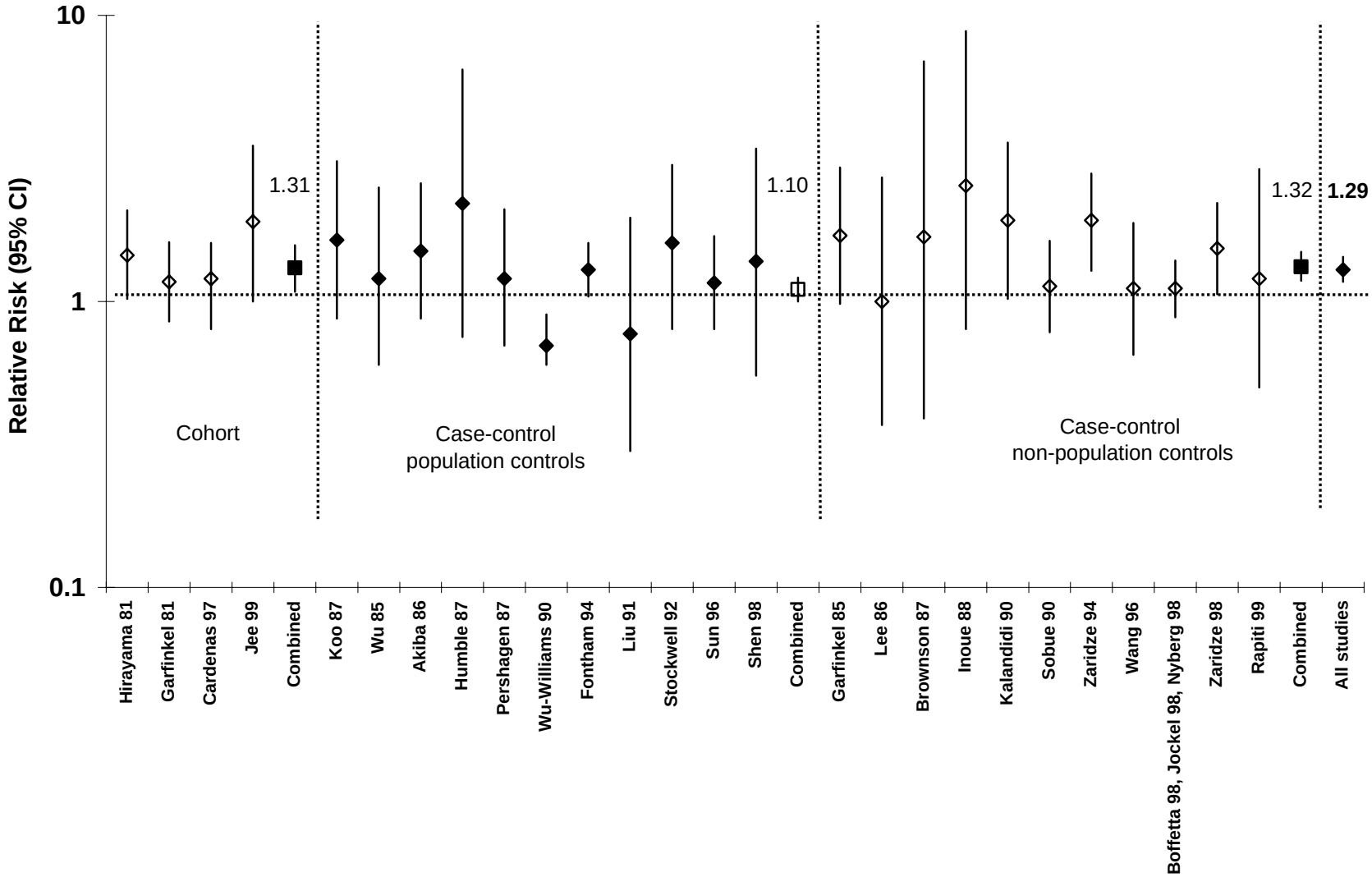


Figure 7.2.1. Lung Cancer Meta-analysis Based on Data from Taylor *et al.*, 2001

7.3. ETS and Cancer Sites Other than Lung that are Associated with Active Smoking: Nasal Sinus, Head and Neck, Cervical and Bladder

7.3.1. ETS and Head and Neck Cancer

7.3.1.1. ETS and All Cancers of the Head and Neck: Previous Studies

The Cal/EPA (1997) did not previously review any studies investigating the association between ETS exposure and cancers of the head and neck.

7.3.1.2. ETS and All Cancers of the Head and Neck: Recent Epidemiological Studies

As summarized in Table 7.3A, two hospital-based case control studies investigated the association between ETS exposure and the risk of malignancies of the head and neck (Tan *et al.*, 1997; Zhang *et al.*, 2000). Both studies included cases of squamous cell head and neck cancers (SCHNC) from a variety of anatomic sub-sites, including lip, tongue, gum, floor of the mouth, oropharynx, nasopharynx, hypopharynx, esophagus, and larynx.

Tan et al. (1997) identified 59 non-tobacco using cases and two sets of controls (853 cancer patients with squamous cell head and neck cancers (SCHNC) and 167 non-SCHNC, nonsmoking patients matched on age, race, sex and alcohol use). The risk estimates were elevated for spousal exposure to ETS [OR 2.80 ($p<0.006$)], workplace ETS [OR 10.16 ($p<0.001$)], or either [OR 5.34 ($p<0.001$)], comparing non-smoking SCHNC cases (all sites combined) to matched non-smoking controls (Table 7.3A). These relatively large risk estimates are impressive; however, the small study size, limited exposure assessment and lack of control for other potential confounders require additional study.

Zhang et al. (2000) included 173 pathologically confirmed cases of SCHNC and 176 cancer-free controls (identified blood bank). The risk of SCHNC was significantly associated with ETS exposure [crude OR 2.8 (95% CI 1.3-6.0)] declining to statistical non-significance after controlling for age, sex, race, education, alcohol, pack-years cigarette smoking and marijuana use [adjusted OR 2.4 (95% CI 0.9-6.8)]. Both adjusted and unadjusted ORs are consistent with Tan *et al.* (1997) noted above. Evidence of a dose-response was also observed [moderate: adjusted OR 2.1 (95% CI 0.7-6.1); heavy: adjusted OR 3.6 (95% CI 1.1-11.5)]. In the analysis restricted to non-active smokers elevated, but non-significant associations between ETS and SCHNC risk remained [crude OR 2.2 (95% CI 0.6-8.4)], again with some evidence of a dose-response [moderate: OR 1.8 (95% CI 0.5-7.3); heavy: OR 4.3 (95% CI 0.8-23.5), p for trend 0.008] (Table 7.3A). This study also is suggestive of a relationship between ETS exposure and SCHNC; however, the small number of nonsmokers and the residual influence of active smoking on the larger risk estimate decrease the study's utility.

Table 7.3A. Association between passive smoke exposure and risk of head and neck cancer in nonsmokers

Case Control Studies	Exposure to Passive Smoking (Cases/Controls)	Relative Risk OR (95% CI or p-value)		
Tan *et al.* (1997)		Total[a]	Male[a]	Female[a]
	Home (43/132)	2.80 (0.0006)	1.15 (0.79)	7.35 (<0.001)
	Workplace (38/128)	10.16 (<0.001)	11.63 (<0.001)	8.89 (0.002)
	Either (44/132)	5.34 (<0.001)	3.75 (0.015)	8.0 (<0.001)
Zhang *et al.* (2000)		Non-Smokers[a]	Adjusted ORs (Includes smokers and nonsmokers)[b]	
	ETS: Never[c]	1.0 (Referent)	1.0 (Referent)	
	Ever	2.2 (0.6-8.4)	2.4 (0.9-6.8)	
	Degree ETS: Never[c]	1.0 (Referent)	1.0 (Referent)	
	Moderate	1.8 (0.5-7.3)	2.1 (0.7-6.1)	
	Heavy[d]	4.3 (0.8-23.5)	3.6 (1.1-11.5)	
		p trend=0.0082	p trend=0.0249	
	ETS Home: Never	1.0 (Referent)	1.0 (Referent)	
	Occasionally	3.2 (1.0-10.4)	1.6 (0.8-3.3)	
	Regularly	1.5 (0.5-4.5)	1.7 (0.8-3.3)	
		p trend=0.4483	p trend=0.1574	
	ETS Work: Never	1.0 (Referent)	1.0 (Referent)	
	Occasionally	2.2 (0.7-6.9)	1.0 (0.5-2.1)	
	Regularly	1.5 (0.5-5.0)	1.0 (0.5-2.1)	
		p trend=0.4670	p trend=0.9240	
	Spousal Smoking: No	1.0 (Referent)	1.0 (Referent)	
	Yes	0.9 (0.2-5.2)	1.7 (0.8-3.7)	

[a]OR equals crude odds ratio
[b]Adjusted for age, race, education, heavy alcohol use, marijuana use, pack-years active smoking
[c]Never exposed to ETS at both home and work
[d]Regularly exposed to ETS at both home and work

7.3.1.3. Summary of ETS and All Cancers of the Head and Neck.

The evidence from these two hospital-based epidemiology studies of the association between ETS and malignancies of the head and neck, although suggestive, remains inconclusive. The two case-control studies found an elevated, but statistically non-significant increase for head and neck cancer risk associated with ETS exposure after adjustment for potential confounders. Both studies are limited by small case numbers, particularly by individual anatomic site and among non-smokers, meager exposure assessment, and selection bias in the hospital-based controls.

7.3.1.4. Nasal Sinus and Nasopharyngeal Cancer

7.3.1.4.1. Active Smoking and Nasal Sinus Cancer

Active, primary smoking is considered a significant causal factor for cancer of the nasal sinus cavity (IARC, 2004a), with highest risk estimates reported for heavy smoking, current tobacco use, and squamous cell carcinomas (Elwood, 1981; Strader *et al.*, 1988; Zheng *et al.*, 1992). For this update, no new primary studies were located.

7.3.1.4.2. ETS and Nasal Sinus Cancer: Previous Findings

Three studies, one cohort (mortality) and two case-control studies (one incidence, one mortality) were previously reviewed by OEHHA (Cal/EPA, 1997). One cohort reported a significant dose-dependent increasing risk of nasal sinus cancer deaths among nonsmoking women relative to husbands' smoking ($p<0.03$) (Hirayama, 1984). The two case-control studies reported elevated non-significant risk among nonsmoking spouses of smokers, both among women (Fukuda and Shibata, 1990) and men (Zheng *et al.*, 1993). These results led OEHHA to conclude that strong evidence exists that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults (Cal/EPA, 1997).

7.3.1.4.3. ETS and Nasal Sinus and Nasopharyngeal Cancers: recent data

No new studies were located that examined the association between ETS and nasal sinus cancer. Two recent case-control studies, one population-based and one hospital-based, reported a positive association between nasopharyngeal carcinoma (NPC) and ETS (Armstrong *et al.*, 2000; Yuan *et al.*, 2000). In contrast, two other case-control studies reported a null or negative association between ETS and NPC (Vaughan *et al.*, 1996; Cheng *et al.*, 1999).

Vaughan et al. (1996) conducted a population-based case-control study at five U.S. cancer registries. Of the 294 eligible cases diagnosed between 1987 and 1993, interviews were completed on 231 individuals, as well as 246 controls. Although strong positive dose-response between NPC and active cigarette smoking was reported, including an adjusted OR of 6.5 for current smokers at the highest dose level (60 pack-years), no association between NPC (differentiated squamous cell NPC) and exposures to ETS was identified in lifetime nonsmokers or former smokers. However, no data or results regarding ETS and NPC were presented in the published report.

Cheng et al. (1999) reported a Taiwanese hospital-based case-control study utilizing 375 histologically confirmed NPC cases and 327 community controls. In the case of active smoking, only slightly elevated but statistically non-significant adjusted risk estimates were reported for current smokers [OR 1.4 (95% CI 0.9-2.1)] or former smokers [OR 1.1 (95% CI 0.6-2.1)]. Among non-smokers, neither childhood nor adult ETS exposure was associated with an elevated risk of NPC [adjusted ORs 0.6 (95% CI 0.4-1.0) and 0.7 (95% CI 0.5-1.2), respectively] after adjustment for age, sex, race, education, and family history of NPC.

Armstrong et al. (2000) conducted a Malaysian-based hospital study (four radiotherapy centers) consisting of 282 of 530 eligible cases identified with histologically confirmed NPC between 1990 and 1992, in which cases consisted of both prevalent and incident cases. A large proportion of identified cases either died or were too ill to participate in the study (125; 24%). Smoking and other data were collected from cases and neighborhood controls via personal

interview. In non-smokers exposed to parental smoking during childhood, a significantly elevated NPC risk was identified [adjusted OR 2.28 (95% CI 1.21-4.28)] after adjustment for multiple dietary factors. However, ETS exposure due to spousal or other household smokers was not associated with elevated NPC risk (data not shown).

Yuan et al. 2000. This population-based case-control study in Shanghai, China consisted of 935 NPC cases and 1,032 community controls. A total of 1,110 histologically confirmed cases of NPC were reported to the Shanghai Cancer Registry between 1987 and 1991, with 935 (84%) participating in the final study. Smoking and other data were obtained during personal interview, with ETS exposure identified for childhood (≤ 18 years), residential adult and workplace exposure. In non-smokers, a significant increase in NPC risk was associated with lifetime ETS among women [adjusted OR 1.95 (95% CI 1.18-3.21)], but not men [adjusted OR 1.29 (95% CI 0.62-2.68)]. Additionally, in women, childhood ETS exposure was also significantly associated with elevated NPC risk, due to maternal smoking [adjusted OR 3.36 (95% CI 1.41-8.05)], paternal smoking [adjusted OR 2.95 (95% CI 1.41-6.19)], and other household smokers [adjusted OR 2.72 (95% CI 1.07-6.92)]. Evidence for a dose response between increasing NPC risk and number of cigarettes/day were observed for maternal (p=0.003) and paternal smoking (p=0.001). In adults, spousal and workplace ETS exposure was significantly associated with an elevated NPC risk among women [adjusted ORs 3.09 (95% CI 1.48-6.46; p=0.003) and 2.84 (95% CI 1.34-6.00; p=0.01), respectively], but not among men. Risk estimates were adjusted for age, sex, education, dietary factors, cooking smoke/fumes, occupational exposure to fumes, history of NPC and chronic ear/nose conditions.

7.3.1.4.4. Summary of ETS and Nasal Sinus and Nasopharyngeal Cancer

As previously determined by OEHHA, "the existing studies consistently show a significant positive association between exposure to ETS and nasal sinus cancer in nonsmokers, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults" (Cal/EPA, 1997). In the absence of newer studies on nasal sinus cancer, this conclusion remains unchanged. Regarding nasopharyngeal cancer, the results of the Yuan *et al.* (2000) study suggest a gender difference in cancer susceptibility in which females are more at risk for nasopharyngeal cancer after ETS exposure. For both males and females there is evidence of a dose-response for childhood exposure to both maternal and paternal smoking, although in males the confidence intervals included no effect. The study by Armstrong *et al.* (2000) did not find an association between nasopharyngeal cancer and ETS exposure in adulthood. However, there was a significant association between childhood exposure to parental smoking and subsequent nasopharyngeal cancer (OR 1.54; p = 0.04). This is consistent with the results of Yuan *et al.* for females and may indicate a developmental window of susceptibility. Thus the more recent studies are considered suggestive of a possible association between childhood ETS exposure and subsequent development of nasopharyngeal cancer.

7.3.2. Cervical Cancer

7.3.2.1. Active Smoking and Cervical Cancer

Epidemiological evidence for the association between active smoking and cervical cancer, both malignant, in situ and intraepithelial neoplasia (CIN), has been derived from a large number of studies (Winkelstein, 1990). Smokers have been found to have an approximately 2-fold

increased risk of cervical cancer. Other risk factors, particularly infection with human papilloma virus (HPV) or a surrogate of potential exposure to HPV (e.g., number of sexual partners or age at first intercourse), strongly influence risk estimates, requiring studies to adjust risk estimates accordingly (Cal/EPA, 1997).

Four additional primary studies were available for review, one cohort and three case-control (two nested in larger cohorts) (Engeland *et al.*, 1996; Deacon *et al.*, 2000; Hakama *et al.*, 2000; Kjellberg *et al.*, 2000). Two studies, Engeland *et al.* (1996) and Hakama *et al.* (2000), reported on active smoking and cervical cancer risk (invasive cancers), and the remaining two studies, Deacon *et al.* (2000) and Kjellberg *et al.* (2000), evaluated smoking exposure relative to risk for in situ cervical cancer (CIN 3), often considered a precursor of invasive cervical cancer. The three more recent studies accounted for other known risk factors, including sexual behavior and human papilloma virus infection (HPV).

Engeland et al. 1996. This Norwegian population-based cohort of 26,000 men and women was followed from 1966 to 1993 to investigate the relationship between smoking and multiple cancer sites. Smoking status was established by baseline questionnaire in 1964-1965. Cancer of the uterine cervix, 86 cases with 99% histologically confirmed, was significantly elevated among smokers compared to never smokers [RR 2.5 (95% CI 1.6-3.9)]; however, the study lacked data on HPV status and other potential confounders. No dose-response relationship was observed.

Deacon et al. 2000. This nested case-control study was conducted in the United Kingdom from a population-based cervical screening cohort. The study included 199 histologically confirmed cases of cervical neoplasia (CIN 3) in women known to be HPV positive (74% response), 181 other HPV positive women without CIN 3, and 203 HPV negative controls (66% response). Data on smoking, reproductive, sexual and other gynecological history were obtained via interview. Among HPV positive women, active smoking was significantly associated with an increased risk of CIN 3, with a significantly increasing trend ($p < 0.0001$) in risk with increasing smoking duration or amount (cigarettes per day, cpd) [1-10 cpd: 1.36 (95% CI 0.73-2.51); 11-16 cpd: 2.20 (95% CI 1.24-3.89); 17+ cpd: 3.06 (95% CI 1.77-5.31)]. No association was observed between smoking and HPV infection.

Hakama et al. (2000) conducted a nested case-control study from three cohorts of women (derived from serum banks) in Finland, Norway, and Sweden, with cancer cases identified through linkage with three population-based cancer registries. A total of 149 cases of squamous cell carcinoma (SCC) of the cervix and 442 controls were included in the analysis. HPV infection past or present was determined through serological analysis. Active smoking was measured via serum cotinine with smokers defined as those with a cotinine level 20 μg/mL or higher. The risk of squamous cell carcinoma was elevated among women seropositive for HPV, *Chlamydia trachomatis* and smoking. Among smokers, in the absence of either infectious agent, the OR for SCC was 1.8 (95% CI 1.1-3.0).

Kjellberg et al. (2000) reported on a population-based Swedish case-control study of 137 women with high-grade cervical neoplasia (CIN 2-3) and 253 matched controls. HPV infection was determined for both active infection (cervical brush samples) and past or present infections (seropositivity). Data on smoking, diet, health, sexual and reproductive history were collected via questionnaire. Active smoking was significantly associated with an elevated risk of CIN 2-3

[OR 2.6 (95% CI 1.7-4.0)]; additional adjustment for HPV status (whether current only or past/present) did not alter this association [ORs 2.5 (95% CI 1.3-4.9) and 3.0 (95% 1.9-4.7), respectively]. Evidence for a dose-response between increasing risk of cervical neoplasia and increasing levels of smoking was also reported (p for trend < 0.001).

7.3.2.2. ETS and Cervical Cancer: Previous Findings

In 1997, OEHHA reviewed one cohort (mortality) and three case-control studies, two of which were designed to investigate the role of smoking, active and passive, in the etiology of cervical cancer (Slattery *et al.*, 1989; Coker *et al.*, 1992). The two cervical cancer specific studies included incident cases and either population- or medical practice-based controls, however, only one included limited data on HPV infection status (surrogate measure as history of genital warts) (Coker *et al.*, 1992). The study lacking an estimate of HPV status (Slattery *et al.*, 1989) found significantly elevated adjusted risk estimates (age, education, number of sexual partners) for ETS exposure and cervical cancer risk. The second study found positive non-significant associations between ETS exposure and the risk of in situ cervical cancer for smoking by husbands [adjusted OR 1.5 (95% C.I. 0.9-6.2)] or others [adjusted OR 1.5 (95% C.I. 0.4-8.4)].

In combination with biochemical studies, the epidemiological evidence suggests the ETS exposure does potentially play a role in increasing cervical cancer risk; however, more studies specifically designed to look at recent/current exposures, exposures outside the home, as well as data on other etiological factors such as HPV infection, are required.

7.3.2.3. Recent Epidemiological Data on ETS and Cervical Cancer

Two new primary studies reporting on the relationship between ETS and cervical neoplasms were located. As part of their study on ETS and lung cancer, Jee *et al*. (1999) (described in Sections 7.2.3 and 7.4.1.5) reported no association between cervical cancer and the husband's smoking (RR 0.9, 95% CI 0.6-1.2). However, one U.S. population-based (large health maintenance organization) cross sectional study evaluated the role of cigarette smoking, both active and passive, on the occurrence of abnormal cervical cytology (Scholes *et al.* 1999). The study included women identified with Class 1 (with normal limits/benign changes) through Class 3 and 4 (mild or moderate dysplasia, CIN 1/2) cervical intraepithelial neoplasia (CIN); no severe dysplasia (CIN 3) or invasive cervical cancer cases were included. Smoking and other data were collected via telephone interview. ETS exposure was limited to spousal/partner smoking. A total of 4,053 women (71%) were interviewed, including 465 with Class 2 (19%) and 117 with Class 3-4 (5%) Pap results. After adjustment for lifetime number of sexual partners, age and age at first intercourse, non-smokers with spousal ETS exposure had an elevated risk of an abnormal (Class 2-4) Pap smear [adjusted OR 1.4 (95% CI 1.0-2.0)]. Similarly, current smokers also had an elevated risk of abnormal Pap smears [adjusted OR 1.4 (95% CI 1.1-1.8)].

Wu *et al*. (2003) investigated the association between ETS exposure and cervical intraepithelial neoplasms among nonsmoking women in Taiwan. The investigators used a community-based nested case-control design on the city of Chia-Yi in Taiwan. The study population consisted of women 19+ years of age participating in a Taiwanese government Pap smear screening program, which was free to participants. There were 420 women out of 32,466 who had newly diagnosed cervical intraepithelial neoplasia (CIN) that were category I or higher. Of 349 of these women

who were biopsied, 116 had definite lesions that exceeded the level II CIN. These women served as the cases. Two controls were assigned to each case, selected at random, and age-matched. Controls had negative pap smears within the same time period as cases and lived in the same area of Chia-Yi. Questionnaires were administered by public health nurses blinded to the hypothesis of the study (but not the case status of the subjects). Questionnaires asked about demographic characteristics, smoking status, history of ETS exposure, exposure to x-rays, hair dyes, sexual and reproductive history, history of cooking tasks and whether ventilated kitchens were used.

The authors defined active smokers as those who had smoked more than one cigarette per day for at least a year. Passive smokers were defined as subjects that had been exposed to the smoke of at least one cigarette per day for at least one year at home or at the workplace. ETS exposure was ascertained for childhood (< 20 yrs) and adulthood (>20 yrs of age). Questions were asked to determine the number of years of exposure, when exposure started or ended, and how many cigarettes were smoked in their presence each day. The investigators used the information to determine pack-years of ETS exposure. Multivariate conditional and unconditional logistic regression was used to explore the association between ETS and case or control status. The final model included controls for education, age at which intercourse first occurred, number of pregnancies, and cooking in unventilated kitchens. Active smokers were discarded from the analysis of ETS association leaving 89 case-control pairs of nonsmokers. ETS at home in adulthood was associated with cervical intraepithelial neoplasia (adjusted OR 2.73; 95% CI 1.31-5.67). There was an elevated but non-significant risk associated with ETS exposure in the workplace (adjusted OR 1.56; 95% CI 0.83-2.92). Childhood ETS exposure was not associated with the development of CIN. Risk was higher for less-educated women than for those with more than a high-school education. A dose-response trend was noted. The group who were exposed to 1-10 cigarettes/day had an OR of 2.13 (95% CI 0.96-4.73) and the OR for the group exposed to more than 10 cigarettes/day was 3.97 (95% CI 1.65-9.55) (p for trend = 0.002). Similarly, when measured as pack-years of ETS exposure, the OR for 1-20 pack-yr was 1.90 (95% CI 0.72-5.03), while the OR for >20 pack-yr was 2.99 (95% CI 1.10-8.09). One major limitation was a lack of information on HPV status. However, the authors note that Taiwanese women are much less sexually active prior to marriage than Western women as culturally virginity at marriage and fidelity in marriage are highly valued. In addition, there is evidence of a dose-response relationship for ETS; the HPV status would not necessarily track with extent of ETS exposure.

7.3.2.4. Biomarkers of Cervical ETS Exposure: Previous Studies

In 1997, OEHHA reviewed five cross-sectional clinical studies reporting the measurement of biological markers of exposure to tobacco smoke among non-smokers (Cal/EPA, 1997). Four studies reported on detectable levels of nicotine and cotinine in the cervical mucus of non-smokers (Sasson *et al.*, 1985; Hellberg *et al.*, 1988; Jones *et al.*, 1991; McCann *et al.*, 1992). Out of the three studies stratifying on the presence or absence of ETS, two reported no difference in levels among ETS exposed women (Hellberg *et al.*, 1988; McCann *et al.*, 1992), while the third reported higher levels of nicotine in women with ETS exposure (Jones *et al.*, 1991). Another, small study reported the presence of potentially tobacco-related DNA-adducts in the cervical epithelium of non-smoking women being surgically treated (hysterectomy or colposcopy) for benign disease (Simons *et al.*, 1993). However, no data on application of these methods to epidemiological investigations of ETS and cervical cancer were presented.

7.3.2.5. Biomarkers of Cervical ETS Exposure: Recent Studies

Two small recent studies measured the levels of carcinogen metabolites (Prokopczyk *et al.*, 1997) or adducts (Melikian *et al.*, 1999) in the cervical mucus or tissue; both studies compared levels between smokers and nonsmokers (see Table 7.3B). Melikian *et al.* (1999) characterized benzo[a]pyrene-related DNA adducts (BPDE) in the cervical tissue of 17 women (8 smokers, 9 nonsmokers). In epithelial tissue the mean adduct level was significantly higher in smokers relative to nonsmokers, with measured means of 3.5 versus 1.9 BPDE adducts/10^8 nucleotides, respectively (P=0.02). No difference in mean levels was observed in stromal tissue (mean 1.8 versus 1.4 adducts/10^8 nucleotides) among smokers and nonsmokers (p=0.48). Prokopczyk *et al.* (1997) compared the levels of a carcinogenic, tobacco-specific N-nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), in the cervical mucus of 14 smokers and 10 nonsmokers. NNK concentrations were significantly higher in smokers (mean 46.9 ng/g range 11.9-115.0 ng/g), relative to nonsmokers (13.0 ng/g, range 4.1-30.8 ng/g) (p=0.004). Although the number of subjects was limited, both studies further demonstrate the ability of tobacco-related metabolites and related-adducts to reach non-respiratory target sites, such as the cervix, indicating that such compounds could play a role in the etiology of cervical cancer.

Table 7.3B. Carcinogenic metabolites and adducts measured in the cervical mucus and cervical tissue of smokers and nonsmokers

Study	Measurement	Mean ± SD	
Melikian *et al.* (1999)	BPDE[a] adducts in cervical tissue	Epithelial tissue (adducts/10^8 nucleotides)	Stromal tissue (adducts/10^8 nucleotides)
Smokers (n = 8)		3.5 ± 1.06, p = 0.02[b]	1.8 ± 0.96, p = 0.48[b]
Nonsmokers (n = 9)		1.9 ± 1.27	1.4 ± 1.1
Prokopczyk *et al.* (1997)	NNK[a]	(ng/g)	
Smokers (n = 15)		46.9 ± 32.5, p = 0.004[b]	
Nonsmokers (n = 10)		13.0 ± 9.3	

[a] BPDE = 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-benzo[*a*]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
[b] Smokers vs. non-smokers.

7.3.2.6. Summary of ETS and Cervical Cancer

The current review agrees with the previous position that there is evidence suggestive of an association between ETS exposure and cervical cancer as stated by OEHHA in 1997 (Cal/EPA, 1997). Although no additional epidemiological studies on ETS exposure and cervical cancer were available for review, the studies on early cervical neoplasia (Scholes *et al.*, 1999; Wu *et al.*, 2003) indicate that, as with active smoking, ETS may have a role in the etiology of cervical cancer. Additional data on the timing of ETS exposure, the influence of confounding factors, particularly HPV infection, as well as utilization of biological markers of exposure and/or effect (e.g. cotinine or nicotine, bimolecular adducts), will be required to substantiate the magnitude of the potential cervical cancer risk due to ETS.

7.3.3. Bladder Cancer

7.3.3.1. Active Smoking and Bladder Cancer

Primary smoking has been well established as a significant cause of bladder cancer (IARC, 1986a). Relative risks for active smoking ranged between 2 to 10 across studies, with variation potentially due to difference in tobacco types and chemical content, as previously reviewed in the OEHHA report. Recent studies support that cigarette smoking significantly increases the risk of bladder cancer among both men and women (see below).

Several recently published case-control studies, including several large pooled European analyses (Brennan *et al.*, 2000, 2001; Fortuny *et al.*, 1999; Pitard *et al.*, 2001), one prospective cohort study (Zeegers *et al.*, 2002) and two U.S. population-based registry studies in Los Angeles (Castelao *et al.*, 2001) and in Iowa (Chiu *et al.*, 2001) further establish active tobacco smoking as a bladder carcinogen. The European pooled analyses reported risk estimates for smokers 2- to 6-fold higher compared to nonsmokers, with an increasing risk of bladder cancer by increasing duration (years) and amounts smoked among men (Brennan *et al.*, 2000; Pitard *et al.*, 2001) and women (Brennan *et al.*, 2001).

Castelao et al. 2001. In this Los Angeles case-control study, ever-active cigarette smokers had a statistically significant elevated risk of bladder cancer [OR 2.5 (95% CI 2.1-3.0)] with risk increasing among active smokers [OR 3.8 (95% CI 3.1-4.7)]. A significant dose-response relationship was observed between amount smoked daily and duration of smoking. Estimates increased substantially with estimation of joint effects of intensity (amount smoked per day) and duration (P interaction 0.016). For example, the bladder cancer risk associated with men smoking 20-39 cigarettes per day increased substantially with duration [<20 years: OR 1.52 (95% CI 1.05-2.21); 20-39 years: OR 2.72 (95% CI 2.10-3.52); ≥40 years: OR 4.87 (3.46-6.84)]. Similar results were observed among women [<20 years: OR 2.65 (95% CI 1.50-4.66); 20-39 years: OR 4.33 (95% CI 2.58-7.27); ≥40 years: OR 4.33 (95% CI 2.02-9.26)]. This study confirmed earlier reports that active smoking increases the risk of bladder cancer, and that the duration and intensity of cigarette smoking increase the risk of bladder cancer.

Chiu et al. 2001. In this Iowa case-control study, there were 1,406 bladder cancer cases and controls with available smoking data (obtained via mailed questionnaire). Individuals were classified as never-smokers if lifetime tobacco use did not exceed 6 months. Risk estimates for bladder cancer were adjusted for age, total dietary energy intake, occupation, vegetable intake, coffee intake, bladder infection and family history of bladder cancer. This study identified risk estimates for "ever" smoking of similar order as the Los Angeles study (Castelao *et al.*, 2001) [ORs 2.5 (95% 2.0-3.1) and 2.7 (95% CI 2.0-3.6), for men and women, respectively]. Bladder cancer risk among current smokers increased with cumulative dose (pack-years) among men [<20 years: adjusted OR 3.9 (95% CI 2.1-7.1); 20-39 years: adjusted OR 2.7 (95% CI 1.7-4.3); >40 years: adjusted OR 4.6 (95% CI 3.4-6.3)] and women [<20 years: adjusted OR 2.1 (95% CI 1.0-4.5); 20-39 years: adjusted OR 4.3 (95% CI 2.6-7.1); >40 years: adjusted OR 4.5 (95% CI 2.8-7.1)].

The strengths of this study, such as the population-based nature of this study, including population-based controls, the relatively high response rate (>85%), and the adjustment for

several potential confounders, provides substantial evidence for an association between active smoking and bladder cancer.

Zeegers et al., 2002. This study, investigating the association between active and passive smoking and bladder cancer, is based on a prospective cohort study of diet and cancer in the Netherlands. The authors employed a case-cohort approach in which the 619 incident cases of bladder cancer were derived from the entire cohort (n = 120,852) while a sub-cohort of 3,346 was followed from 1986 to 1992 for vital status information. At baseline, the study population of 55-69 year old men and women completed self-administered questionnaires on cancer risk factors. The data collected included age at first and last exposure to smoking, smoking frequency and duration, tobacco form (cigarette, pipe, cigar), and cigarette brand and type (filtered or not). ETS exposure was determined from questions on the smoking habits of parents and spouses, as well as from data regarding work and "private" exposures. Risks were estimated using exponentially distributed failure time regression models. A large number of potential confounders were considered but only those that altered the risk of bladder cancer by more than 10% were incorporated into the final model. For this reason, the RRs reported were adjusted only for age and gender.

As reflected in Table 7.3C, compared to never smoking, active smoking was significantly associated with bladder cancer incidence with significant dose-response trends measured either as cigarettes per day or duration of exposure. In addition, younger age at first exposure was associated with increased risk. There was also a significant trend of decreasing risk with increasing time since smoking cessation.

Table 7.3C. Active Smoking and Risk of Bladder Cancer

Smoking feature	Cases in cohort	Person-years	RR	95% CI
Never	55	7,276	1.0	
Ex-smoker	263	7,001	2.1	1.5-3.0
Current	282	5,664	3.3	2.4-4.0
Cigarettes/day				
< 5	30	1,488	1.8	1.1-2.9
5 -<10	59	1,826	2.4	1.6-3.7
10 -<15	87	2,463	2.2	1.5-3.3
15 -<20	93	1,780	3.4	2.3-5.0
20 -<25	120	2,329	3.2	2.2-4.7
≥25	115	1,900	3.7	1.5-5.4
		trend	p < 0.01	
Duration (yrs)				
<10	10	632	1.4	0.68-2.9
10-<20	39	1,592	1.8	1.1-2.8
20-<30	63	2,506	1.7	1.1-2.6
30-<40	125	3,213	2.7	1.9-3.9
40-<50	220	3,807	3.4	2.4-4.8
≥50	79	565	5.4	3.5-8.5
		trend	p <0.01	
Cessation (yrs)				
<1	295	5,821	3.4	2.5-4.7
1-<10	112	2,240	2.9	2.0-4.3
10-<20	71	2,324	1.7	1.1-2.5
20-<30	54	1,527	1.9	1.2-2.9
≥30	11	723	0.81	0.4-1.6
		trend	p <0.01	

7.3.3.2. ETS and Bladder Cancer: Previous Findings

In the previous OEHHA report (Cal/EPA, 1997) two case-control studies reporting on the association between ETS exposure and bladder cancer were reviewed (Kabat *et al.*, 1986; Burch *et al.*, 1989). Neither study demonstrated a significantly increased risk associated with ETS exposure. Both studies had limited power due to small sample sizes and poor ETS exposure measurements, leading to the conclusion that the epidemiological evidence for a relationship between ETS and bladder cancer remains inadequate.

7.3.3.3. ETS and Bladder Cancer: Recent Studies

Zeegers et al., 2002. This study was described in the previous section. Exposure to parental smoking or high levels of ETS at work elevated bladder cancer risk but not significantly (1.2, 95% CI 0.56-2.4 and 1.4, 95% CI 0.70-2.6, respectively). There was no evidence of an association between ETS exposure from an ex- or current smoking partner. This is in contrast to

the highly significant association this study found for the association between active smoking and bladder cancer. It is questionable, however, how unexposed the reference population is since the estimate for work exposure compares "high" versus "low" ETS rather than ETS exposure with no exposure. The estimates based on partner smoking status (never, ex, current) do not reflect other potential sources of ETS. A more complete evaluation of actual ETS exposure is needed to adequately address the question of the role of ETS exposure in bladder cancer.

7.3.3.4. Biomarkers of Bladder Carcinogens from ETS Exposure: Previous Findings

OEHHA previously described two cross sectional studies reporting concentrations of hemoglobin adducts of 4- and 3-aminobiphenyl (4- and 3-ABP), two indicators of exposure to tobacco smoke, among non-smokers (Bartsch *et al.*, 1990; Maclure *et al.*, 1989). Both studies demonstrated a positive association between reported ETS exposure and adduct concentrations (Cal/EPA, 1997).

7.3.3.5. Biomarkers of Bladder Carcinogens from ETS Exposure: Recent Data

No new primary studies were located.

7.3.3.6. Summary of ETS and Bladder Cancer

As stated in the previous OEHHA report (Cal/EPA, 1997), the evidence from the epidemiological studies of ETS and bladder cancer remains inconclusive. The two ETS specific case-control studies in the previous document and the cohort study cited here found no significant increased bladder cancer risk associated with exposure; serious limitations existed in these studies. However, the biochemical evidence from two biomarker studies was more suggestive of a potential association. Both studies identified higher levels of hemoglobin adducts of the bladder carcinogen 4-aminobiphenyl in nonsmokers exposed to ETS, providing supporting evidence "that nonsmokers exposed to ETS may be at increased risk of bladder cancer."

7.4. ETS and Cancer Sites Where Previous Reviews Have Concluded that Evidence for the Role of Active Smoking is Supportive or Equivocal for Causation: Breast, Stomach, Brain, Leukemia, Lymphomas and Non-Hodgkin's Lymphomas, Other Rare Childhood Cancers

7.4.1. Breast Cancer

7.4.1.1. Active Smoking and Breast Cancer

7.4.1.1.1. Introduction and Previous Findings

Although a number of studies investigating the association between active smoking and breast cancer were available for review in the previous OEHHA report, the overall results were inconclusive, with the majority of studies finding no association or a weak usually statistically non-significant positive association (Cal/EPA, 1997).

As outlined in the previous report, the ability to reach a consistent conclusion is inhibited by various weaknesses found in many older studies. These include bias in the selection of cases and controls from either hospitals (potentially biasing risk downward since controls may have ETS related disease and therefore higher than background exposure) or breast cancer screening programs (potentially biasing risk upward since self selection for screening may select those with lower ETS exposure). Additionally, the older studies of active smoking and breast cancer risk often compare smoking women, whether ever or current smokers, with nonsmoking women regardless of exposure to ETS, and often lack adjustment for other known risk factors (i.e., menstrual and reproductive factors, family history, alcohol intake, social class). When only studies that utilize a never active/never passive exposed reference group are examined, a stronger association between both active and passive smoke exposure and breast cancer is evident (see discussion in Section 7.4.1.4. and 7.ApA.2). The only previously reviewed study that utilized a never active/never passive smoking definition of non-exposure was Morabia *et al.* (1996). Originally designed to investigate the association between ETS and breast cancer, this study reported a significantly elevated breast cancer risk for ever active or current smokers. The prospective study by Calle *et al*. (1994) found significant associations with breast cancer mortality and current smoking at baseline, number of cigarettes per day, years smoked, and age at initiation. Adjustment for known breast cancer risk factors did not change these relationships. In general, cancer mortality studies (such as Calle *et al*., 1994) understate the relationship between disease and exposure, particularly in a chronic disease with good survival such as breast cancer (at least at early diagnosis).

7.4.1.1.2. Recent Surgeon General and IARC Reports

The Surgeon General's 2004 report on active smoking (U.S. DHHS, 2004c) reviewed studies published from September 1992 through 1999 and a few additional up to 2001. The Surgeon General's (U.S. DHHS, 2004c) interpretation of the data on active smoking relies on essentially the same data set examined by OEHHA (1997) and in this report up to 1999, but considered few studies reported between 2000 and 2002. OEHHA considered 23 studies published between 2000 and 2005 whereas the Surgeon General report considered 5 of those studies. Similarly, IARC (2004a) evaluated mostly studies published prior to 1999 with 4 studies published between 2000 and 2002.

The Surgeon General's report concludes that "the epidemiological evidence provides no support for an overall relationship, neither causal nor protective, between active smoking and breast cancer" (U.S. DHHS, 2004c). The report states on page 307, "In conclusion, hypotheses that women with higher levels of exposure to cigarette smoking (i.e., heavy smokers and those who have been smoking since an early age) would have elevated risks of breast cancer have not been supported by data from large studies" and "This null relationship is consistent with the two hypothesized mechanisms, antiestrogenic effects and carcinogenic exposures, that imply countervailing consequences of smoking that both increase and decrease the risk for breast cancer."

The IARC report emphasized the Collaborative Group on Hormonal Factors in Breast Cancer Study (2002). The report concludes based on the overall results that most epidemiological studies have found no association with active smoking after control for confounders and note that the pooled analysis (Collaborative Study) found no effect. The report also notes that in the Collaborative Study no attention was paid to the reported associations with passive smoking, nor was information obtained on age of smoking initiation or the amount smoked.

7.4.1.1.3. Recent Epidemiological Data

Several recently reviewed studies on the association between active smoking and breast cancer demonstrate an increased risk (incidence or mortality). These elevations in breast cancer risk reached statistical significance in most of the recently reviewed studies overall or in some strata, in either active or former smokers after adjustment for multiple reproductive and other risk factors (Millikan *et al.*, 1998; Lash and Aschengrau, 1999; Jee *et al.*, 1999; Johnson *et al.*, 2000; Marcus *et al.*, 2000; Morabia *et al.*, 2000; Egan *et al.*, 2002; Reynolds *et al.,* 2004a; Hanaoka *et al*., 2005; Gram *et al*., 2005). Population based case-control studies found current smoking or former smoking was related to significantly increased breast cancer risk with estimates ranging up to 2.3, varying by age or menopausal status; however, studies were often limited in the number of premenopausal cases. Additionally, evidence for a dose response relationship between breast cancer risk and duration or amount of active smoking was noted in several studies (Millikan *et al.*, 1998; Johnson *et al.*, 2000; Terry *et al*., 2002; Band *et al*., 2002; Kropp and Chang-Claude, 2002; Reynolds *et al*., 2004a; Gram *et al*., 2005).

The more recent epidemiological studies are described in Appendix 7A at the end of Chapter 7. The following conclusions are based on those studies.

7.4.1.1.4. Active Smoking: Discussion and Conclusion

While there continues to be some heterogeneity in study results, overall, the studies presented in Appendix 7A in this update provide evidence of a role for active smoking in causation of breast cancer, and include evidence of dose-response. In 11 of 13 studies examining breast cancer risk from active smoking compared to a referent of never smoking women not exposed to ETS (Figure 7.4.1 below), point estimates were greater than 1 (many of them significantly so). Of the six studies considered by OEHHA as "most informative" based on best exposure assessment and design (see Section 7.4.1.4) (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Hanaoka *et al*., 2005), all have point estimates above unity (Figure 7.4.1 and Figure 7.ApA.1). There are now studies providing some evidence for gene-environment interactions, as well as studies demonstrating susceptible subpopulations with highly significantly increased breast cancer risk associated with active smoking (e.g., those

when comparing smokers to never-active never-passive nonsmokers (OR 2.3; 95% CI 1.2-4.5) after accounting for a number of confounders including reproductive health, SES, and alcohol consumption. When childhood exposures were included, risks increased.

Timing of smoking initiation was also investigated in various studies, with several finding that earlier age of smoking onset or initiating active smoking prior to first childbirth strengthened the reported association (Lash and Aschengrau, 1999; Marcus *et al.*, 2000: Egan *et al*., 2002; Band *et al.,* 2002; Reynolds *et al*., 2004a; Gram *et al*., 2005). Johnson *et al*. (2003), Band *et al*. (2002), and Lash and Aschengrau (1999) found increased risks which reached statistical significance in parous women related to number of years of smoking before a first full-term pregnancy.

Considering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and elevated breast cancer risk.

7.4.1.2. ETS and Breast Cancer

7.4.1.2.1. Introduction and Previous Findings.

Previously, OEHHA examined the association between ETS exposure and breast cancer in four analytical epidemiology studies (one cohort and three case controls studies) (Hirayama, 1984; Sandler *et al.*, 1985a; Smith *et al.*, 1994; Morabia *et al.*, 1996), only one of which was initially designed to investigate the role of ETS in breast cancer (Morabia *et al.*, 1996). Although all four studies were suggestive of an association between ETS exposures and increased risk of breast cancer, risk estimates were modestly elevated and usually not statistically significant. Elevated risk estimates were also not consistent across subsets of women. Some studies found no association with active smoking, but an association with passive smoking. Additionally, no indication of increasing risk of breast cancer with increasing dose or exposure intensity was observed. Overall, the results were considered inconclusive by OEHHA (Cal/EPA, 1997).

Since only brief mention was made of the above studies in the Cal/EPA (1997) document, and since they are used in the development of the summary statistics presented in the conclusion of this chapter, they are summarized below. In addition, the description of an older study by Hirose *et al*. (1995) is also included here since it was not reviewed in the 1997 report.

Hirayama (1984) examined mortality in a prospective cohort of 91,540 nonsmoking wives in Japan during 16 years beginning in 1965. Participants were interviewed in 1965 and tracked by establishing a record linkage system between the risk factor records and death certificates. In his original study he did not report on breast cancer risk other than to mention that it was possibly associated. However, Judson Wells has published more detailed breast cancer mortality data provided to him by Dr. Hirayama in letters to the editor in the American Journal of Epidemiology (Wells, 1991; 1998b). The overall adjusted relative risk in nonsmoking wives exposed to spousal ETS was 1.32 (95% C.I. 0.83-2.09).

Sandler et al. (1985a) examined cancer risk associated with passive exposure to spousal smoking. In this case-control study, cases (n = 518) were 15-59 years of age from the tumor registry of the North Carolina Memorial Hospital diagnosed with cancer in 1979-1981. Controls (n = 518) were matched by sex, age and race. Data collected by mailed questionnaire included

age, race, gender, marital status, occupation, education, and personal and spousal smoking histories. Passive smoke exposure was estimated from the number of years of marriage during which the spouse smoked.

After adjustment for age and education, the risk of cancer among smokers and nonsmokers combined for all sites was 1.6 (95% CI 1.2; 2.1), and for breast cancer specifically, 1.8 (95% CI 1.0; 3.7). Among nonsmokers separately, the risk for breast cancer was 2.0 (95%CI 0.9; 4.3) compared to 2.8 (95% CI 1.0; 7.6) for smokers. While these numbers may suggest an elevated risk for breast cancer from ETS, the number of cases was small (n = 32) and the confidence interval included no effect. For the purpose of developing a summary statistic at the end of this chapter, a summary overall risk estimate was calculated by Wells using data obtained from Dr. Sandler. The overall RR of breast cancer in passively exposed women was 1.62 (95% CI 0.76; 3.44) (Wells, 1998a). A similar statistic was calculated for premenopausal breast cancer by Wells (1991) based on case and control data from Dr. Sandler (personal communication). The calculated OR was 7.1 (95% CI 1.6; 31.3).

Interviews of 649 relatives of subjects showed good agreement between subjects' and relatives' responses regardless of case/control status, suggesting minimal recall bias. There were no estimates of the intensity of ETS exposure, nor exposure from sources other than the spouse. The non-exposed referent likely included individuals exposed to ETS from other sources such as work. Confounders such as diet, health and other lifestyle characteristics were apparently also not adjusted for in the analysis.

Smith et al., 1994. This case-control study examined the relation between breast cancer risk and alcohol consumption, active and passive smoking, and caffeine among women in the UK. It included women diagnosed with breast cancer between 1982 and 1985 before the age of 36. For the analysis of passive smoking, information was obtained by self-administered questionnaire on 170 matched case-control pairs regarding passive smoke exposure in childhood (< age 16), and in adulthood from cohabitants, work and other sources.

In an unmatched analysis of the entire group, there were elevated breast cancer risks associated with ETS exposure during childhood only (RR 1.32, 95% CI 0.16; 10.80) and adulthood only (RR 3.13, 95% CI 0.73; 13.31), but neither was statistically significant. Also non-statistically significant risks were noted for the combined exposure, RR 2.63 (95% CI 0.73; 9.44), and for total lifetime exposures of 1-200 cig-yrs, RR 2.82 (95% CI 1.00; 7.93); > 200 cig-yrs, RR 2.24 (95% CI 0.75; 6.58). For the purpose of developing a summary statistic at the end of this chapter, a summary overall risk estimate was calculated using component risks and confidence intervals reported in the paper for non-smokers (1-200, >200 cig-yrs, Table 5 of Smith *et al*., 1994). We derived crude cell counts from data provided in Smith *et al*. (1994) and if necessary used methods described in Greenland and Longnecker (1992) to obtain missing cell information. From cell counts we calculated a risk estimate that combined all exposure groups. Using a search technique within Microsoft Excel software (Solver tool), adjusted cell counts were calculated from the adjusted RRs. Confidence intervals from these adjusted cell counts were obtained using the Woolf method described in Schlesselman (1982). The RR for breast cancer was 2.53 (95% CI 1.12; 5.71); note that all these women were premenopausal at diagnosis. These values were adjusted for age, region, age at menarche, nulliparity, age at first full-term

pregnancy, breastfeeding, oral contraceptive use, family history of breast cancer, own smoking, biopsy for benign breast disease, and alcohol use.

Information on passive smoke exposure was obtained via a self-completed questionnaire returned by mail, thus minimizing interviewer bias, but the possibility of recall bias remained.

Hirose et al. (1995) conducted a case-control study of the risk factors for breast cancer in relation to menopausal status. Self-administered questionnaires were given to first-visit outpatients at the Aichi Cancer Center Hospital in Japan from 1988 to 1992. Data on occupation, medical history, anthropometrics, marital status, family history of breast cancer, dietary, smoking and drinking habits, reproductive history, and exercise were collected from 36,944 women prior to disease diagnosis. For the study, 1,052 histologically-confirmed breast cancer cases (607 premenopausal, 445 postmenopausal) were compared with 23,163 non-cancer outpatient controls.

From unconditional logistic regression analyses adjusted for age and year of first visit, passive smoking represented a significant risk for postmenopausal (OR 1.39, 95% CI 1.04; 1.85), but not for premenopausal women (OR 1.15, 95% CI 0.91; 1.46). Unfortunately, passive smoking was not subjected to multivariate analysis to control for potential confounding. Additional concern is raised due to the use of non-cancer outpatient controls. Thus the apparent link between ETS exposure and breast cancer must be interpreted with caution since the analysis was not adjusted for potential confounders nor did it take into account potential sources of ETS exposure other than spousal smoking.

Morabia et al. (1996) examined the relationship of breast cancer with active and passive smoking among Swiss women in a population-based case control study. Cases (n = 244) were women <75 years old with a first diagnosis of invasive breast cancer in 1992-1993, while population controls (n = 1,032) were 30-74 years of age. Data were collected by interview with questions covering the major known or postulated risk factors for breast cancer as well as smoking history. Smoke exposure data were recorded year by year from age ten to the date of the interview, and included both passive and active exposures, duration of exposures (hours per day) and intensities (cigarettes per day). In this study, passive exposure was defined as having been exposed to ETS for at least one hour per day for at least 12 consecutive months. Multivariate analyses were adjusted for age, education, BMI, age at menarche, age at first live birth, oral contraceptive use, history of familial breast cancer and cancer biopsy. Dietary data were available for 150 cases and 336 controls, and were used to adjust the multivariate analyses of the whole group (n = 1,276) for alcohol and saturated fat intake.

Passive smoke exposure was associated with an elevated breast cancer risk [OR 2.3 (95% CI 1.5-3.7)] which increased after adjustment for dietary intake [OR 3.2 (95% CI 1.7-5.9)]. Breast cancer risk was also estimated for premenopausal women resulting in a multivariate OR of 3.6 (95% CI 1.6; 8.2) for ever passive exposure.

A strength of this study's design was its ability to quantify potential selection, recall and detection biases. Selection bias was assessed by collecting smoking status on non-participants; the authors indicated there was some *"slightly conservative selection bias* (that) *may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their*

true smoking status." Interviewers were blind to the interviewees' case-control status. No evidence for differential recall between controls and cases was found based on questions regarding attitudes towards ETS exposure. This study thus supports an association of both passive and active smoking with breast cancer.

7.4.1.2.2. ETS and Breast Cancer: Recent Epidemiological Data.

Tables 7.4.1I through 7.4.1M summarize results from published primary studies investigating the association between ETS exposure and breast cancer risk. Several cohort and case-control studies have reported on breast cancer risk and exposure to ETS (Millikan *et al.*, 1998; Jee *et al.*, 1999; Lash and Aschengrau, 1999; Zhao *et al.*, 1999; Delfino *et al.*, 2000; Johnson *et al.*, 2000; Liu *et al.*, 2000; Marcus *et al.*, 2000; Wartenberg *et al.*, 2000; Egan *et al.*, 2002; Kropp and Change-Claude, 2002; Reynolds *et al*., 2004a; Shrubsole *et al*., 2004; Gammon *et al*., 2004). In contrast to previously reviewed studies (Cal/EPA, 1997), many of these more recent reports accounted for a number of covariates that affect breast cancer risk and diagnosis, and utilized never-smoking and not exposed to ETS as the referent exposure definition. The majority of studies presented risk estimates for ETS related to spousal or residential exposure, including spousal only (Jee *et al.*, 1999) or spousal and other smokers in the home (Millikan *et al.*, 1998; Lash and Aschengrau, 1999; Johnson *et al.*, 2000; Marcus *et al.*, 2000; Wartenberg *et al.*, 2000; Egan *et al.*, 2002, Reynolds *et al*., 2004a). A few studies assessed breast cancer risk associated with ETS exposure at work (Johnson *et al.*, 2000; Wartenberg *et al.*, 2000; Egan *et al.*, 2002; Shrubsole *et al*., 2004). Some studies evaluated breast cancer risk in relation to age or menopausal status (Millikan *et al.*, 1998; Morabia *et al.*, 1998; Delfino *et al.*, 2000; Johnson *et al.*, 2000; Morabia *et al.*, 2000; Hanaoka *et al*., 2005). It should be noted that the age or menopausal status in the case-control studies is obtained at diagnosis, but in the cohort studies this information was obtained at enrollment. Although the authors report results by age or menopausal status in some of the cohort studies, the actual age or menopausal status at diagnosis is not identified. This likely misclassifies as premenopausal many who are actually postmenopausal at diagnosis. Some studies evaluated breast cancer risk modification due to genotypic variation in metabolic enzymes, and tumor hormone receptor status (Millikan *et al.*, 1998; Morabia *et al.*, 1998, 2000). As discussed in the conclusions section, overall, the weight of evidence (including toxicology of smoke constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS and breast cancer in younger primarily premenopausal women. Individual studies are discussed below.

7.4.1.2.2.1. Description of More Recent Studies

Millikan et al., 1998. An analysis based on an on-going population-based case-control study, the Carolina Breast Cancer Study (CNCS), examined the effects of active smoking and genetic variation of N-acetylation metabolism (NAT). This report analyzed data from 498 cases and 473 controls with risk estimates adjusted for age, race, reproductive factors, alcohol, and family history of breast cancer. Data were presented for breast cancer risk and ETS exposure (restricted to women never-active smokers with residential exposure after age 18). A small, statistically non-significant, elevated risk of breast cancer associated with residential ETS exposure was reported for all women combined [adjusted OR 1.3 (95% CI 0.9-1.9)], being slightly higher in pre- compared to postmenopausal women [premenopausal adjusted OR 1.5 (95% CI 0.8-2.8); post menopausal adjusted OR 1.2 (95% CI 0.7-2.2)] (Table 7.4.1I). As with active smoking, the effect of NAT1*10 allele or NAT2-rapid/slow acetylation on modifying breast cancer risk with passive smoking was limited (Table 7.4.1K). In premenopausal women, the association of

passive smoke (again compared with never-active smokers/no ETS exposed women) with breast cancer was associated with an elevated, but non-significant risk [adjusted OR 1.7 (95% CI 0.7-4.3)] among women with the NAT1*10 allele which appears stronger than the OR for women with the NAT1-non*10 allele [OR 1.3 (95% CI 0.5-3.2)]. No difference was observed among postmenopausal women. A limitation of this study is the use of a referent population in which adult exposure to ETS was determined by a single question (have you lived with a housemate since the age of 18 years who smoked?). This would result in a referent group containing ETS exposed (e.g., those exposed at work or other settings), biasing results towards the null. A strength of the study is its restriction of the study population to never active smokers, which prevents potential confounding from active smoking.

Jee et al., 1999. This Korean prospective cohort study reported the effects of spousal smoking on the incidence of cancer in women ages 40 and over. A total of 158,927 of 260,359 (61%) eligible non-smoking wives completed an annual examination and questionnaire in 1992 through a Korean health insurance provider. Data was collected from both spouses. Though no data on other sources of ETS were presented, Jee notes that 1.1% of his wives were current smokers, and 0.6% were ex-smokers. Women in Korea do not frequently meet socially with men other than their husbands so their tobacco smoke exposure comes mostly from their husband or an occasional father-in-law. Childhood exposure was not addressed. The incidence of breast cancer was slightly elevated, but not statistically significant, among women married to ex-smokers [adjusted RR 1.2 (95% 0.8-1.8)] and current smokers [adjusted RR 1.3 (95% CI 0.9-1.8] after adjustment for age, socioeconomic status, residency, husband's vegetable intake, and husband's occupation (Table 7.4.1L). Although the limited number of breast cancer cases (n=138) inhibits the ability to stratify by exposure duration with sufficient statistical power, the risk of breast cancer was highest among wives married to current smokers for greater than 30 years [RR 1.7 (95% CI 1.0-2.8)] (no trend data shown). The brief follow-up, only through December 1997 (3.5 years), and restriction of case identification to hospital discharge summaries, may have limited the measurement of cancer burden in this population. Another limitation of this study was lack of consideration of time-since-first-exposure when examining risk by years of passive smoke exposure. Since cancer risk generally goes up with time-since-first-exposure (effect modification), the increased risk seen after 30 years of passive smoking may have been due to increased time-since-first-exposure.

Lash and Aschengrau, 1999. This U.S. case-control study identified 334 incident cases of breast cancer from 1983 to 1986 among residents of five Massachusetts communities. Odds ratios were adjusted for age, parity, family history of breast cancer, body mass index, history of benign breast disease or other breast cancer diagnosis, and history of radiation therapy. Ever active, passive only or nonsmoker (no active or passive) status was determined via interview; the assessment of passive smoking only considered residential exposure. Age of first exposure and total duration of exposure to ETS were evaluated. Odds ratios were adjusted for age, parity, family history of breast cancer, body mass index, history of benign breast disease or other breast cancer diagnosis, and history of radiation therapy. Some odds ratios were additionally adjusted for alcohol consumption.

Passive only smokers had a statistically significantly elevated risk of breast cancer after further adjustment for alcohol [adjusted OR 2.0 (95% CI 1.1-3.7)], when using a never-active, never-passive definition of non-exposure, approximately equal to the risk found in this same study for

ever-active smokers (Table 7.ApA.5). Odds of breast cancer varied inversely with duration of exposure to passive smoke [≤20 yrs: OR 3.2 (95% CI 1.5-7.1); >20 yrs: OR 2.1 (95% 1.0-4.1)] (Table 7.4.1J). In contrast to results for active smoking, passive smoking breast cancer risk was not dependent on, or varied substantially by, exposure prior to versus after first pregnancy. Age of first exposure to passive smoking influenced the risk of developing breast cancer (Table 7.4.1J). Risk of breast cancer increased in women with exposure at younger ages [< 12 yrs old: OR 4.5 (95% CI 1.2-16); 12-20 yrs old: OR 3.8 (95% CI 1.1-13); ≥ 21 yrs old: OR 2.4 (95% CI 0.9-6.1)]. In ever-active smoking women, breast cancer risk was elevated with exposure to passive smoke at younger ages (e.g., living with another active smoker)[< 12 yrs old: OR 7.5 (95% CI 1.6-36); 12-20 yrs old: OR 3.9 (95% CI 0.8-20); ≥ 21 yrs old: OR 4.7 (95% CI 1.6-14)].

This was a retrospective study so some recall bias may be expected. The authors note: *"However, the substantial associations that were found were within the strata defined by time periods calculated from a series of responses. We do not expect these derived exposures to be susceptible to recall bias."* While SES was not measured directly, several potential surrogates such as educational level were added to the regression analysis and found to not significantly affect the results.

Zhao et al., 1999. This case control study was undertaken to identify risk factors for breast cancer among 265 cases in Chengdu, China. Women with breast cancer confirmed by surgery or biopsy were matched to controls by age, living area, profession and education. Data collected by questionnaire included demographics, menstruation history, pregnancies, history of breast disease, breast feeding, oral contraceptive use, active and passive smoking history, alcohol and tea consumption, and other dietary factors. Conditional logistic multivariable regression analysis was based on single factor analysis.

Based on the data provided, the crude risk (OR) of breast cancer among never-smokers exposed to ETS was 2.38 (95% CI 1.66; 3.40). In premenopausal women, the OR was 2.56 (95% CI 1.63-4.01) and in postmenopausal women, 2.38 (95% CI 1.17-3.76) (personal communication between Kenneth Johnson and Zhao, May 2001). This study found elevated risks for breast cancer with passive smoking, as well as for a history of benign breast disease, time from menarche to menopause of ≥ 35 years, oral contraceptive use, and the consumption of bee extract. Risk reduction was associated with alcohol and tea consumption, breast-feeding, and the consumption of fish, vegetables and bean products. However, the analyses were unadjusted for these factors. This and the small size of this study were limitations.

Delfino et al., 2000. This U.S. case-control study recruited women (113 cases, 278 controls with benign breast disease) with suspicious breast masses detected either clinically or by mammography. Smoking status, active and passive, was collected via questionnaire prior to biopsy diagnosis. Passive exposure was considered high if one had lived with a smoker in their home, either usually or some of the time. It was labeled low if this rarely or never occurred. No consideration was made of other possible sources of smoke exposure. Overall, an elevated non-significant effect of passive smoking on breast cancer risk was observed [OR 1.32 (95% CI 0.69-2.52)] compared to never exposed (active or passive) women (all control group), but the analysis did not account for active smoking by the subjects (Table 7.4.1I) or ETS exposure at the workplace. However, when the study population was restricted to never active smokers, the OR for high adult ETS exposure utilizing low-risk controls was 1.86 (95% CI 0.81-4.27). In another

analysis of never active smokers, passive smoking was positively, but not statistically significantly (small sample size, 21 cases) associated with breast cancer risk, among premenopausal women [OR 2.69 (95% CI 0.91-8.00)], but not among postmenopausal women [OR 1.01 (95% CI 0.45-2.27)]. Additionally, no interaction between NAT2 genotype and passive smoking was found. However, the study lacked sufficient power to detect small influences of NAT2 genotype alone on breast cancer risk. This study may have included women with significant non-residential ETS exposure among the never exposed referent group. Limitations of the study include lack of control in some analyses for active smoking by the subjects and an apparent lack of adjustment for alcohol consumption. Prior to biopsy, women took self-administered questionnaires on risk factors. The study included only subjects whose questionnaires were returned by mail prior to receiving diagnosis. Eligible patients, participants and interviewers were all blind to case/control status. Interviewer and reporting bias were thus minimized. Participation rates were similar between those with and those without a diagnosis of cancer.

Johnson et al., 2000. This population-based case-control study utilized data from the Canadian National Enhanced Cancer Surveillance System including 805 premenopausal and 1,512 postmenopausal women with incident primary breast cancer cases. ORs were adjusted for alcohol, education, age, age at first childbirth, adult height, age at menarche, BMI, parity, physical activity and residence. Among never-active smokers the adjusted ORs for breast cancer risk and ETS exposure were 2.3 (95% CI 1.2-4.6) and 1.2 (95% CI 0.8-1.8) for premenopausal and postmenopausal women, respectively (compared to never exposed women, Table 7.4.1I). For all never smokers exposed to ETS, the OR is 1.48 (95% CI 1.06-2.07) (Johnson, 2005). Adjusted premenopausal risk estimates associated with childhood ETS exposure in never-active smokers were 1.6 (95% CI 0.6- 4.4) for childhood only exposure and 2.6 (95% CI 1.2-5.5) for child and adult passive exposure. In this study, childhood included ages 0-19 years. In contrast, no statistically significant elevation in risk was observed for childhood ETS exposure among never-active smoking postmenopausal women [ORs 0.9 (95% CI 0.4-2.0) and 1.3 (95% CI 0.8-2.0), childhood only and childhood/adult combined ETS exposure, respectively].

Additionally, a dose-response relationship between exposure to passive smoking, residential and/or occupational, and breast cancer risk was observed among never-active smokers in premenopausal women [1-6 yrs: OR 1.2 (95% CI 0.4-3.4); 7-16 yrs: OR 1.8 (95% CI 0.7-4.9); 17-21 yrs: OR 2.0 (95% CI 0.8-5.0); 22-35 yrs: OR 3.3 (95% CI 1.5-7.5); 35+ yrs: OR 2.9 (95% CI 1.3-6.6), p for trend 0.0007]. This was not observed in postmenopausal women. This dose-response relationship between total residential and occupational years of ETS exposure and breast cancer risk strengthens the findings for an association (Table 7.4.1J).

In this study, questionnaires were mailed, thereby eliminating interviewer bias. ETS questions were among many others on breast cancer (BC) risk factors. Data from subjects with one of 18 other cancers, including a large sample of lung cancer cases, were also collected in the same data collection (the National Enhanced Cancer Surveillance System). Possible recall or response bias was examined by comparing 71 never smoking women with lung cancer and 714 never smoking women controls, the same pool of controls used for the breast cancer analysis. They found an age-adjusted OR of 1.2 (95%CI 0.7; 7.1) for the association between lung cancer and years of home ETS, similar to estimates found in recent meta-analysis. The authors use the lung cancer results to suggest that bias is likely not seriously affecting the breast cancer risk estimate.

Furthermore when Johnson *et al*. examined the risk of active smoking in the traditional way (ignoring ETS exposure) the observed breast cancer risk was 1.0 for premenopausal women and 1.2 for postmenopausal women, consistent with other studies using contaminated referent populations in the literature. Strengths of the study included adjustment for known risk factors such as alcohol and education, and restriction of the population to never active smokers to avoid confounding from active smoking. A limitation of the study was lack of consideration of time-since-first-exposure in the dose-response analyses where dose was length of ETS exposure.

Rookus et al. (2000) described in an abstract their analysis of a Dutch population-based case-control study (n = 918) of breast cancer and oral contraceptives, in which lifetime histories of active and passive smoking were collected by interview. Passive smokers were defined as lifetime non-smokers with at least 20 years daily domestic or occupational exposure to ETS, or if someone smoked daily in their bedroom for more than one year. ORs were adjusted for lifetime physical activity level and other potential confounders. When passive smokers were included in the reference group of never smokers, the ORs for current and ex-smokers were 1.0 (95% CI: 0.8-1.3) and 1.3 (95% CI: 1.0-1.6), respectively. When passive smokers were excluded from the reference group, the risk of breast cancer among passive smokers was increased (OR: 1.2, 95% CI: 0.8-1.7). This risk was comparable to the risks of current smokers and ex-smokers relative to non-exposed controls (OR: 1.2, 95% CI: 0.8-1.6 and 1.4, 95% CI: 1.0-2.0, respectively). Differential effects of passive exposure before first pregnancy or on P53 over-expression were not detected. This study is of interest in that ETS exposure from both domestic and occupational situations was measured, and it directly addresses the concern that many studies may miss the effect of active smoking if passive smoking is inadequately measured and controlled for. The authors state: "In conclusion: passive smoking seems to slightly increase the risk of breast cancer comparable to the risk increase following active smoking. Therefore, in studies on active smoking and breast cancer risk, the risk estimates will be biased to zero if passive smokers are included in the reference group."

Woo et al. (2000) described a population-based, nested case-control study in Washington County, MD. In 1975, the smoking status of adult household members was determined by census. Incident breast cancer cases (n = 706) during the subsequent 17 years were identified among women census participants through the Washington County Cancer Registry, along with age matched controls (n = 1,426). For all never active smokers, passive smoke exposure was not associated with breast cancer overall (OR 1.04, 95% CI 0.83-1.33). This was also true for postmenopausal never smokers (OR 0.91, 95% CI 0.71-1.18). (Postmenopausal was defined as age ≥ 50 years; it is assumed that this refers to age at diagnosis although the report does not state this explicitly.) However, there was a significantly elevated risk of breast cancer in premenopausal never-smoking women exposed to ETS, relative to those not exposed (OR = 2.78, 95% CI 1.37 - 5.63). Determination of ETS exposure status appears from the limited report to have been on the basis of cohabitation with a smoker at the time of the census. As noted elsewhere, this ignores other ETS exposure situations (e.g., occupational) that are significant for many study populations, and also does not provide information on age or parity at the time of exposure. No efforts to control for confounding factors are described. In spite of these limitations of the study, the authors note an association between ETS exposure and premenopausal breast cancer, although the overall result for all cases (pre- and postmenopausal) is nonpositive. This is consistent with several other studies reporting increased risk of premenopausal breast cancer.

Liu et al. (2000) conducted a case-control study from 1994-1996 in China, to investigate the roles of ETS exposure and other early life factors in the etiology of breast cancer. The study included 186 cases of histologically confirmed breast cancer in women, 24 to 55 years of age, who were diagnosed in a university teaching hospital. Controls, matched for age at diagnosis, date of diagnosis, and marital and never-smoking status, were selected from cancer-free women visiting the same facility. A standardized questionnaire was used in interviews to collect historical information about ETS exposure during childhood (<10 years of age), youth (10-16 years of age) and adulthood. For the two early periods, data regarding passive smoke exposure, body weight and height, history of diseases leading to hospitalization, life stress, and family economic situation were collected. For adulthood, information was also collected on passive smoke exposure at work. In the final multiple logistic regression analyses, ORs were calculated for each of the following factors after controlling for the other listed factors: passive smoking at home in childhood, passive smoking at home in adulthood, passive smoking in the workplace in adulthood, age at menarche, low body weight in childhood, overweight in adulthood, family economic situation in youth, history of hospitalized diseases in childhood and youth, history of benign breast disease, and history of life stress.

ETS was significantly associated with an increased risk for breast cancer following exposure at home in childhood (OR 1.24, 95% CI 1.07; 1.43), at home in adulthood (OR 4.07, 95% CI 2.21; 7.50), and in the workplace (OR 1.27, 95% CI 1.04; 1.55). Of the listed factors, only age at menarche was not associated with increased risk. The above mentioned statistics are striking in light of this study being relatively small, thus limiting its ability to detect robust associations. The study population was hospital-based and may not be representative of the general population. Recall bias is a concern regarding the early-life exposures and conditions. We were unable to obtain the raw data or other clarifying information from the author and thus consider that these statistics must be evaluated with caution.

Marcus et al., 2000. This population-based case-control study, the Carolina Breast Cancer Study, analyzed data from 864 incident breast cancer cases (diagnosed between May 1993 and May 1996) and 790 controls, to evaluate the relationship between adolescent exposure to ETS and breast cancer risk. Overall response was 77% cases and 68% controls. Residential exposure to ETS prior to age 18 (in a combined grouping of ever and never active smokers) was not associated with an increased risk of breast cancer [adjusted OR 1.1 (95% CI 0.9-1.3)] after adjustment for race and age at diagnosis/selection. Results did not differ by years of exposure or early/late age at diagnosis (< 50 years vs. ≥ 50 years). Exclusion of active smokers from the analysis of passive smokers for exposure before age 18 reduced the risk estimate to below unity [adjusted OR 0.8 (95% CI 0.6-1.1)] (Table 7.4.1I). The data in this paper are of limited usefulness in evaluation of breast cancer risk from passive smoking in non-smokers, since the only assessment of risk to nonsmokers looked solely at residential passive smoke exposure before age 18 and not for any other time period or source (i.e., occupational).

The authors suggest that differential recall between cases and controls regarding adolescent smoke exposure was unlikely since an association between adolescent smoke exposure and breast cancer is not generally perceived. On the other hand, the authors acknowledge that misclassification is likely regarding the timing of thelarche vis-à-vis smoke exposure but they suspect it would be non-differential.

Morabia et al., 2000, 1998. This population-based case-control study in Geneva, Switzerland investigated the association of breast cancer with passive and active smoking (Morabia *et al.*, 1996, described in Cal/EPA, 1997). Two hundred and forty-four cases were enrolled (71 percent of eligible cases) in an earlier study (Morabia *et al.*, 1996); however, biological samples were obtained from 170 of the possible 205 eligible cases still alive and residing in Geneva (Morabia *et al.*, 2000). In the more recent analysis by these investigators, the additional influence on risk of slow and fast acetylation, based on genotypic variation in N-acetyltransferase 2 (NAT2), was also determined (Morabia *et al.*, 2000). In never active smoking women, pooling premenopausal and postmenopausal women, the adjusted OR of breast cancer was 3.1 (95% CI 1.5-6.0) for ever passive smokers (adjusted for age, education, and family history of breast cancer) compared to never-exposed women (no active or passive smoking exposure). After stratification by NAT2 status, breast cancer risk with ever passive smoking increased for high acetylators (all women). In premenopausal women, the NAT2 genotype did not influence the adjusted OR 3.2 (95% CI 1.2-8.7). However, among postmenopausal women, a statistically significant association with breast cancer was found in fast acetylators with ever passive smoking [adjusted OR 11.6 (95% CI 2.2-62.2)], with no effect observed in slow acetylators [adjusted OR 1.1 (95% CI 0.3-4.3)] (Table 7.4.K).

Passive tobacco smoking was a risk factor for both estrogen receptor positive (ER+) and negative (ER-) tumors among both pre- and postmenopausal women (Morabia *et al.*, 1998). For all women combined (pre- and postmenopausal), passive smoking risk for ER- tumors was similar to the risk for active smoking [age-adjusted OR 3.8 (95% CI 1.5-10.0)]. ER+ breast cancer risk among passive smokers was lower [age-adjusted OR 1.8 (95% CI 1.1-3.0)].

Wartenberg et al., 2000. This large cohort study examined the association between breast cancer mortality and ETS exposure from spousal smoking. As part of an American Cancer Society prospective cohort (CPS-II), a cohort of 146,488 never smoking, single-marriage women was derived from a total female enrollment of 676,306 in 1982. Breast cancer death rates among women with husbands that smoked were compared with women married to nonsmokers. The CPS-II is a convenience sample (volunteer recruitment and enrollment) across the United States and Puerto Rico. Data on a variety of demographic and personal risk factors were identified via questionnaire. After 12 years of follow-up (through December 1994), 669 breast cancer-related deaths occurred. Overall, no association between ETS exposure (as defined by a smoking spouse) and death from breast cancer was observed [RR 1.0 (95% CI 0.8-1.2)] (Table 7.4.1L). Breast cancer death rates did not vary between never-smoking women married to nonsmokers, former smokers, or current smokers (age adjusted and multivariate-adjusted rates). Additionally, breast cancer mortality rates did not show a statistically significant increase with spousal smoking intensity (packs per day), spousal duration (years of smoking), or spousal cumulative exposure (pack-years). A statistically insignificant elevation in risk of death due to breast cancer was observed in women married before age 20 to current smokers [RR 1.2 (95% CI 0.8-1.8). Relative risk estimates were adjusted for multiple factors including age at entry into the study (in 1982), race, education, history of breast cancer in primary relative, multiple reproductive factors, alcohol, body mass index, multiple dietary factors, and occupation. For the purpose of developing a summary statistic at the end of this chapter, a summary risk estimate was calculated for premenopausal women using component risks and confidence intervals reported in the paper for non-smokers (combining risk ratios for current and former smoking spouses for age < 50 years; table 6). We derived cell counts from data provided in Wartenberg *et al*. (2000) using

methods described in Greenland and Longnecker (1992) to obtain missing cell information. From cell counts we calculated a risk estimate comparing the combined exposure groups to the referent. Confidence intervals were obtained using the Woolf method described in Schlesselman (1982). Thus, for premenopausal women the derived RR is 1.15 (95% CI 0.82-1.60).

Although, the study's large size and prospective design lend strength to investigating the association between breast cancer death and spousal ETS exposure, breast cancer mortality (as opposed to incidence) is a more limited outcome for identifying overall risk of breast cancer. Death due to breast cancer depends on many factors, particularly stage at initial diagnosis, and access to and quality of treatment, which influence survival. As an overall outcome measure, breast cancer mortality remains imprecise, and may severely underreport the total breast cancer burden in a study population. Concerns have been raised that the lack of measure of nonspousal ETS exposure diluted this study's ability to identify an association between breast cancer risk and passive smoking (Johnson, 2001; Wells, 2001). In response, Wartenberg *et al.* (2001) reiterated that no association was observed between breast cancer risk and self-reported exposure either at work [RR 0.8 (95% CI 0.6-1.0)], at other locations [RR 0.9 (95% CI 0.7-1.2)], or when all sources were combined and examined according to daily hours of exposure (data available on 128,295 women) (Wartenberg *et al.*, 2000). Nevertheless, since the ETS exposures other than from spouse were included in the questionnaire only at one time, namely, at enrollment, the potential for substantial historic exposure misclassification exists (Johnson, 2001). Another limitation was lack of consideration of time-since-first-exposure in the dose-response analyses.

Nishino et al. (2001) investigated the effects of spousal smoking among a cohort of 9,675 lifetime non-smoking women completing mailed self-administered questionnaires in 1984 (total response rate of 96% for men and women). Individuals were followed for 9 years with cancer cases identified through record linkage with a population cancer registry. ETS exposure was based on spousal smoking at time of initial survey.

The adjusted relative risk for breast cancer associated with having a smoking husband was not elevated [RR 0.58 (95% CI 0.32-1.1) Table 7.4.1L]. No change to this inverse relationship to breast cancer risk was reported after additional adjustment for alcohol, dietary factors, and residential area.

Although the study adjusted for several potentially important confounding factors, including dietary intake of vegetables, it was limited by a single ETS measurement at baseline and by not including sources of ETS exposure other than husband (other residential, occupational, or childhood). Also, according to the authors, "In this study, women were not asked about their marital status in the baseline survey, so most unmarried women, who are a high-risk group for breast cancer, were categorized as not being passive smokers. This may have been why the breast cancer risk was lower with passive smoking exposure…." Thus, the authors conclude, this study must be interpreted with caution with respect to the association between passive smoking and breast cancer.

Egan et al. (2002) used the U.S. Nurses' Health Study cohort to analyze the influence of active and passive smoking on the incidence of invasive breast cancer. Although the Nurses' Health Study was established in 1976, this analysis includes 78,206 women followed prospectively from 1982 until June 1996, reporting 3,140 cases of invasive breast cancer. The relative risks of

breast cancer for passive smoking among never-active smokers remained near unity for several exposures including maternal smoking [adjusted RR 0.98 (95% CI 0.70-1.38)], or smoking by both parents [adjusted RR 0.92 (95% CI 0.76-1.13)]. Paternal smoking alone had a slightly elevated but non-significant positive association with breast cancer [adjusted RR 1.12 (95% CI 0.99-1.27)] (Table 7.4.1L). Current passive smoking (as reported in 1982 questionnaire) was also unrelated to breast cancer risk, either at home or work [adjusted RR 1.00 (95% CI 0.83-1.20)], or both settings combined [adjusted RR 0.90 (95% CI 0.67-1.22)]. The risk associated with cohabitating with an active smoker for 30 or more years was not elevated [adjusted RR 1.03 (95% CI 0.86-1.24)] (Table 7.4.1M). For the purpose of developing a summary statistic at the end of this chapter (Section 7.4.1.3), a summary risk estimate was calculated for women using component risks and confidence intervals reported in the paper for non-smokers (combining risk ratios for currently exposed at work or home in table 1 of the paper using methods previously described for Smith *et al*., 1994). The resulting RR for all women ever exposed to ETS is 1.06 (95% CI 0.90-1.25).

This large, prospective study fails to find an association between passive smoking and breast cancer risk. However, the passive smoking analyses reported for this study did not exclude all women with regular passive smoking exposure (childhood or adult) from the referent exposure category. This potential misclassification of passive-smoking status may significantly inhibit the ability to observe an association. Additionally, occupational exposure to ETS was based on one historical time point, in 1982, limiting the ability to establish lifetime workplace exposure. Since over one half of the entire cohort was reported to be active smokers and most reported initiation of smoking by 22 years of age, a large percentage of the "never active smokers" would have likely had significant exposure to ETS in nursing school and hospital training during a susceptible time period (prior to first pregnancy). These factors could lead to misclassification of ETS exposed nonsmokers as non-exposed, thereby reducing apparent risk. While there was no direct control for SES in this study it is assumed that since this is a cohort based on occupation and education level, the socioeconomic status is relatively homogeneous.

Kropp and Chang-Claude, 2002. This case-control study examined the association between active and passive smoke exposure and breast cancer risk in women up to 50 years of age in two regions of southern Germany. It was based on a population-based study of breast cancer conducted from 1992-1995. Cases (among never active smokers) were defined as having incident in situ or invasive breast cancer diagnosed under the age of 51 (n = 197), and were matched by age and study region to 459 randomly selected controls. Data on demographics, anthropometrics and potential risk factors were collected by self-administered questionnaire. Detailed smoking histories were obtained in 1999 from surviving patients during a followup telephone interview, and included information on age at start of smoking, amount and frequency of tobacco use, intensity of inhalation and date of changes in smoking habits. Passive smoke exposure was assessed for the childhood household, the adult household and for work. Ever passive smokers had an average ETS exposure of more than 1 hour per day for at least a year in either childhood or adulthood. The referent exposure category included only never smokers who had no residential or occupational ETS exposure. Multivariate analyses were adjusted for number of months of breastfeeding, BMI, education, family history, menopausal status and alcohol intake. Number of pregnancies, use of oral contraceptives, age at menarche and at first pregnancy, were found not to influence estimates and were not included in the statistical models. There was no control for diet or other medical conditions. After stratification for age (in 5-year

increments), ever passive exposure was associated with an adjusted OR for breast cancer of 1.59 (95% CI 1.06; 2.39) (Table 7.4.1I). The timing of ETS exposure in relation to breast cancer was also examined. ETS exposure only during childhood was not significantly associated with increased risk [OR 1.11 (95% CI 0.55; 2.27)]. However, significant risks were associated with exposure as an adult [OR 1.86 (95% CI 1.16; 2.98)] or during both childhood and adulthood [OR 1.63 (95% CI 1.03; 2.57)]. Regardless of its intensity (low or high), passive smoke exposure elevated the risk of breast cancer among nonactive smokers.

Because of its case-control design, this study may be susceptible to recall bias especially with respect to childhood exposure. However, the results of the telephone interview, conducted in 1999, were consistent with those of the questionnaires in the 1992-1995 study upon which the current study was based, thus increasing confidence in the more recent responses. The authors note that there was "*no great change in recall for active smoking between the first questionnaire and the follow-up interview even though smoking was only a minor aspect of the initial questionnaire. Taking into account the good quality of the other assessed factors, it seems unlikely that the reporting of active or passive smoking should be greatly biased by case/control status*."

Chang-Claude et al. (2002) examined the role of polymorphisms in the N-acetyltransferase 2 (NAT2) gene in the effects of active and passive smoke exposure on breast cancer risk. The current study, conducted in 1999-2000, was based on a population-based case-control study of 706 breast cancer patients and 1,381 controls conducted in Germany in 1992-1995. Data, including active smoking, were collected by self-administered questionnaire. Questions about childhood, adult and workplace smoke exposures were included. The reference group contained neither ever-active smokers (>100 cigarettes in their lifetimes) nor ever-passive smokers (> 1 hr ETS per day for at least 1 year).

Smoke exposure was associated with increased risks of breast cancer that were similar in passive (OR 1.5, 95% CI 1.0; 2.2) and active (OR 1.4, 95% CI 0.9; 2.2) smokers. ETS exposure in childhood was not associated with increased risk. However, among adult rapid acetylators with long-term ETS exposure, there was a significantly elevated risk (OR 2.91, 95% CI 1.12; 7.59) that was not seen among slow acetylators.

This study was limited by its small size and recall bias was possible. However, as noted in the related study above, it was unlikely that reporting of active or passive smoking would be biased by case/control status.

Lash and Aschengrau, 2002. This case-control study of the association between active or passive smoking and breast cancer was conducted in a manner similar to their earlier study on this same topic (Lash and Aschengrau, 1999), but in a different population. The 666 cases were diagnosed with invasive breast cancer between 1987 and 1993 and, along with 615 controls, were drawn from residents of eight Massachusetts towns on Cape Cod. Smoking status was determined as ever active, ever passive only, and never active never passive. Odds ratios were adjusted for a history of radiation therapy, BMI, family history of breast cancer, histories of breast cancer and/or benign breast disease, alcohol consumption, age at first birth and parity.

In contrast to their previous study (Lash and Aschengrau, 1999), for passive only smoking no association with the risk of breast cancer was found based on duration of exposure (0-20, 20-40, >40 yrs) or age at first residence with a smoker. When the first pregnancy was used to demarcate ETS exposure, there was a slight but not statistically significant risk associated with ETS only exposure prior to the first pregnancy (OR 1.1, 95% CI 0.64-1.9). Passive exposures before and after, or exclusively after the first pregnancy were associated with even lower ORs (0.85, 95% CI 0.56-1.3 and 0.55, 95% CI 0.31-0.96, respectively).

The cases in this study were matched to controls by age and vital status but no information was provided on either the age distribution or the menopausal status of the participants, both of which may be important in the interpretation of the reported null result. The only information in the paper regarding potential bias is: *"Given that smoking history and history of residential passive smoke exposure should be well recalled, and given that an earlier investigation using a similar survey and population yielded causal results, we doubt that non-differential misclassification of exposure status accounts for the null results reported here."*

These results are in apparent conflict with the authors' earlier study. The present study was published as a brief communication and a more detailed report addressing these issues may be forthcoming.

Shrubsole et al. (2004) analyzed data from the population-based Shanghai Breast Cancer Study (SBCS) to investigate the association between ETS exposure and the risk of breast cancer in women 25-64 years of age. Interviews of 1,459 women with breast cancer and 1,556 controls, frequency matched for age, provided data on demography, menstrual and reproductive history, diet, cancer and other disease history, weight, and physical activity. Questions about passive smoke exposure were added seven months after the initiation of the study, and collected data on exposures both at home (spousal) and at work from 1,119 cases and 1,231 controls. The analyses specifically excluded women with past or current histories of active smoking. Unconditional logistic regression was used to obtain risk estimates after controlling for breast cancer in a first-degree relative, history of fibroadenoma, ages at menarche, first live birth and menopause, BMI, physical activity, age, education, and menopausal status.

There was not a significant association between workplace ETS exposure and breast cancer among postmenopausal women. However, among premenopausal women (OR 1.6; 95% CI 1.0-2.5) and all women combined (OR 1.6; 95% CI 1.0-2.4), the association approached significance at the highest exposure levels with a significant dose-response trend (P for trend =0.02, 0.03, respectively; Table 7.4.1J). There was no apparent association of breast cancer with spousal smoking. While the combination of spousal exposure and high exposure at work resulted in elevated risk, these results were not statistically significant. For the summary risk estimates presented in Section 7.4.1.3, an ever-exposed grouping was created (as described for Smith *et al.*, 1994) by combining workplace only (OR 1.1; 95% CI 0.8-1.5), husband only (OR 0.9; 95% CI 0.7-1.2), and husband and workplace (OR 1.1; 95% CI 0.8-1.4) categories yielding an OR 1.02 (95% CI 0.81-1.29). A similar procedure was performed for evaluating premenopausal women yielding an OR 1.10 (95% C I 0.83-1.46).

Strengths of this study include its large size, population-based design and high participation rate. It is limited by having no exposure data on household ETS sources other than the husband, or on

passive smoke exposure during childhood. As a result, there may have been some exposure misclassification that contributed to the observed results. Interviews were conducted in person and may have been subject to interviewer bias. Assessment of workplace ETS exposure was limited to the preceding five years but assumed to reflect longer-term exposure. However, this assumption was not verified. Selection bias is thought to have been limited by the population-based design and the high participation rate (91.1%). The data in general are suggestive of increased risk for breast cancer among premenopausal women exposed to ETS at work.

Reynolds et al. (2004a) conducted a prospective analysis of breast cancer risk associated with passive and active smoking in the California Teacher Study (CTS), a large cohort of professional school employees. Of the 329,000 eligible women, 35% (116,544) were included in the study and followed from 1995 to 2000. A survey at baseline collected information on smoking history among active and former smokers, as well as on passive exposure among never-smokers. Never-smokers were categorized as passively exposed if they reported ever having lived with a smoker. This group was subdivided based on the period of ETS exposure: during childhood only, only as an adult, or with exposure during both periods. No other sources of ETS exposure were included. Other risk factors included in multivariate analyses were age, ethnicity, family history of breast cancer, alcohol consumption, age at menarche, pregnancy history, physical activity, BMI, menopausal status, and estrogen hormone therapy. While socioeconomic status was not explicitly addressed in this analysis, the nature of the cohort likely limits disparity in this variable. Among the 116,544 women in the cohort, 2,005 breast cancer cases were identified. The subset of never-smoking women (n = 76,189) included 1,150 breast cancer cases. Hazard ratios (HR) were estimated based on Cox proportional hazard regression models.

This study found no association between passive smoke exposure and breast cancer among never-smokers regardless of exposure period (childhood, adult, both), or menopausal status (Table 7.4.1L). It should be noted, however, that in this study premenopausal status is actually women who were pre- or perimenopausal at enrollment. A significant percentage of these would have become postmenopausal during the 10 year study and some cases termed “premenopausal” would have actually been postmenopausal at diagnosis. While this study has the advantages of being large, prospective, and designed specifically to examine breast cancer, the current analysis is limited in its assessment of ETS exposure. Characterizing exposure solely based on living with someone who smokes gives no information on intensity or duration of exposure and may miss significant exposures from other sources. Indeed, the authors note that beginning in the 1980s, the major exposure source was non-residential rather than residential for this cohort (Reynolds 2004b). This could lead to nondifferential exposure misclassification that could significantly dilute the apparent risk. In addition, since the exposure assessment was only made at baseline, there is no information regarding possible changes in smoke exposure or in other risk factors. In this context, the lack of association between ETS and breast cancer is difficult to interpret.

Gammon et al. (2004) utilized data collected for the Long Island Breast Cancer Study Project to evaluate the effects of both active and passive tobacco smoke exposure on breast cancer incidence. Cases were women residents of Nassau and Suffolk Counties on Long Island of any age or race newly diagnosed with in situ or invasive breast cancer between August 1, 1996 and July 31, 1997. The racial distribution indicated study participants were primarily Caucasian, and subject education levels were high. Information on active and passive smoke exposure (in the

home only), alcohol use, menstrual history, hormone use, demographics, physical activity, pregnancy history, occupational history, residency history, pesticide use, and a number of other factors were obtained by interviewer-administered questionnaire. Breast cancer risk was evaluated in relation to active smoking, passive exposure only, active and passive exposure or neither, using unconditional logistic regression and accounting for a large number of covariates. These covariates included parity, age at menarche, number of live births, lactational history, oral contraceptive use, hormone replacement therapy, body mass index, family history of breast cancer, dietary intake of fruits and vegetables, and several other factors. Work exposure and other exposure to ETS were not evaluated in this study.

For all women, there was no statistically significant elevation in odds ratio compared to never exposed for passive smoking only (residential exposure), active smoking, or both active and passive smoking (Table 7.4.1.J). Risk appears to be elevated slightly for active plus passive smokers, although not significantly. The authors note that the OR increases slightly to 1.22 (95%CI 0.90-1.66) for ETS exposure when exposure is of long duration (>361 months).

The analyses of smoke exposure (active, passive or otherwise) did not indicate elevated risks for childhood exposure (prior to age 18), exposure before first full-term pregnancy, by menopausal status, body mass index, alcohol intake, use of oral contraceptive, or use of hormone replacement therapy. In those with a family history of breast cancer, exposure to passive smoke only is associated with elevated risk (OR 1.49), but with broad confidence interval including no effect (95%CI 0.79-2.82).

When data for ever passively exposed to spousal smoking (as opposed to any residential exposure) were examined, significantly elevated risks were noted for exposure for 1-181 months (OR1.50; 95%CI 1.05-2.14) or for 326 months or longer (OR2.10; 95%CI 1.47-3.02) (Table 7.4.1J); risks for exposures to spousal smoking for 182-325 months were not elevated (although they had the fewest cases in this category). These data thus provide some evidence of an association between long-term exposure to passive smoking from the spouse and elevated risk of breast cancer.

This study's strengths include: accounting for a large number of confounders, an overall large sample of cases and controls, a lifetime assessment of residential passive smoke exposure and active smoking history, and a referent group that excluded active smokers. However, similar to many ETS studies, data on sources of exposure other than that in the home are lacking. Thus there may be nonsmokers in the non ETS-exposed category that were exposed to ETS at work. This type of misclassification biases towards the null.

Hanaoka et al., (2005) investigated the role of tobacco smoke exposure in the etiology of breast cancer in a prospective cohort study of middle-aged Japanese women. In 1990, a self-administered questionnaire collected baseline data on personal and family medical histories, smoking habits, alcohol use, dietary habits and other lifestyle factors. Passive smoking was defined as a history of exposure to residential ETS or routine exposure to ETS in any work and/or public setting. The age at onset (before or after 20 years of age) for residential exposure and frequency of exposure (for current occupational/outside home exposure) were also determined. Cancer incidence and mortality data were collected during follow-up through the end of 1999. Of the 21,805 women participating in the study, 180 developed breast cancer.

Relative risks were estimated by the Cox proportional hazards model with adjustment for age, area, education, employment status, BMI, family history of breast cancer, benign breast disease, age at menarche, parity, menopausal status, and hormone and alcohol use. Fruit and vegetable consumption were not included as they had little effect on the estimates. No data were available on breast-feeding.

There was a significantly elevated risk of breast cancer among premenopausal never-smoking women with ETS exposure (RR 2.6, 95% CI 1.3; 5.2) (Table 7.4.1L). However, after menopause, no elevated risk was evident. Among all women (pre- and postmenopausal), active smoking was associated with an elevated risk of breast cancer that was of borderline statistical significance (RR 1.7, 95% CI 1.0; 3.1), while the risk for passive exposure in never smokers (RR 1.10; 95% CI 0.80-1.60) was not significant.

In pre-, but not postmenopausal women, ETS exposure in occupational and/or public settings was associated with an elevated breast cancer risk (RR 2.3, 95% CI 1.4; 3.8). Also in these settings, a significant exposure-response trend was observed [almost none, RR 1.0; 1-3 days/month, RR 0.6 (95%CI 0.4; 2.4); >1 day/week RR 2.2 (95% CI 1.4; 3.7); p for trend 0.002] (Table 7.4.1M).

This prospective population-based study has the advantages of general applicability and limited recall or selection bias. This is the first prospective cohort study to utilize a referent population that excluded both ETS exposure in childhood and from adult residential and occupational sources. Smoking habits and passive exposures were assessed in more than one environment, and thus better capture the subjects' actual exposures than studies based on marriage to a smoking spouse. However, no biochemical determination of exposures was done and exposure was only assessed at baseline for occupational/outside home sources. Cessation of smoke exposure during the 10-year follow-up could result in some misclassification that might bias the results towards the null. Some strata in the analysis are only sparsely populated thus limiting the study's power to detect an effect in those strata. Nevertheless, this study provides clear evidence that both passive and active smoking significantly increase the risks of breast cancer among premenopausal women, and that there is significant exposure-response for passive smoking. In this study, postmenopausal women were not found to be at higher risk from passive smoke exposure.

7.4.1.2.3. Meta-analysis

Three meta-analyses have appeared in the recent literature, one as a published paper (Khuder and Simon, 2000), one in a book chapter (Morabia *et al*., 2001), and another in a published letter (Wells, 1998a). In addition, OEHHA presents a meta-analysis below.

Khuder and Simon (2000) conducted a meta-analysis of eleven studies published between 1984 and 2000 that examined the association between ETS and breast cancer. The bulk of these studies, comprising three cohort and eight case-control studies, have been reviewed in this and the previous OEHHA document (Cal/EPA, 1997). Due to heterogeneity among the studies, a random-effects model was employed that gave a combined risk estimate (OR) of 1.41 (95% CI 1.14-1.75). This estimate was based on both published and unpublished studies. The estimate from the seven published studies was similar (OR 1.43; 95% CI 1.10-1.85). Among seven studies that stratified by level of passive exposure, the ORs for the lowest level of exposure

ranged from 0.80 to 3.10, and for the highest levels, from 1.10 to 3.20. A positive dose-response relationship was reported in all seven studies, with a significant test for trend in two cases. All studies in this analysis found elevated risks, seven of which were statistically significant, thus supporting an association of ETS exposure with breast cancer.

Morabia *et al*. (2001) conducted a meta-analysis of six studies of breast cancer and passive smoking, including 5 case-control and one prospective study, and provide a pooled risk estimate for these studies indicating significant associations between ETS exposure and breast cancer (OR1.7; 95% CI 1.3-2.3). Four of these studies were evaluated by Wells (1998a), who derived a pooled estimate of 1.71 (95% CI 1.30-2.25).

Thus, meta-analytic studies provide, statistically significant point estimates for breast cancer which indicate a modest association with ETS exposure. Our own meta-analysis discussed below also provides positive statistically significant effect estimates for breast cancer risk [OR 1.25 (95% CI 1.08-1.44) overall for 19 studies; 1.68 (95% CI 1.31; 2.15) for premenopausal women in 14 studies).

7.4.1.3. OEHHA Summary Risk Estimates

OEHHA worked with Dr. Kenneth Johnson (Health Canada) to review published studies reporting on breast cancer risk associated with passive smoking among women who report never having smoked, and to conduct meta-analysis of those studies. The studies were then classified by their ability to identify a measure of lifetime exposure to ETS (Table 7.4.1A below). Studies of passive smoking and breast cancer from 1984 through January 2005 were identified through a literature search, reviews of the literature, and data call-in (as discussed in Chapter 1). Minimum criteria for inclusion in the meta-analysis were: 1) the study was published in the peer reviewed literature; 2) the study utilized established epidemiologic design (case-control or cohort study); 3) a quantitative measure of exposure to passive smoke was reported; 4) the study allowed examination of the effect of passive smoking among never-smoking women. Several studies abstracted in this section failed to meet these criteria and were not included in the meta-analysis because they were published only as abstracts (Rookus *et al*., 2000; Woo *et al*., 2000), did not present separate data for never smokers (Marcus *et al*., 2000), or had data that appeared inconsistent and that could not be verified by contacting the author (Liu *et al*., 2000). As noted in Chapter 1, the overall meta-analysis uses risk estimates from individual studies that are based on the least stratification in order to represent the "overall exposed" versus referent group. Thus, the pooled estimates are biased towards the null as the analysis does not incorporate elevated risk estimates for higher exposure groups, or other susceptible populations. We also conducted meta-analysis of data for women who were premenopausal or younger than age 50 at diagnosis in the case-control studies or at baseline in the cohort studies. A version of this analysis, authored by Dr. Johnson, has been published (Johnson, 2005).

7.4.1.3.1. Overall Risk in Women of All Ages

Nineteen studies were utilized for a meta-analysis, which yielded a summary risk estimate of 1.25(CI 1.08-1.44) for breast cancer overall in all exposed women (see Table 7.4.1B and Figure 7.4.2 below). However, the risk estimates were heterogeneous ($p<0.001$). OEHHA separately evaluated studies which included all major sources of lifetime passive smoke exposure (combined childhood residential, adult residential and occupational as defined in Table 7.4.1A

below). When the summary was limited to the five studies which satisfied this exposure assessment criteria (all were case-control studies), the summary risk estimate was 1.91 (95% CI 1.53 - 2.39) and statistical tests were consistent with homogeneity (p= 0.235). This is consistent with the analyses by Wells (1998a), Morabia *et al*. (2001), and Khuder and Simon (2000) cited above. Using just the studies that did not include all major sources of lifetime passive smoke exposure, the estimated summary risk was 1.06 (95% CI 0.96-1.17). Among these studies, the cohort studies and the case-control studies yielded summary estimates of 1.02 and 1.14 respectively. These results support the assertion that poor exposure assessment biases the results towards the null.

7.4.1.3.2. Risk in Younger (Primarily Premenopausal) Women

Analysis of the 14 studies where passive smoking-premenopausal breast cancer risk estimates could be established yielded a summary risk estimate of 1.68 (95% CI 1.31 - 2.15). (See Table 7.4.1C and Figure 7.4.3 below.) Here as well, the estimates were heterogeneous. Ten studies had individual risk estimates of 1.5 or higher for younger, primarily premenopausal women. In the five studies which adequately assessed major sources of lifetime passive smoke exposure, the summary risk estimate for premenopausal breast cancer was 2.20 (95% CI 1.69-2.87). For these five studies the statistical test for heterogeneity was consistent with homogeneity (p= 0.354). Combining the studies in which important passive sources were missed yields a pooled risk estimate of 1.33 (95% CI 1.04 – 1.70). Breast cancer is a common disease and ETS is a widespread and frequent exposure; an effect estimate of even 1.25 implies a large number of women will be impacted by ETS exposure. More importantly, the effect estimate for younger, primarily premenopausal women derived from studies with the best exposure assessment indicates a strong (>2) and consistent association.

Table 7.4.1A. Quality of Exposure Assessment in Studies of ETS and Breast Cancer Risk.

	Environmental Tobacco Smoke Exposure Assessment					
Study	**Summary of Exposure Measures**	**Childhood Exposure**	**Adult Residential Exposure**	**Occupational Exposure**	**Other Exposure**	**Important Exposure Missed?**
Hirayama, 1984	husband's smoking history	No	husband's smoking history	No		likely
Sandler *et al.,* 1985b	childhood and husband's history	Years smoked by parents and others in household	husband's smoking history	No		likely
Smith *et al.,* 1994	lifetime residential and occupational	detailed history	detailed history	detailed history		unlikely
Morabia *et al.,* 1996	lifetime residential and occupational and social	detailed history	detailed history	detailed history	social	unlikely
Millikan *et al.,* 1998	adult residential	No	housemate's smoking	No	No	likely
Lash and Aschengrau, 1999	lifetime residential	Yes	Yes	No		likely
Zhao *et al.,* 1999	lifetime passive smoking history	Yes	Yes	Yes	Yes	unlikely
Jee *et al.,* 1999	husband's smoking history	No	husband's smoking history	No		likely
Delfino *et al.,* 2000	adult residential	No	adult residential	No	No	likely
Johnson *et al.,* 2000	lifetime residential and occupational	# of smokers in each residence	# of smokers in each residence	For each job: # of smokers who smoked regularly in immediate work area		unlikely
Wartenberg *et al.,* 2000	husband's smoking history	No	husband's smoking history	No*		likely

* Current occupational exposure in 1982 collected, but only husband's smoking history used for main analysis and husband's history not used in analysis of 1982 cross-sectional exposure.

Table 7.4.1A. Quality of Exposure Assessment in Studies of ETS and Breast Cancer Risk.

	Environmental Tobacco Smoke Exposure Assessment					
Study	**Summary of Exposure Measures**	**Childhood Exposure**	**Adult Residential Exposure**	**Occupational Exposure**	**Other Exposure**	**Important Exposure Missed?**
Liu *et al.,* 2000	Childhood, youth, adult, home work, #cpd	Yes	Yes	Yes	No	unlikely
Nishino *et al*., 2001	Currently living with smoker(s) in 1984	No	Husband, wife, parents, children or others living in household who smoke (currently in 1984)	No	No	likely
Egan *et al*., 2002	Parental, years lived as adult with a smoker, current (1982) home and work.	Mother, father or both parents smoked	Years lived with smoker, current 1982	Current, in 1982 only	No	likely
Lash & Aschengrau, 2002	Lifetime residential	Yes	Yes	No	No	likely
Kropp & Chang-Claude, 2002	Years exposed to age 50	Years exposed	Years exposed	Years exposed	No	unlikely
Gammon *et al.,* 2004	Adult residential	No	Yes	No	No	likely
Reynolds *et al*., 2004a	Lifetime residential	Yes	Yes	No	No	likely
Shrubsole *et al*., 2004	Husband and workplace	No	Husband's smoking	During prior 5 years	No	likely
Hanaoka *et al*., 2005	lifetime residential, outside home cross section at baseline	Yes	Ever lived with regular smoker	Current 1990 only	Current 1990	likely

Table 7.4.1B. Summary estimates for passive smoking and overall breast cancer risk when compared to women who reported no active smoking and no regular ETS exposure

Study	Study Design[a]	Important ETS Exposure Missed	Relative Risk[b]	95% Confidence Interval Lower	Upper	Statistical Weight (Random Effects)
Hirayama 1984	cohort	likely	1.32	0.83	2.09	9.03
Sandler *et al.* 1985b	cc	likely	1.62	0.76	3.44	4.91
Smith *et al*., 1996.	cc	unlikely	2.53	1.12	5.71	4.39
Morabia *et al.* 1996	cc	unlikely	2.30	1.50	3.70	9.24
Millikan *et al.*1998	cc	likely	1.30	0.90	1.90	10.93
Lash & Aschengrau, 1999	cc	likely	2.00	1.10	3.70	6.63
Delfino *et al*, 2000	cc	likely	1.86	0.81	4.27	4.26
Zhao *et al* 1999	cc	unlikely	2.38	1.66	3.40	11.28
Jee *et al.*1999	cohort	likely	1.30	0.90	1.80	11.57
Johnson *et al.* 2000	cc	unlikely	1.48	1.06	2.07	11.86
Wartenberg *et al.* 2000	cohort	likely	1.00	0.80	1.20	15.18
Nishino *et al.*2001	cohort	likely	0.58	0.32	1.10	6.48
Kropp & Chang-. 2002	cc	unlikely	1.59	1.06	2.39	10.18
Lash & Aschengrau, 2002	cc	likely	0.85	0.63	1.10	13.26
Egan *et al.* 2002	cohort	likely	1.06	0.90	1.25	16.08
Reynolds *et al*., 2004a	cohort	likely	0.94	0.82	1.07	16.73
Shrubsole *et al*., 2004	cc	likely	1.02	0.81	1.29	14.44
Gammon *et al*., 2004	cc	likely	1.04	0.81	1.35	13.86
Hanaoka *et al*., 2005	cohort	likely	1.10	0.80	1.60	11.57
Meta-analysis Results						**Test for heterogeneity**
Summary RR[c] all studies			1.25 (1.11)[d]	1.08 (1.04)	1.44 (1.19)	p<0.001
Summary RR - important ETS sources collected			1.91 (1.89)	1.53 (1.57)	2.39 (2.27)	p=0.235
Summary RR - important ETS sources missed			1.06 (1.03)	0.96 (0.96)	1.17 (1.11)	p=0.106
Cohort studies - important ETS sources missed			1.02 (1.01)	0.92 (0.93)	1.14(1.10)	p=0.229
Case-control studies - ETS sources missed			1.14 (1.08)	0.94 (0.95)	1.38 (1.23)	p=0.094

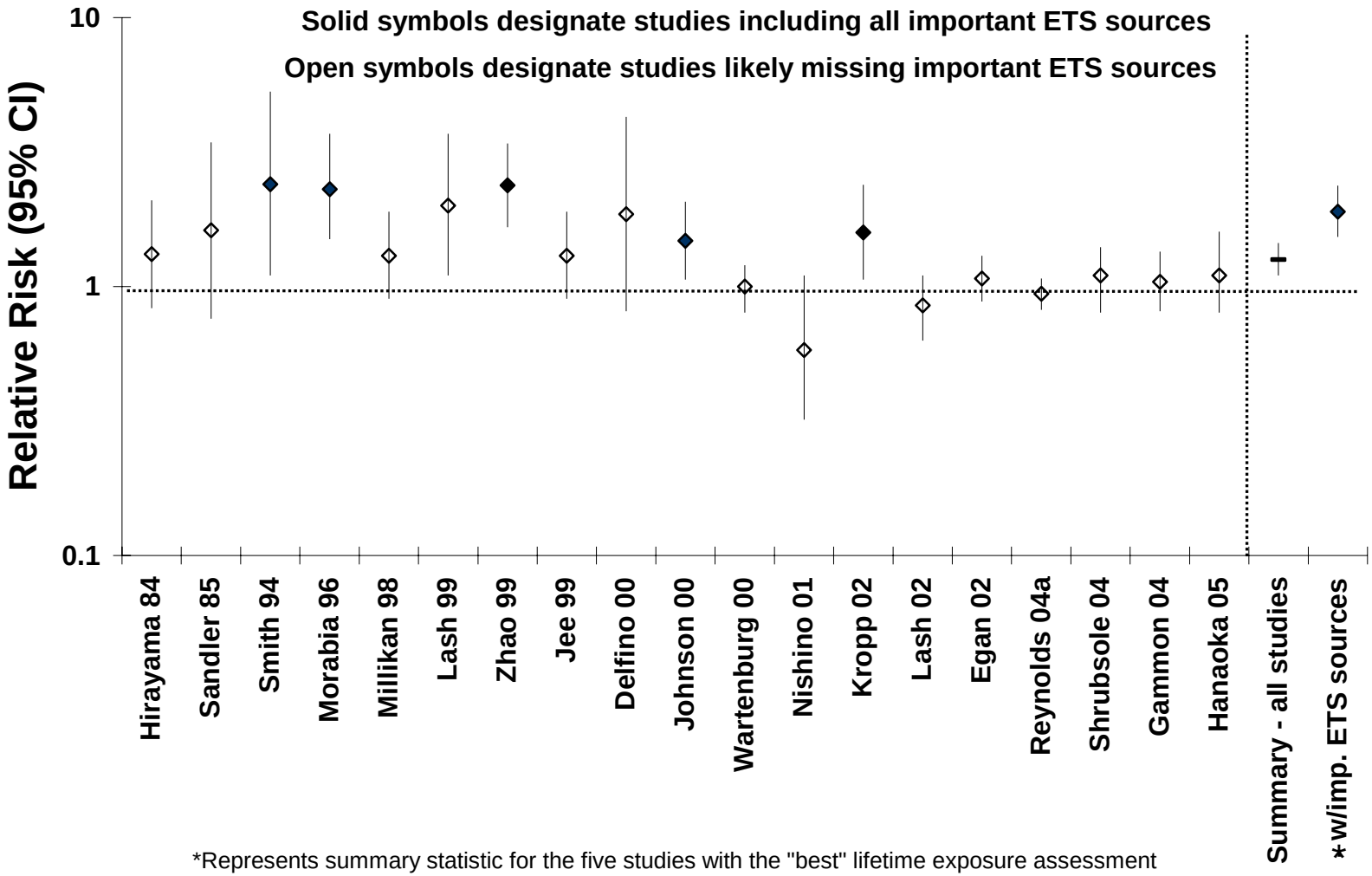
[a] cc = Case-Control.

[b] Odds ratios assumed to be a reasonable approximation for the relative risk in case-control studies. Weighting reported is for full model.

[c] Summary RR estimates were calculated using the method of DerSimonian and Laird.
Note: For several studies, summary overall risk estimates had to be calculated using component risks and confidence intervals reported in the paper and combined using methods described under Smith *et al*. (1994) and other individual study reviews. For several of the earlier studies, risk estimates for the desired comparisons were published in letters by Wells (1991, 1992a, 1998a) after personal communication with the authors. Combined estimates: Hirayama 1984, Wells letter (1998a). For Smith *et al.* (1994), estimated overall passive smoking risk calculated by summarizing the adjusted lifetime exposure categories (1-200, > 200 cigarette-years); Zhao *et al*. (1999) estimates from personal communication from author (to K. Johnson) correcting misprint in original paper; Johnson *et al*. (2000) combined estimates for pre- and postmenopausal risks; Egan *et al*. (2002) combined currently exposed at work and home; Shrubsole *et al.* (2004) combined husband or workplace only and husband and workplace exposure. Smith *et al*. (1994) and Kropp and Chang Claude (2002) studies only include younger women.

[d] Parentheses in summary RRs denote fixed effects model.

Fig. 7.4.2 OEHHA summary estimates for passive smoking and overall breast cancer risk when compared to women who reported no active smoking and no regular ETS exposure.



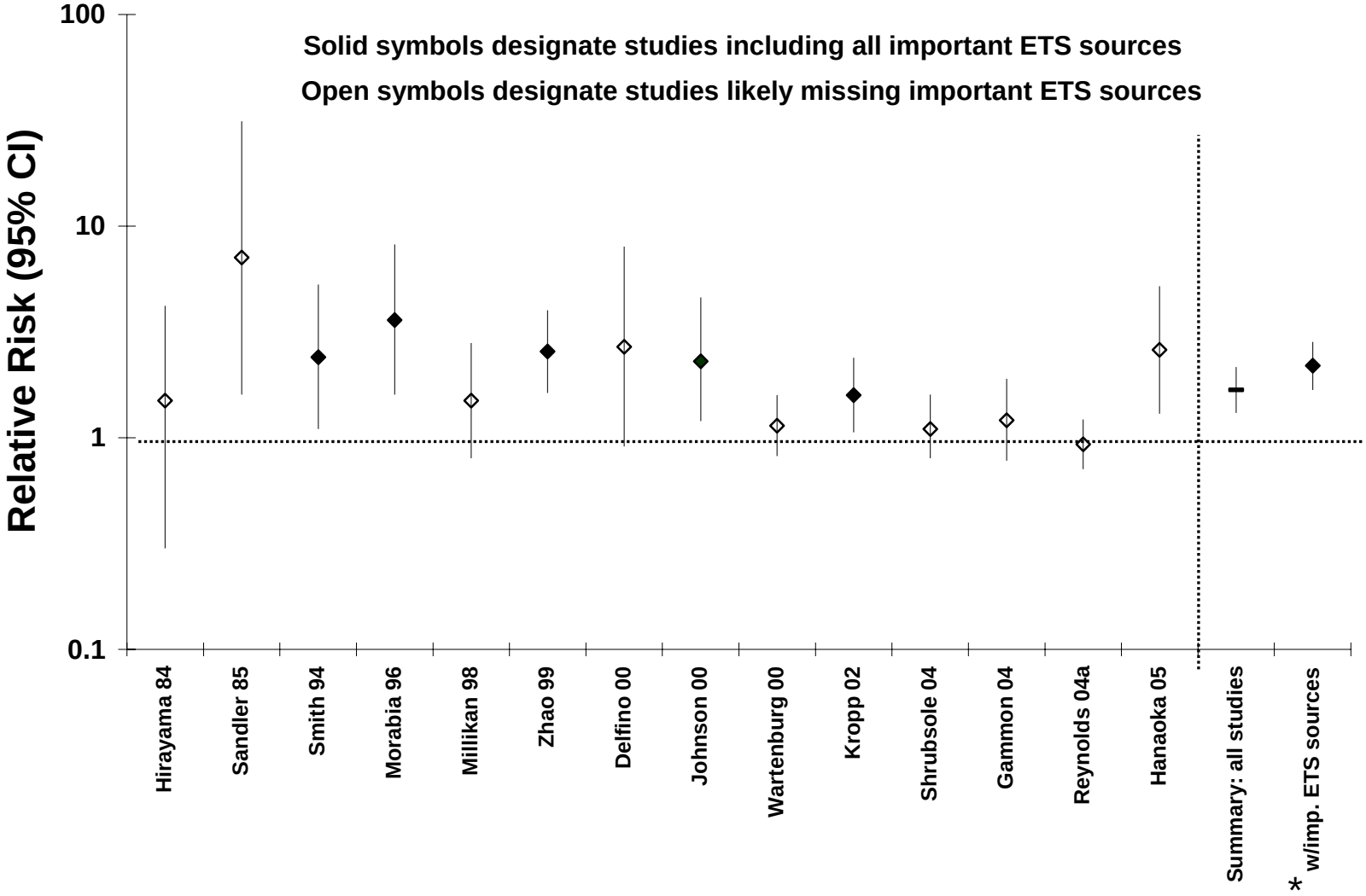
*Represents summary statistic for the five studies with the "best" lifetime exposure assessment

Table 7.4.1C Summary risk estimates for ETS and breast cancer in premenopausal women when compared to women who reported no active smoking and no regular ETS exposure

Study	Study Design[a]	Important ETS Exposure Missed	Relative Risk	95% Confidence Interval Lower	Upper	Statistical Weight (Random Effects)
Hirayama 1984[b]	cohort	likely	1.50	0.50	4.20	2.39
Sandler 1985[c]	cc	likely	7.10	1.60	31.3	1.43
Smith 1994[d]	cc	unlikely	2.53	1.12	5.71	3.38
Morabia 1996	cc	unlikely	3.60	1.60	8.20	3.37
Millikan 1998	cc	likely	1.50	0.80	2.80	4.44
Delfino 2000	cc	likely	2.69	0.91	8.00	2.32
Zhao 1999[e]	cc	unlikely	2.56	1.63	4.01	5.69
Johnson 2000	cc	unlikely	2.30	1.20	4.60	4.16
Wartenberg 2000[f]	cohort	likely	1.15	0.82	1.60	6.58
Kropp 2002	cc	unlikely	1.59	1.06	2.39	6.03
Shrubsole 2004[g]	cc	likely	1.10	0.83	1.46	6.96
Gammon 2004	cc	likely	1.21	0.78	1.90	5.73
Hanaoka 2005	cohort	likely	2.60	1.30	5.20	4.03
Reynolds 2004a	cohort	likely	0.93	0.71	1.22	7.04
Meta-analysis Results						**Test for heterogeneity**
Summary RR [h] all studies			1.68 (1.38)[i]	1.31 (1.21)	2.15 (1.56)	$p < 0.001$
Summary RR - important ETS sources collected			2.20 (2.18)	1.69 (1.70)	2.87 (2.79)	$p = 0.354$
Summary RR - important ETS sources missed			1.33 (1.17)	1.04 (1.01)	1.70 (1.36)	$p = 0.032$
Cohort studies - important ETS sources missed			1.27 (1.11)	0.86 (0.91)	1.86 (1.35)	$p = 0.051$
Case-control studies - important ETS sources missed			1.47 (1.26)	1.00 (1.01)	2.16 (1.56)	$p = 0.082$

[a] cc = Case-Control.
[b] Based on estimates published in letters by Wells (1991,1992a,1998a) after personal communication with the authors. Premenopausal estimate obtained by using husband age category of 40-49 years (Wells, 1991).
[c] Based on estimates published in letters by Wells (1991,1992a,1998a)
[d] Smith *et al*. (1994), estimated overall passive smoking risk calculated by summarizing the adjusted lifetime exposure categories (1-200, > 200 cigarette-years)
[e] Zhao *et al.* (1999), premenopausal data from personal communication (K. Johnson) with author, based on menopausal status at time of diagnosis.
[f] Wartenberg *et al.* (2000), combined data for current and former spousal smoking age < 50 at baseline table 6.
[g] Shrubsole *et al*. (2004) combined husband or workplace only and husband and workplace exposure
[h] Summary RR estimates were calculated using the method of DerSimonian and Laird.
[i] Parentheses in summary RRs denote fixed effects model.

Fig. 7.4.3 Summary risk estimates for ETS and breast cancer in premenopausal women



*Represents summary statistic for the five studies with the "best" lifetime exposure assessment.

7.4.1.4. Discussion of ETS and Breast Cancer

Many population-based case-control studies (as well as three cohort studies), controlling for several important reproductive, dietary and other potential confounding factors, have identified elevated breast cancer risks for residential and occupational exposure overall or in individual strata. Higher risks were noted in several studies for breast cancer diagnosed in women under age fifty (primarily premenopausal), or with long duration or high intensity exposure. The toxicological data on carcinogenicity of tobacco smoke constituents (see Table 7.4.1E) strongly support that the risk associated with ETS exposure is highly plausible.

Several population-based case-control studies reported evidence of a positive dose-response relationship with passive smoking, particularly among premenopausal women (Morabia *et al*., 1996; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Shrubsole *et al*., 2004). Adjusted ORs were around 3.0 in the highest exposure categories (Johnson *et al.*, 2000). Breast cancer risk appears stronger for certain subgroups of women based on menopausal status or age, timing of exposure (childhood or prior to first pregnancy).

7.4.1.4.1. Criteria for Determining Most Informative Studies

Studies that were the best methodologically, especially with respect to exposure assessment, were emphasized by OEHHA in our weight-of-evidence evaluation. Several characteristics of study design and analysis in the individual studies reviewed affect their utility in determining whether there is a relationship between ETS exposure and breast cancer. While in general these factors (e.g., adequate exposure assessment and minimized exposure misclassification) are important for all epidemiologic studies, they are of particular importance in establishing the framework for evaluating the quality of these studies and have not been met by the majority of them. These factors are above and beyond the usual considerations such as study design, sample size, and adequacy of approach to bias and confounding (as discussed in chapter 1). These study characteristics include:

1) Exposure assessment - Factors deemed to enhance study quality include an historical determination of lifetime exposure to tobacco smoke including estimation of childhood and adult exposures, and both residential and occupational and other non-residential exposures. Exposure assessments that specifically attempt to ascertain exposures during multiple time periods are preferable to those relying upon a single point in time (e.g., current or at baseline).

2) Referent population – Studies which utilize an “unexposed” referent population that attempts to limit or eliminate those with ETS exposure are considered superior. In other words, the exposed group should be compared to those with no (or at least limited) ETS exposure from all sources and time periods. Those studies which failed to collect the desirable information delineated in #1 above are unable to satisfy this criterion.

3) Potential windows of susceptibility and timing of diagnosis – Studies which include examination of peri-pubertal adolescent and prepregnancy/nulliparous exposures are preferable. Reporting pre- and postmenopausal status ideally at the time of diagnosis, or at a minimum at baseline (as was done in many of the existing cohort studies) is desirable, particularly with adequate sample size.

4) Given that all of the criteria above relating to sources, quantity, and timing of exposure are satisfied, a prospective study is considered of higher quality than an equally strong case-control study.

Utilizing the above quality framework, six studies examining the association between ETS exposure and breast cancer are considered to meet these criteria (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Hanaoka *et al*., 2005) and are considered to be the best studies methodologically and, therefore, most informative (see Table 7.4.1A). Hanaoka's exposure measures are more limited than the others (occupational exposure was measured only for current exposure at enrollment), and so Hanaoka *et al*., (2005) was excluded from the stratified meta-analysis of best exposure assessment studies. However, it was the best of the prospective cohort studies reviewed and included the minimum characteristics noted above. Thus, OEHHA included Hanaoka *et al*., (2005) in our group of most informative studies. Previous cohort studies were problematic due to limited exposure ascertainment. In particular, the referent groups contained individuals exposed to ETS from workplace or other sources and/or during childhood. The discussion below will highlight the findings of these studies as well as include discussion of the overall weight of evidence from all epidemiologic studies and other supporting evidence.

The importance of the effect of exposure misclassification by having passive smokers in the referent group has been demonstrated in active smoking studies (Morabia *et al.*, 1996; Lash and Aschengrau, 1999; Johnson *et al.*, 2000; Kropp and Chang-Claude, 2002). Morabia *et al*. (1996) and Kropp and Chang-Claude (2002) each evaluated the influence on estimated breast cancer risk of the referent group by comparing smokers to all non-smokers (commonly utilized in studies) and smokers to a referent group of non-smokers having no spousal, residential or workplace ETS exposure. The risk estimates were higher when comparison was made to a never passive, never active group (see Table 7.4.1D). Johnson *et al.* (2000) demonstrated that comparison of smokers' breast cancer risks to never passively exposed non-smokers moved the breast cancer risk estimate upwards, and the estimate became statistically significant. This demonstrates the problem of limited exposure assessment. In most of the passive smoking studies of ETS, poor exposure assessment results in a referent population contaminated with ETS-exposed individuals, thus biasing results towards the null.

Table 7.4.1D. Utilizing Unexposed Referent Raises Risk Estimate (within study comparison, Morabia *et al*., 1996)

Exposure	Smokers vs non-smokers with no ETS	Smokers vs non-smokers (includes ETS exposed)
Active 1-9 cpd	2.2 (1.0; 4.4)	1.2 (0.8; 2.0)
10-19 cpd	2.7 (1.4; 5.4)	1.7 (1.1; 2.5)
≥ 20 cpd	4.6 (2.2; 9.7)	1.9 (1.2; 2.9)
Ever passive	3.2 (1.7; 5.9)	

(There were similar within-study findings in Johnson *et al*., 2000, Lash and Aschengrau, 1999, and Kropp and Chang Claude, 2002)

7.4.1.4.2. Evidence of Causality

7.4.1.4.2.1. Biological Plausibility

There are extensive data showing carcinogenesis in animals at a number of relevant sites by individual chemical components of tobacco smoke. These included some components that are actually more abundant in sidestream or environmental tobacco smoke than in mainstream smoke. The occurrence of these established carcinogens in tobacco smoke is important evidence of biological plausibility of the hypothesized causal association (see discussion of causal criteria in Chapter 1). This argument may be re-examined with specific reference to the question of whether exposure to tobacco smoke (by active or passive smoking) is plausibly associated with breast cancer in humans. Table 7.4.1E lists 20 chemicals identified in tobacco smoke that are listed as carcinogens by IARC, and which induce mammary tumors. The table provides the IARC classification: 1 carcinogenic to humans; 2A probably carcinogenic to humans; 2B possibly carcinogenic to humans. The table is not by any means an exhaustive list of the tobacco smoke components that may be carcinogenic to the mammary gland. The limitations on the extent to which tobacco smoke constituents have been adequately tested for carcinogenesis at any site were noted in the discussion at the beginning of this chapter. This applies to an even greater degree to mammary carcinogenesis, since this site has been examined in screening assays considerably less often than sites such as the skin or the lung.

It is assumed in this discussion that there is concordance between animal and human susceptibility to carcinogenesis, with regard both to active chemicals and site of action. This is a reasonable, if not infallible, assumption. Indeed it may if anything understate the number of potential human mammary carcinogens since this appears to be a relatively susceptible site in humans. Some rodent strains show high sensitivity to mammary carcinogenesis, whereas others do not. (No assumption is necessarily being made about the relative potency of any of these mammary carcinogens in animals *vs*. humans, although the probability of observing an effect in a relatively small-scale animal bioassay is greater for a potent carcinogen.)

Several polycyclic aromatic hydrocarbons that occur in tobacco smoke are known mammary carcinogens in laboratory animals. Cavalieri *et al.* (1989) identified dibenzo[a,l]pyrene as an extremely potent carcinogen in both skin and mammary tissue of the mouse. Arif *et al.* (1999) described this compound as “one of the most potent animal carcinogens and mutagens”. They showed formation of persistent DNA adducts in rat mammary tissue following injection of dibenzo[a,l]pyrene. These adducts were of the diol-epoxide type identified as the reactive intermediate in carcinogenesis by many other polycyclic aromatic hydrocarbons.

Table 7.4.1E. Mammary Carcinogens Found in Tobacco Smoke.

Compound	Cigarette main-stream smoke (amount per cigarette) [a]	Cigarette side-stream smoke (amount per cigarette) [b]	Cigarette smoke-polluted environments [c]	Cigar (C) or Pipe (P) smoke (µg/100 g) [d]	IARC Classific-ation[e]	Mammary gland tumors: Affected Species [f]
Aromatic hydrocarbons						
Benzene	28 - 106 µg	71 - 134 µg	5 - 22 µg/m^3	P: 34400 C: 9200-24600	1	Mouse
Benzo[a]pyrene	5.6 - 41.5 ng	52 - 95 ng	0 - 3.6 ng/m^3	C: 1.8-5.1 P: 8.4	2A	Rat
Dibenz[a,h]anthracene	4 ng	[g]			2A	Mouse [h]
Dibenzo[a,e]pyrene	Present				2B	Rat[i]
Dibenzo[a,h]pyrene	Present				2B	Rat[i]
Dibenzo[a,i]pyrene	1.7 - 3.2 ng				2B	Rat[i]
Dibenzo[a,l]pyrene	Present				2B	Rat[i]
Nitrosamines						
N-nitrosodiethylamine	0 - 25 ng		Up to 8.6 ng/m^3		2A	Rat
N-Nitrosodi-*n*-butylamine	0 - 3.0 ng				2B	Mouse
Aliphatic compounds						
Acrylamide	Present				2A	Rat
Acrylonitrile	8 - 39 µg	24 - 44 µg			2B	Rat
1,3-Butadiene	24 - 123 µg	81 - 135 µg	19 µg/m^3		2A	Mouse, rat
Isoprene	288 - 1193 µg	743 - 1163 µg	83 - 150 µg/m^3	C: 24500-63300	2B	Rat
Nitromethane	0.5 - 0.6 µg				2B	Rat[j]
Propylene oxide	0 - 100 ng				2B	Rat[k]
Urethane	20 - 38 ng				2B	Mouse, hamster
Vinyl chloride	11 - 15 ng			C: 0.14-0.27	1	Rat, mouse, hamster

Table 7.4.1E. Mammary Carcinogens Found in Tobacco Smoke.

Arylamines and nitroarenes						
4-Aminobiphenyl	2 - 8 ng	21 – 32 ng			1	Rats
Nitrobenzene	25 µg				2B	Mice[l]
ortho-Toluidine	30 - 200 ng				2A	Rats

Footnotes:

[a] IARC (2004a) citing preferentially Table 1.10 (the 1999 Massachusetts Benchmark Study), or else Table 1.14.
[b] IARC (2004a), citing Table 1.3 (the 1999 Massachusetts Benchmark Study)
[c] IARC (2004a), citing mainly Jenkins *et al*., 2000
[d] IARC (1986a) and IARC (2004a).
[e] IARC classification 1 = carcinogenic to humans; 2A = probably carcinogenic to humans; 2B = possibly carcinogenic to humans.
[f] NTP: 10th Annual Report on Carcinogens (2002) unless otherwise indicated
[g] Blank cell = no data available
[h] IARC (1973b).
[i] Cavalieri *et al*. (1989; 1991).
[j] IARC (2000).
[k] IARC (1994b).
[l] IARC (1996a).

A number of investigators have shown that human breast tissue is susceptible to formation of DNA adducts and oncogene mutations as a result of exposure to polycyclic aromatic hydrocarbons, including exposures as a result of smoking (Li *et al.,* 1999; Perera *et al.,* 1995; Conway *et al.*, 2002; Santella *et al.,* 2000; Rundle *et al.,* 2000; Li *et al.,* 2002). Metabolites and DNA adducts in urine and placenta have also been observed in humans exposed to polycyclic aromatic hydrocarbons from environmental sources including environmental tobacco smoke (Anderson *et al.,* 2001; Whyatt *et al.,* 1998a).

It is clear that mammary epithelium is capable of metabolic activation of carcinogens (reviewed by Phillips *et al*., 2001). Firozi *et al*. (2002) and Li *et al*. (1996) measured aromatic DNA adducts in breast tissue from cancer patients and controls. They found higher levels of DNA adducts in smokers than in non-smokers, and in non-cancerous tissue adjacent to a tumor than in tissue from the actual tumor. Dependence of adduct levels on polymorphisms of Cyp1A1 and NAT2 (genes specifying enzymes important in PAH metabolism) was also noted in smokers but not in non-smokers. Gene-gene interaction was noted in smokers with certain CYP1A1 and GSTM1 null polymorphisms combined having much higher levels of DNA adducts than either individually. Their findings suggest that polymorphisms of CYP1A1, GSTM1, and NAT2 significantly affect either the frequency or the level of DNA adducts in normal breast tissues of women with breast cancer, especially in smokers. Similarly, Faraglia *et al.* (2003) examined both normal and cancerous breast tissues from breast cancer patients for adducts related to 4-aminobiphenyl, a known carcinogen and tobacco smoke constituent. For normal tissues of current smokers, former smokers and non-smokers, a significant linear trend ($p = 0.04$) was observed between DNA adducts and smoking status. Consideration of both active and passive status (never either, ever passive only, ever active only, ever both) also showed a linear trend in the level of DNA adducts in normal tissue with smoking status ($p = 0.03$). An increase in adduct levels in normal tissue with passive smoking status alone (never, former, current) was seen but the trend was not statistically significant ($p = 0.14$). A significant limitation of the data set examined in this study was the small number of cases reporting neither active nor passive smoking. These studies provide evidence that carcinogens in cigarette smoke reach mammary tissue and form DNA-adducts.

The evidence with regard to plausibility of a causal association between environmental exposure to tobacco smoke and breast cancer thus includes the occurrence of identified carcinogens as components of ETS, demonstration of carcinogen-DNA adduct formation in breast tissue, demonstration of metabolic capability of mammary epithelium to biotransform carcinogens such as PAHs to the active metabolite, and demonstration that these compounds do, in fact, reach and damage human mammary tissue as a result of direct smoking or environmental exposures. This chain of evidence indicates that a causal association is highly plausible, both for active (Hecht, 2002) and passive smoking.

7.4.1.4.2.2. Consistency

A number of studies examining the association of ETS exposure with risk of breast cancer have identified elevated risks for younger, primarily premenopausal women. 13 of 14 of these studies found risks greater than one and 7 of these were statistically significant. These findings are evident across study design and geographical regions (see Figure 7.4.4 below). Several studies showed evidence of dose-response. The majority of studies: 1) adjusted for major risk factors, including reproductive history 2) attempted to assess risk for ETS exposure beyond the home

(Johnson *et al.*, 2000; Wartenberg *et al.*, 2000; Kropp and Chang-Claude, 2002; Shrubsole *et al.*, 2004; Hanaoka *et al.,* 2005); and 3) assessed risk based on timing of exposure, either during childhood (Morabia *et al.*, 1996;Johnson *et al.*, 2000; Reynolds *et al.*, 2004a), or relative to first pregnancy (Morabia *et al.*, 1996,; Kropp and Chang-Claude, 2002; Gammon *et al.*, 2004).

In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause risk estimates cluster around a null association (see Figure 7.4.4).

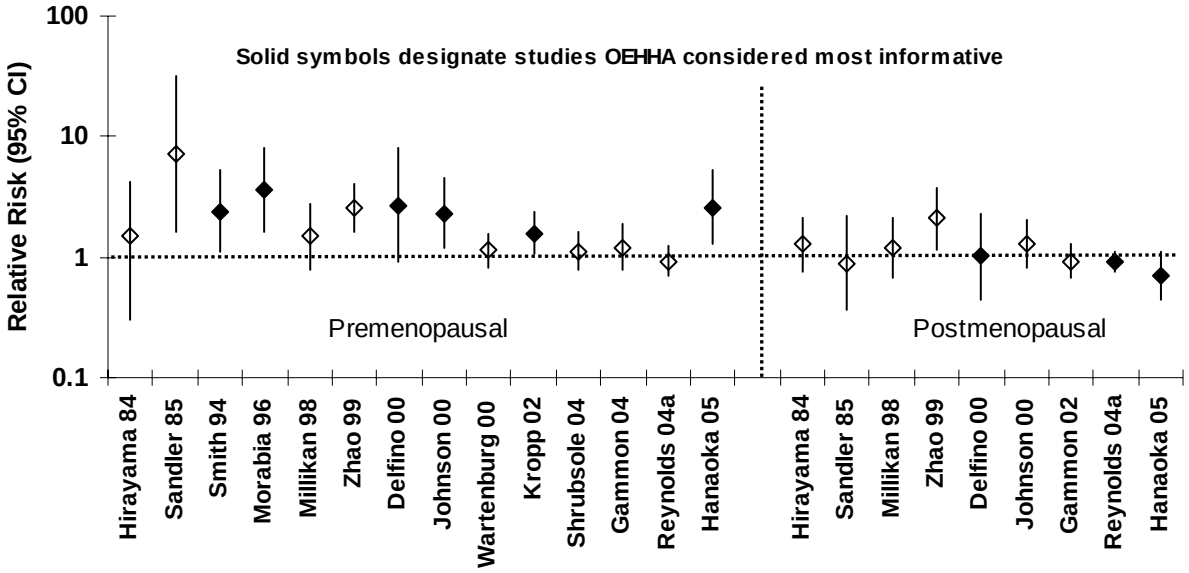


Figure 7.4.4. Comparison of studies examining ETS and breast cancer risk in pre- and postmenopausal women

7.4.1.4.2.3. Strength of Association

7.4.1.4.2.3.1. Younger Primarily Premenopausal Women

In the 14 studies that evaluated younger, primarily premenopausal women, there is a strong association between ETS exposure and breast cancer risk. All but one of these studies found risk estimates between 1.10 and 7.10 of which seven were statistically significant (Table 7.4.1C). All of the six studies considered by OEHHA to be most informative, as described in Section 7.4.1.4.1, found risk estimates of 1.59 or greater and were statistically significant (Table 7.4.1G). A summary risk estimate of 1.68 (95% CI 1.31-2.15) for breast cancer diagnosed in younger primarily premenopausal women was obtained in our meta-analysis of 14 studies. The meta-analysis of the 5 better exposure studies for premenopausal women results in a pooled risk estimate of 2.2 (95% CI 1.69-2.87).

7.4.1.4.2.3.2. Overall (Women of All Ages)

Of the 19 studies presenting summary estimates for passive smoking comparing non-smoking women with ETS exposure to those who reported no active smoking and no regular exposure to ETS reviewed for this document, 15 reported point estimates greater than one and six of these had 95% confidence intervals that excluded unity. OEHHA's meta-analysis obtained a pooled risk estimate of 1.25 (95% CI 1.08-1.44) for these 19 studies. The pooled risk estimate for the 5 studies (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002) that were considered unlikely to have missed assessing other important sources of ETS exposure was 1.91 (95% CI 1.53-2.39). Of the six studies considered by OEHHA to be most informative (the above five plus Hanaoka *et al*., 2005; see Section 7.4.1.4.1) in this assessment, all had positive risks ranging from 1.10-2.53 (Table 7.4.1F), and in all but Hanaoka *et al*., (2005) the 95% confidence intervals excluded unity.

Table 7.4.1F Breast Cancer risk with passive smoking for women of all ages (OEHHA most informative studies)

Study	Relative Risk	95% Confidence Interval	
		Lower	Upper
Smith *et al*., 1994	2.53	1.12	5.71
Morabia *et al*., 1996	2.30	1.66	3.66
Zhao *et al*., 1999	2.38	1.66	3.40
Johnson *et al*., 2000	1.48	1.06	2.07
Kropp and Chang-Claude, 2002	1.59	1.06	2.39
Hanaoka *et al*., 2005	1.10	0.80	1.60

Table 7.4.1G Breast Cancer risk with passive smoking for premenopausal women (OEHHA most informative studies)

Study	Relative Risk	95% Confidence Interval	
		Lower	Upper
Smith *et al*., 1994	2.53	1.12	5.71
Morabia *et al*., 1996	3.60	1.59	8.15
Zhao *et al*., 1999	2.56	1.63	4.01
Johnson *et al*., 2000	2.30	1.28	4.15
Kropp and Chang-Claude, 2002	1.59	1.06	2.39
Hanaoka *et al*., 2005	2.60	1.30	5.20

7.4.1.4.2.3.3. Confounding

Residual confounding is a concern when the estimated size of the association is low, as is the case for some of the breast cancer studies and for the pooled overall risk estimate. However, most of these studies adjusted for known major risk factors for breast cancer. In addition, several of the risk estimates from individual studies are above 2. It is unlikely an unknown confounding factor, which would have to be associated with both breast cancer and second-hand smoke exposure, would account for these risk estimates in younger (mostly premenopausal) women. In

most studies examined, adjusting for known confounders had little impact on the level of association between ETS and breast cancer. All of the six studies considered by OEHHA as most informative considered, and adjusted in the final model when appropriate, measures of reproductive factors (parity, age at first childbirth, age at menarche, etc.), alcohol consumption, and oral contraceptive use. Four or five of six studies also controlled for BMI, SES (or surrogates), breastfeeding, and family history. As noted above (Section 7.4.1.4.2.2), there are consistent findings of a positive association between ETS and breast cancer in women diagnosed at younger age (primarily premenopausal). Within the same group of studies there are several which present separate analysis for diagnosis post-menopause (older age). These results are generally null. It is unlikely that bias or confounding would produce an association in younger (mostly premenopausal) but not older (postmenopausal) women within the same studies.

7.4.1.4.2.4. Dose-Response Gradient

Several studies examining ETS exposure and breast cancer present evidence of a dose response (Hirayama, 1984; Jee *et al*., 1999: Johnson *et al*., 2000; Kropp and Chang-Claude, 2002: Shrubsole *et al.,* 2004; Hanaoka *et al*., 2005) (Table 7.4.1H). Hanaoka *et al*. found a relative risk for breast cancer of 2.3 (95% CI 1.4-3.8) in women who were premenopausal at cohort baseline and exposed to ETS in occupational and/or public settings. A significant exposure-response trend was observed (p = 0.002; see Table 7.4.1 G). Shrubsole *et al*. (2004) found adjusted ORs of 0.9, 1.0, 1.1, and 1.6, respectively (p for trend 0.03) for breast cancer in premenopausal women from workplace exposures of 1-59, 60-179, 180-299, and 300+ minutes/day,. Kropp and Chang-Claude (2002) report an OR of 1.42 for lifetime exposure of 1-50 hours/day-years, and an OR of 1.83 for > 50 hours/day-years (p for trend 0.009) in premenopausal women. Johnson *et al.* (2000) observed a dose-response gradient for premenopausal women for increasing levels of passive smoke exposure (residential plus occupational) in smoker-years (p=0.03). Jee *et al*. (1999) reported relative risks of 1.2 (95% CI 0.8-1.8), 1.3 (95% CI 0.9-1.8), and 1.7 (95% CI 1.0-2.8) for wives of ex-smokers, current smokers, and current smokers who smoked ≥ 30 years, respectively. Morabia *et al*. (1996) evaluated exposures of cases and controls starting at age 10 years in hrs/day - years. They reported ORs of 2.2 (95% CI 1.3-3.7) and 2.5 (95% CI 1.5-4.2) for ever passive exposures of 1-50 hr/day-yrs and >50 hr/day-yrs, respectively. The overall relative risk for ETS exposure in Hirayama's study was 1.32 but for never smoking women ages 50-59 whose spouses smoked more than 20 cigarettes/day the RR was 2.68 (95% CI 1.24-5.43) (Hirayama, 1984,1992).

While six new cohort studies (five incidence and one mortality) reviewed for this update provided inconsistent evidence of a dose response association between ETS exposure and breast cancer risk (Jee *et al.*, 1999; Wartenberg *et al.*, 2000; Nishino *et al.*, 2001; Egan *et al.*, 2002, Reynolds *et al*., 2004a; Hanaoka *et al*., 2005), ETS exposure assessment was limited, often to a single cross-sectional (baseline) assessment, thus limiting the studies' ability to find evidence of a dose-response gradient. As noted above, Hanaoka *et al.*, (2005), Jee *et al.*, (1999), and Hirayama (1984) provide evidence of a dose response.

Table 7.4.1H Evidence for a Dose Response in Passive Smoking Studies

Study	Setting	Findings OR or RR (95% CI)
Hanaoka *et al.* 2005	Premenopausal Occupational or public settings (d/mo)	Almost none 1.0 1-3 d/mo 0.6 (0.4-2.4) > 1 d/wk 2.2 (1.4-3.7) p trend 0.002
Shrubsole *et a*, 2004*l*	Premenopausal Workplace passive exposure minutes per day (mpd)	1-59 mpd 0.9 (0.6-1.4) 60-179 mpd 1.0 (0.7-1.6) 180-229 mpd 1.1 (0.7-1.7) 300+ mpd 1.6 (1.0-2.5) p trend = 0.03
Kropp & Chang-Claude, 2002	Lifetime ETS Hours/day-years (h/d-y)	1-50 h/d-y 1.42 (0.90-2.26) > 50 h/d-y 1.83 (1.16-2.87) p trend 0.009
Johnson *et al*, 2000.	Premenopausal Lifetime residential and occupational exposure in smoker-years (s-yr)	1-13 s-yr 1.5 (0.5-4.4) 14-32 s-yr 2.0 (0.9-4.5) 33-70 s-yr 2.9 (1.3-6.6) >70 s-yr 3.0 (1.3-6.6) p trend 0.03
Jee *et al*, 1999.	Husband's smoking status	Ex-smoker 1.2 (08-1.8) Current smoker 1.3 (0.9-1.8) ≥ 30 yrs smoking 1.7 (1.0-2.8)
Morabia *et al*., 1996	Ever Passive exposure	1-50 hrs/day-yrs 2.2 (1.3-3.7) >50 hrs/day-yrs 2.5 (1.5-4.2)
Hirayama, 1984/1992	Husband's smoking cigarettes/day (age 50-59)	1-19 cigarettes/day 1.3 (0.59-2.86) > 20 cigarettes/day 2.68 (1.24-5.43)

7.4.1.4.3. Limitations of Studies

Limitations of studies are described in the summaries of the individual epidemiological studies. The majority of studies controlled for alcohol consumption. A number controlled for SES, race and education, education and income, or education only. As well, the adjusted and the crude or age-adjusted results for the studies examined rarely differ substantially. Theoretically, since breast cancer is associated with higher SES, and higher SES is associated with lower likelihood of passive smoke exposure (Reynolds, 2004c), the odds ratios for breast cancer in passive smokers may have been biased to be too low in the absence of control for SES. Not controlling for SES or alcohol could impact the results strongly only if these factors were strong risk factors for breast cancer and they were highly correlated with passive smoking exposure.

Increasing alcohol consumption has been correlated with higher likelihood of ETS exposure (Reynolds *et al*., 2004c) as well as increasing hours per week of exposure (Friedman *et al*., 1983). The association between alcohol consumption and breast cancer is a relatively weak effect. Johnson *et al*. (2000) found ORs of 1.0, 1.2, and 1.1 for < 0.5, 0.5-3.5, and > 3.5 drinks/week. The Collaborative Group's analysis of 53 studies (2002) found no increased risk with up to 14 grams/day of alcohol consumption. At 15-24 grams/day the RR was 1.19. Relatively few women drink more than that; Reynold's *et al*. (2004b) found that amongst the California Teacher's Cohort, only 8% consumed more than 20 grams/day of alcohol. A

relatively infrequent behavior which is associated with only a small increase in relative risk such as this could not substantially alter the breast cancer risk estimates found in younger/premenopausal women. It should be noted that in most studies that examine alcohol, controlling for this risk factor has little impact on the risk estimates.

While SES may not be directly adjusted for in many studies, in general, the greater rates of breast cancer (between 1.1 and 2.0) found in women of higher SES are thought to largely reflect differing reproductive patterns such as parity, age at first birth, and age at menarche (Kelsey and Horn-Ross, 1993). These, along with other surrogates of SES such as education are routinely included in the multivariate analyses and inclusion of an additional variable for SES would not significantly alter the model. In addition, while Reynolds (2004b) found a significant positive correlation between a summary SES metric and former active smoking they found a non-significant negative correlation with passive smoke exposure.

Another limitation in several studies examining dose-response was lack of consideration of time-since-first-exposure in the dose-response analyses. Increased years of smoking may have been associated with longer time-since-first-exposure, and cancer risk generally goes up with time-since-first-exposure (effect modification), thus the dose–response results may have been influenced by time-since-first-exposure. As well, increased time-since-quitting may have been associated with longer time-since-first-exposure. The odds ratios in the shorter time-since-quitting periods may have been biased to be too low compared to longer time.

7.4.1.4.4. Bias in Case-Control Studies

Exposure reporting bias in case-control studies can occur if interviewers probe more deeply with cases (not a problem with self-administered questionnaires) or when cases remember past exposure better than controls (recall bias). These biases are more apt to occur if interviewers or subjects are not blinded to the main hypothesis(es) of the study. Fortunately, such bias is unlikely here since a possible link of smoking or ETS to breast cancer is not commonly known to the public nor previously accepted by the scientific community.

Two of the better quality studies (Johnson *et al*., 2000 and Morabia *et al*., 1996) examined potential bias within their studies. Morabia found that the perception of passive smoking did not change by case/control status. Johnson's multi-cancer study found that lung cancer risk assessed using the same target control group observed risks consistent with the previous literature. Both of these findings were interpreted as suggesting that recall bias was not a likely explanation for the study findings. OEHHA believes that most studies considered in this review adequately addressed potential for exposure reporting bias and those that did not were given less weight.

Both case-control and cohort studies may suffer from interviewer or recall bias since the subjects of the latter are typically adults at entry and are asked to report about ETS during earlier periods of life where exposure may be critical.

7.4.1.4.5. Controversies Regarding Relative Potency of Active and Passive Smoking

In the previous document (Cal/EPA, 1997) and elsewhere, the inconsistent results of studies available at that time examining active smoking and breast cancer were felt to undermine any determination of an association between passive smoking and breast cancer. The Surgeon-General's report (U.S. DHHS, 2004c) on active smoking concluded that there is no effect of

active smoking on breast cancer risk and, therefore, did not consider the effects of ETS in any detail. However, the only study cited as a source of information on passive smoking in the Surgeon General's 2004 report is Morabia *et al.* (1996). This contrasts with the analysis by OEHHA of four studies of ETS exposure and breast cancer noted in the earlier report (Cal/EPA, 1997), including Morabia *et al.* (1996), and twenty two studies which have appeared since 1997. Similarly, the recent IARC report (2004a) on carcinogenicity of tobacco smoke argues that "the lack of an association between active smoking and breast cancer weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer". Neither the Surgeon General's report (U.S. DHHS, 2004c) nor IARC (2004a) provide detailed analysis of the passive smoking literature on breast cancer. Nonetheless, it is important to acknowledge a wide distribution of opinion on whether ETS exposure is associated with breast cancer in non-smoking women, and the widespread perception that active smoking is not associated with breast cancer, so there could not be an association with passive smoking.

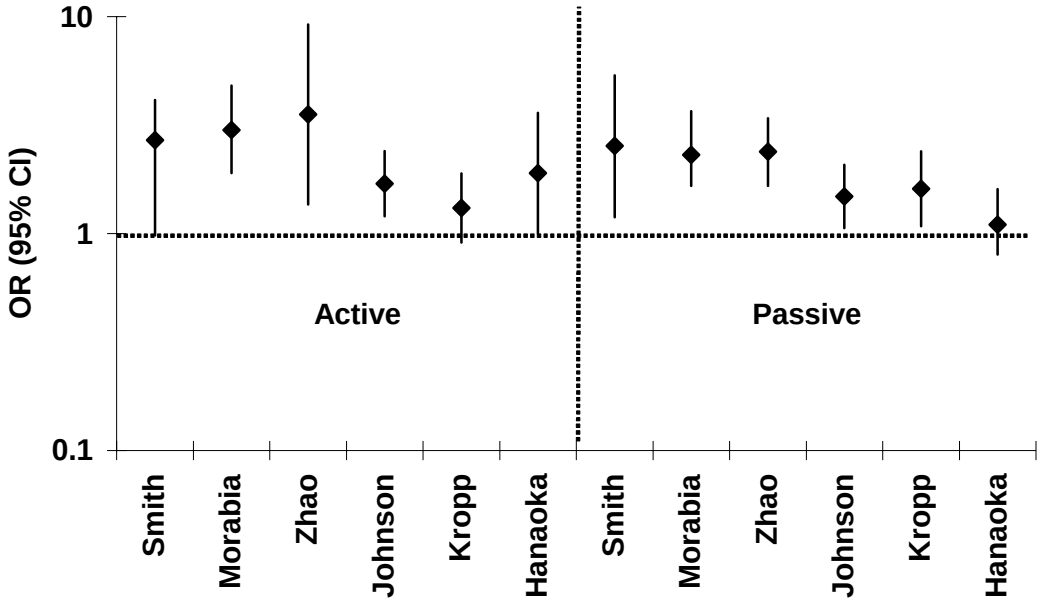
While there continues to be some heterogeneity in study results, overall, the studies presented in this update (along with in vitro and animal data on carcinogenesis) provide some evidence of a role for active smoking in causation of breast cancer. There are now studies providing evidence for gene-environment interactions and susceptible subpopulations with highly significant increased breast cancer risk associated with active smoking (e.g., those with familial high risks in Couch *et al*., 2001). Furthermore, there are studies demonstrating significant risks related to the hormonal receptor status of the tumor (Manjer *et al*., 2001; Morabia *et al*., 1998). Finally, six recent prospective cohort studies found statistically significant elevated breast cancer risk associated with active smoking for at least some of the metrics of exposure (Egan *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*. 2004a, Hanaoka *et al.*, 2005; Zhang *et al*., 2004; Gram *et al*., 2005). Thus, newer data provides evidence supportive of a causal association between breast cancer and active smoking (see Chapter 7, Appendix A). Nearly all studies that utilize a non-active/non-passive smoking referent population in which an attempt has been made to quantify the estimate of ETS exposure from numerous sources (not just spousal) find significant associations with breast cancer in at least some age or susceptibility groupings for both active and passive smoking (see figure 7.4.5 below).

Now that the association with active smoking has become considerably strengthened, and in our view provides evidence supportive of a causal association between active smoking and breast cancer, the emphasis of the argument that ETS does not cause breast cancer has shifted to the relative potency of active and passive smoking. Reasons given for concluding that the active smoking data undermine associations seen in the passive data included:

- The size of the association seen in active smokers is comparable to those noted in passive smoking: e.g., no dose response gradient between active and passive smokers is evident in the data.
- Active smokers are also passive smokers.

Several hypotheses have been suggested as explanations for the apparently flat dose-response for breast cancer between active and passive smoking. These hypotheses have been examined in various studies and reviews (Lash and Aschengrau, 1999, 2002; Morabia, 2002; Russo and Russo, 1994; Terry and Rohan, 2002; Band *et al*., 2002). Some discussion of these hypotheses, and newer data on active smoking and breast cancer risk follows.

Figure 7.4.5. Comparison of breast cancer risk from active and passive smoke exposure in studies considered most informative by OEHHA (see section 7.4.1.5).



7.4.1.4.5.1. Anti-estrogenicity of Active and Passive Smoking

Causal preventive effects from the anti-estrogenic activity of current active smoking may obscure any overall association between active smoking and breast cancer. Active smoking results in earlier age at menopause, increased risk of osteoporosis, and decreased effectiveness of hormone replacement therapy for osteoporosis (Baron *et al*., 1990; Jensen and Christiansen, 1988; Terry and Rohan, 2002) compared to nonsmokers (which would include passive smokers). These effects are evidence of the anti-estrogenicity of active smoking. The Surgeon General's report (U.S. DHHS, 2004c) on active smoking notes the potential competing effects between anti-estrogenicity and carcinogenicity on breast tissue in active smokers. Terry and Rohan (2002) note in their review of cigarette smoking and breast cancer that there is evidence to suggest active smoking influences the metabolism of estrogens resulting in more of the 2-hydroxy estradiol, which is a much less active estrogen, and less of the 16-hydroxy estradiol metabolite, which is a much more active estrogen. Several studies found statistically significant elevated breast cancer risks for ex-smokers even when current smoker's risks were not statistically significantly elevated (Millikan *et al*., 1998; Manjer *et al*., 2001; Egan *et al*., 2002). This is consistent with an anti-estrogenic effect of active tobacco smoking which is theorized to partly counter the carcinogenic effects of smoke constituents in the breast. The investigation by Band *et al*. (2002) (described in Appendix 7A) provides strong support for the competing effects of active smoking on breast cancer due to anti-estrogenic effects and presence of mammary carcinogens. The competing effect of anti-estrogenicity from active smoking is also supported by the finding of elevated risks of ER- and PR- tumors which are not estrogen-dependent, but not ER+ and PR+ tumors which depend on estrogen for growth, in premenopausal women associated with current or former active smoking (Manjer *et al*., 2001), an effect seen in some but not all

studies that evaluated this. Thus, the competing effects of antiestrogenicity and carcinogen exposure affect the breast cancer risk in active smokers. Even though active smokers are also passive smokers and likely experience higher carcinogen exposure than passive smokers, the anti-estrogenic effects of active smoking would to some extent mitigate the breast cancer risk.

The anti-estrogenic effects noted in the studies above are comparing smokers to nonsmokers (a group containing those passively exposed). Thus, the findings reflect, at least in part, the comparative effects of active to passive smoking. Few studies have looked directly at the effects of passive smoking relative to non-smokers not passively exposed. One new study of age at menopause and ETS exposure reviewed in chapter 5 of this document (Cooper, 1999) failed to find a lower age at menopause in women exposed to ETS from living with a smoker. These results are not in agreement with those of Everson *et al.* (1986), who found a decrease of 2 years in age at menopause among nonsmoking women whose spouses smoked compared to those whose spouses did not smoke. Neither paper recorded cigarettes smoked per day by the spouses or workplace exposure to ETS. Overall, there is limited data on the effect of ETS exposure on measures related to estrogenicity but the existing data suggest that active smoking may be more anti-estrogenic than passive exposure. More studies are needed to confirm this difference.

7.4.1.4.5.2. Exposure Misclassification

Because the magnitude of effect of passive smoking is similar to that of active smoking, studies should not have women exposed to ETS in the unexposed referent group. The studies of active and passive smoking reviewed here have fairly consistently indicated an underestimation of risks when exposure history was limited. Studies with more complete exposure ascertainment that limited ETS-exposed women in the "non-exposed" referent group consistently demonstrated higher breast cancer risks in both active and passive smoking studies. This was also seen in analyses within studies (Morabia *et al*., 1996; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002). Studies utilizing a limited evaluation of exposure, such as a single question about spousal smoking at baseline, have also been shown to underestimate risk of lung cancer (Johnson *et al*., 2001) and cardiovascular disease (Whincup *et al*., 2004). In addition, Whincup *et al*. (2004) evaluated cotinine at baseline in their prospective study as the measure of exposure, and showed that the risk of CHD was more strongly associated with cotinine levels in their analysis in the earlier years of follow-up than in the later years, as the exposure measure was further removed in time. This is an important exposure assessment problem in cohort studies that only evaluate exposure at baseline. Thus for many of the active and passive smoking studies, contamination of the referent group with individuals exposed to ETS biases the risk estimates downwards.

7.4.1.4.5.3. Windows of Susceptibility

Human breast tissue may be more vulnerable to exposure to tobacco smoke during certain critical time periods, for example, between menarche and first pregnancy, as is the case with ionizing radiation. Epidemiologic studies that do not evaluate ETS exposure peripubertally or prior to first pregnancy may misclassify the biologically relevant exposure and thus fail to detect a real association. The concept of windows of susceptibility around puberty and before the first pregnancy is biologically plausible in consideration of the development of breast tissue. Developmental periods include embryonic stages of nipple epithelium, puberty, pregnancy and lactation (Russo and Russo, 1994) during which the cells of the lobules and ductules divide and differentiate. Subsequent pregnancies promote differentiation of those cells which remain undifferentiated after the first pregnancy. A series of studies using a rodent model of mammary

carcinogenesis (reviewed by Russo and Russo, 1994) demonstrated that the mammary carcinogen dimethylbenzanthracene binds more readily *in vitro* to those cells that are not yet differentiated In addition, early stage cells present primarily prior to puberty in mammary tissue are more readily transformed *in vivo* by chemical carcinogens than those present after puberty, which in turn are more sensitive to transformation than those cells present following pregnancy and lactation. Studies of girls treated for Hodgkins lymphoma by radiation (Bhatia *et al*., 1996; Aisenberg *et al*., 1997), girls evaluated for scoliosis (Doody *et al*., 2000), and studies of Japanese bomb survivors (NRC, 1990; Tokanuga *et al*., 1994) clearly indicate that peripubertal radiation exposure greatly increases the risk of early-onset breast cancer. In addition, epidemiological studies show early age at first pregnancy as well as multiple pregnancies protect against breast cancer. Thus epidemiological data also support the concept of windows of susceptibility to exposure to carcinogens for breast tissue.

ETS exposure can occur before and during puberty from parental smoking while actual mainstream smoke exposure generally starts well into puberty to post-puberty and continues on into adulthood. Thus, there may be different patterns of exposure of infants and children relative to older children and adults to ETS versus mainstream smoke. The interaction of differing exposure patterns by age and type of smoke (mainstream versus ETS) may contribute to the apparent similarity of risk from ETS and active smoking with respect to breast cancer.

7.4.1.4.5.4. Similar Risks Observed in Active and Passive Smoking Studies.
The elevated risks of breast cancer from both active and passive smoking are similar; thus, the dose-response "curve" for passive and active smoking is non-monotonic. This may be due to a number of factors including a competing anti-estrogenic effect of active smoking discussed above, or saturation of some important process in carcinogenesis (e.g., metabolism of the carcinogen). The explanatory hypothesis of a non-monotonic dose response for the mammary carcinogenic effect of tobacco smoke, especially toward the higher dose ranges associated with active smoking, succeeds in unifying to a substantial degree all of the observed epidemiological results, without having to resort to any extraordinary deconstruction of the relevant studies. The converse hypothesis, that there is no such carcinogenic effect of environmental tobacco smoke, requires detailed, and individually different, dismissals of a substantial number of studies by assuming unproven statistical imbalances, unidentified confounders, and failure of recognized methods for dealing with confounding and covariance. In order to explain the null results of Wartenberg *et al*. (2000), and other large prospective studies where tobacco smoke exposure in the referent group was inadequately determined, it is necessary only that the risk for active smokers be reduced to approximately that experienced by passive smokers, not to zero.

7.4.1.5. Conclusions – ETS and Breast Cancer

7.4.1.5.1. Breast Cancer in Younger, Primarily Premenopausal Women

In the 14 studies that evaluated younger, primarily premenopausal women, there is a strong and consistent association found between ETS exposure and breast cancer risk. Thirteen of these studies found risk estimates between 1.10 and 7.10 of which seven were statistically significant (Table 7.4.1C). All of the six studies considered by OEHHA to be most informative found risk estimates of 1.59 or greater and were statistically significant (Table 7.4.1G). The meta-analysis of breast cancer risk for younger women obtained a risk estimate of 1.68 (95% CI 1.31-2.15),

and the meta-analysis of the better exposure studies for premenopausal women results in a pooled risk estimate of 2.2 (95% CI 1.69-2.87).

Overall, the weight of evidence (including toxicology of tobacco smoke constituents, epidemiological studies, and breast biology) is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women (see Figure 7.4.4). It must be noted here that the cohort studies which evaluated menopausal status or age as a surrogate did so at enrollment, not at diagnosis (or death, as in Wartenberg *et al.* 2000*).* Thus, when these studies report breast cancer risk in "premenopausal" women, they really are referring to women who were premenopausal or younger than age 50 (versus postmenopausal or older than 50) at enrollment. The case-control studies generally considered either age or actual menopausal status at diagnosis for the cases. Thus, it is more accurate to indicate that risks were higher in women whose breast cancer was diagnosed either premenopausally or at younger ages (less than 50 years).

If younger, primarily premenopausal women are the most at risk for breast cancer from ETS exposure, then the cohort studies determining menopausal status at baseline introduce a systematic bias towards the null. This results from incorporating into the "premenopausal" group women diagnosed with breast cancer post-menopause. This misclassification of age or menopausal status may be another reason that many cohort studies overall have shown less of an effect of passive smoking on breast cancer than the case control studies.

ETS appears to present a substantial breast cancer risk relative to other environmental exposures, as much as they are known.

7.4.1.5.2. Breast Cancer in Older PostMenopausal Women

The evidence of an association between ETS exposure and elevated breast cancer risk is more persuasive for those diagnosed at younger ages (mostly premenopausal) than for women diagnosed at older (postmenopausal) age. There were nine studies from which we could extract breast cancer risk estimates for postmenopausal women. In contrast to the findings in younger women, in studies which reported statistics for women diagnosed with breast cancer after menopause risk estimates cluster around a null association (see Figure 7.4.4). There are, however, elevated risk estimates in some studies for postmenopausal women either overall or in specific strata. In addition, it should be noted that there are many studies that show statistically significant elevated risks for breast cancer in postmenopausal active smokers (see Appendix A, Tables 7.ApA1-4). The evidence to date for older/postmenopausal women is, therefore, considered inconclusive. Further research indicating a positive association would be necessary prior to altering this finding.

Table 7.4.1l. Passive smoking and breast cancer risk: case-control studies

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Sandler *et al*. (1985b)[a]	All ages	Spousal	19/76	1.94	0.9-4.2	A, E, R
United States, 1979-1981	Premenopausal	Spousal	6/27	7.1	1.6-31.3	
Case Source = tumor registry	Postmenopausal	Spousal	13/49	0.9	0.4-2.2	
Controls = population	Non-smokers	Spousal	32/177	1.62	0.76-3.44	
Smith *et al*. (1994)	Diagnosis < 36 yrs.	No ETS	48/63	--	Ref	A, AF, AL, AM, BF, FH, HB,
United Kingdom, 1982-1985	Adult only	Partner only	46/37	1.58	0.81-3.10	OC
Case Source = regional registry	Adult only	All sources	16/14	3.13*	0.73-13.31	
Controls = regional registry	Child or adult[b]	Total lifetime	204/199	2.53	1.12-5.71	
Morabia *et al*. (1996)	Never active	No ETS	23/241	--	Ref	A, AF, AM, BMI, E, FH, OC
Switzerland, 1992-1993		All sources	98/379	2.3*	1.5-3.7	
Case Source = Clinic/Breast lab						
Controls = population						
Millikan *et al.* (1998)	Never active	No ETS	89/88	--	Ref	A, AF, AL, AM, FH, HB, P, R
Carolina Breast Cancer Study	Total study	ETS after age 18	158/165	1.3	0.9-1.9	
United States, 1993-1996	Premenopausal	No ETS	52/49	1.0	Ref	A, AF, AL, AM, FH, HB, P, R
		ETS after age 18	71/61	1.5	0.8-2.8	
Case Source = population registry	Postmenopausal	No ETS	37/39	1.0	Ref	A, AF, AL, AM, FH, HB, P, R
Controls = population		ETS after age 18	87/104	1.2	0.7-2.2	
Lash and Aschengrau (1999)	Never active	Never passive	40/139	--	Ref	A, AL, BMI, EC, FH, HB, HR,
United States, 1983-1986		Passive only	80/267	2.0	1.1-3.7	P
Case Source = general population	Relative to 1st	Only Before	6/15	2.8	0.8-9.9	A, BMI, EC, FH, HB, HR, P
Controls = population	Pregnancy	Only After	35/102	2.4	1.2-5.1	
		Both Before/After	21/63	2.2	1.1-4.7	

[a] From Wells (1998a) letter, Am J Epidemiol 147; 991-2. Low = no/rare residential ETS; High = usual/sometimes residential ETS

[b] Derived from Smith *et al.* (1994) Table 4 all non-smokers by combining total lifetime exposure categories as described in our review of study.

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age at menopause; BF = months breast feeding; BMI = Body mass index; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; FP = Fertility problems; HB = History benign breast disease; HR = History radiation; I = Income; M = Menopausal status; OC = Oral contraceptive use; P = Parity; PH = Physical Activity; PSH = passive smoking from husband; R = Race; RE = Residence; W = weight;; WH = waist to hip ratio.

Table 7.4.1l. Passive smoking and breast cancer risk: case-control studies

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Zhao *et al.* (1999)	Premenopausal	Passive only		2.56	1.63-4.01	Unadjusted
China (time not specified)		Overall risk	265/265	2.38	1.66-3.40	
Delfino *et al.* (2000)	No active	No passive	33/96	--	Ref	A, FH, M
United States (time not specified)		Passive only	16/44	1.78	0.77-4.11	*Estimates w/ low-risk controls
Case Source = Clinic/Breast	Never smokers,	Low	33/96	1.00	Ref	A, FH, M
Centers	Adult Exposure*	High	31/51	1.50	0.79-2.87	
Controls = Clinic/Breast Centers	Premenopausal		21/DNS	2.69	0.91-8.00	A, FH, M
	Postmenopausal		DNS	1.01	0.45-2.27	
		Overall risk		1.86	0.81-4.27	
Johnson *et al.* (2000)	Premenopausal	No active/passive	14/35	--	Ref	A, AF, AH, AL, AM, BMI, E, P,
Canada, 1994-1997		Passive only	208/194	2.3	1.2-4.6	PH, RE
Case Source = Population Registry	Exposure Timing	Child only ETS	15/24	1.6	0.6-4.4	
Controls = Population		Adult ETS only	50/43	2.6	1.1-6.0	
		Child & Adult ETS	143/124	2.6	1.2-5.5	
	Postmenopausal	No active/passive	52/92	1.0	Ref	A, AF, AH, AL, AM, BMI, E, P,
		Passive only	334/406	1.2	0.8-1.8	PH, RE
	Exposure Timing	No active/passive	52/92	--	Ref	A, AF, AH, AL, AM, BMI, E, P,
		Child only ETS	15/31	0.9	0.4-2.0	PH, RE
		Adult ETS only	83/109	1.1	0.6-1.8	
		Child & Adult ETS	234/266	1.3	0.8-2.0	
		Overall risk		1.48	1.06-2.07	
Marcus *et al.* (2000)	ETS prior to age 18	No ETS exposure	257/248	--	Ref	A, R, includes ever active
United States, 1993-1996		Exposure	603/603	1.1	0.9-1.3	smokers in
Carolina Breast Cancer Study		No ETS/No Active	99/119	--	Ref	Exposed groups
		Exposure	603/542	0.8	0.6-1.1	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age at menopause; BF = months breast feeding; BMI = Body mass index; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; FP = Fertility problems; HB = History benign breast disease; HR = History radiation; I = Income; M = Menopausal status; OC = Oral contraceptive use; P = Parity; PH = Physical Activity; PSH = passive smoking from husband; R = Race; RE = Residence; W = weight;; WH = waist to hip ratio.

Table 7.4.1l. Passive smoking and breast cancer risk: case-control studies

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Kropp and Chang-Claude (2002)	Never active	No passive	44/144	--	Ref	AL, BF, BMI, E, FH, M
Germany 1992-1995		Any passive	153/310	1.59	1.06-2.39	
		Former passive	92/191	1.55	1.00-2.40	
		Current passive	61/119	1.67	1.04-2.69	
		Overall risk		1.59	1.06-2.39	
Lash and Aschengrau (2002)	Passive smokers	Never	80/53	1.0	Ref	AF, AL, BMI, EC, FH, HB, P
United States, 1987-1995		Ever passive	361/366	0.72	0.55-0.95	
		Overall risk		0.85	0.63-1.10	
Shrubsole *et al.* (2004)		No passive	176/184	1.0	Ref	A, AF, AM, AME, BMI, E, I,
China 1996-1998	All women	Spouse only	231/289	0.9	0.7-1.2	M, PH
Shanghai Breast Cancer Study		Work only	170/158	1.1	0.8-1.5	
		Spouse and work	287/305	1.1	0.8-1.4	
	Premenopausal	Spouse and work	536/599	1.10	0.83-1.46	
		Overall risk		1.02	0.81-1.29	
Gammon *et al.* (2004)		Spousal (mo)				
United States 1996-1997	Ever passive	Never exposed	155/170	1.0	Ref	A, BMI at age 20, FH, FP,
Case source = pathology depts.	Premenopausal	ETS only	163/166	1.21	0.78-1.90	HB, M, P, W
Controls = Population	Post menopausal	ETS only	280-291	0.93	0.68-1.29	
		Overall risk		1.04	0.81-1.35	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age at menopause; BF = months breast feeding; BMI = Body mass index; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; FP = Fertility problems; HB = History benign breast disease; HR = History radiation; I = Income; M = Menopausal status; OC = Oral contraceptive use; P = Parity; PH = Physical Activity; PSH = passive smoking from husband; R = Race; RE = Residence; W = weight;; WH = waist to hip ratio.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Morabia *et al*. (1996)	Never active	No ETS	23/241	--	Ref	A, AF, AM, BMI, E, FH, OC
Switzerland, 1992-1993		1-50 hrs/day-year	44/185	2.2	1.3-3.7	
Case Source = Clinic/Breast lab		> 50 "	54/191	2.5	1.5-4.2	
Controls = population		All sources	98/379	2.3*	1.5-3.7	
Lash and Aschengrau (1999)	Passive-only	Duration Years				
United States, 1983-1986		Never	40/139	1.0	Ref	A, BMI, EC, FH, HB, HR, DE
		≤ 20	28/56	3.2	1.5-7.1	
		> 20	43/148	2.1	1.0-4.1	
Case Source = general population		Age First Exposure				
Controls = Population		< 12 yrs old	14/25	4.5	1.2-16.0	A, BMI, EC, FH, HB, HR, P
		12-20 yrs old	11/30	3.8	1.1-13.0	
		≥ 21 yrs old	34/118	2.4	0.9-6.1	
	Ever active	Age First Exposure				
		< 12 yrs old	26/33	7.5	1.6-36.0	A, BMI, EC, FH, HB, HR, DA,
		12-20 yrs old	10/31	3.9	0.8-20.0	C, DE
		≥ 21 yrs old	46/105	4.7	1.6-14.0	

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Johnson *et al.* (2000)	Premenopausal	Never regular ETS[a]	14/35	--	Ref	A, AF, AH, AL, AM, BMI, E, P,
Canada, 1994-1997	Duration residential	1-6 years	15/24	1.2	0.4-3.4	PH, RE
	plus occupational	7-16 years	21/23	1.8	0.7-4.9	
Case Source = Population Registry	ETS	17-21 years	25/34	2.0	0.8-5.0	
Controls = Population		22-35 years	76/57	3.3	1.5-7.5	
		≥ 36 years	71/56	2.9	1.3-6.6	
				p trend = 0.0007		
		1-13 smoker-years[b]	14/20	1.5	0.5-4.4	A, AF, AH, AL, AM, BMI, E, P,
		14-32 smoker-years	47/57	2.0	0.9-4.5	PH, RE
		33-70 smoker-years	65/58	2.9	1.3-6.6	
		≥ 71 smoker-years	82/59	3.0	1.3-6.6	
				p trend = 0.03		
	Postmenopausal	Never regular ETS	52/92	--	Ref	A, AF, AH, AL, AM, BMI, E, P
	Duration residential	1-30 years	117/152	1.1	0.7-1.9	
	plus occupational	31-56 years	110/129	1.3	0.8-2.1	
	ETS	> 57 years	107/125	1.3	0.8-2.1	
				p trend = 0.27		
		1-45 smoker-years	105/155	1.0	0.6-1.7	
		46-89 smoker-years	114/126	1.3	0.8-2.1	
		> 89 smoker-years	115/125	1.4	0.9-2.3	
				p trend = 0.07		

[a] Sum of the total yrs residential exposure and total yrs occupational exposure

[b] Sum of lifetime residential exposure (# smokers in home × yrs) plus sum of occupational exposure (# employees who smoked regularly in immediate area × # yrs at that job)

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Lash and Aschengrau (2002)	Passive smokers	Duration ETS (yrs)				
United States, 1987-1995		Never	80/53	1.0	Ref	AF, AL, BMI, EC, FH, HB, P
		0-< 20	54/49	0.87	0.59-1.3	
		20-< 40	79/58	0.94	0.66-1.3	
		≥ 40	31/34	0.75	0.47-1.2	
		Age first lived with smoker				
		< 12	66/44	0.99	0.67-1.4	
		12-20	20/20	0.84	0.49-1.4	
		> 20	58/57	0.79	0.54-1.1	
		Pregnancy demarcated passive				
		All before first	23/11	1.1	0.64-1.9	
		Before + after first	59/42	0.85	0.56-1.3	
		All after first	19/32	0.55	0.31-0.96	
		Never gave birth	58/43	1.0	0.60-1.8	
Kropp and Chang-Claude (2002)	Passive	Never ETS	44/144	--	Ref	AL, BF, BMI, E, FH, M
		1-10 years	20/43	1.51	0.78-2.95	
Germany 1992-1995		≥ 11 years	68/154	1.45	0.92-2.29	
		Only as adult	65/113	1.80	1.12-2.89	
	Lifetime passive	1-50 hrs/day-years	64/149	1.42	0.90-2.26	
		≥ 50 hrs/day-years	88/153	1.83	1.16-2.87	
				P trend = 0.009		

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Shrubsole *et al*. (2004)	Total group	Work none	176/184	--	Ref	A, AF, AM, AME, E, FH, HB, P, PH, PSH, WH
China, 1996-1998		1-59 min/d	108/139	0.9	0.6-1.3	
Shanghai Breast Cancer Study		60-179	138/143	1.1	0.8-1.6	
		180-299	99/99	1.1	0.8-1.7	
		300+	112/82	1.6	1.0-2.4	
				P trend = 0.02		
	Premenopausal	Work none	113/126	--	Ref	
		1-59 min/d	83/117	0.9	0.6-1.4	
		60-179	102/114	1.0	0.7-1.6	
		180-299	80/86	1.1	0.7-1.7	
		300+	92/97	1.6	1.0-2.5	
				P trend = 0.03		
	Postmenopausal	Work none	63/58	--	Ref	
		1-59 min/d	25/22	1.1	0.5-2.3	
		60-179	36/29	1.3	0.6-2.6	
		180-299	19/13	1.4	0.6-3.7	
		300+	20/15	1.4	0.6-3.1	
				P trend = 0.37		

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1J. Passive smoking and breast cancer risk: case-control studies which assessed dose-response

Case-control Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Gammon *et al*. (2004)	Total Group	Never ETS	155/170	1.0		A, BMI, FH, FP, HB, M, P
		Passive Only	443/457	1.04	0.81-1.35	Weight in prior year
		Active Only	127/131	1.06	0.76-1.48	
		Passive and Active	631/625	1.15	0.90-1.48	
	Ever Passive Only	1-192 months	83/83	1.07	0.73-1.57	
	Spouse + other	193-360	161/205	0.84	0.62-1.14	
		361+	194/166	1.22	0.90-1.66	
	Ever Passive Only	1-181 months	85/69	1.50	1.05-2.14	
	Spouse exposure	182-325	66/79	1.01	0.70-1.47	
		326+	109/68	2.10	1.47-3.02	
	Ever passive only	1-304 months	60/59	0.97	0.64-1.47	
	Parental exposure	305-548	191/199	1.03	0.79-1.33	
	Prior to age 18	549+	567/617	0.93	0.78-1.12	

Factors adjusted for: A=Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; BF = months breast feeding; BMI = Body mass index; C = # cigarettes/day; DA = duration active smoker; DE = duration ETS; E = Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HR = History radiation; M = menopausal ststus; P = Parity; PH = Physical Activity; RE = Residence.

Table 7.4.1K. Passive smoking and breast cancer risk: case-control studies with gene modification

Case-control Study	Genotype and Menopausal Status								Factors Adjusted
Millikan *et al.* (1998)	PREMENOPAUSAL				POSTMENOPAUSAL				
	NAT1*10		NAT1-non*10		NAT1*10		NAT1-non*10		
Never Active Smokers w/ ETS exposure									
No ETS	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	A, AF, AL, AM, FH, HB, P, R
ETS after age 18	1.7	0.7-4.3	1.3	0.5-3.2	1.2	0.6-2.6	1.3	0.5-3.6	
	NAT2-rapid		NAT2-slow		NAT2-rapid		NAT2-slow		
Never Active Smokers w/ ETS exposure									
No ETS	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	A, AF, AL, AM, FH, HB, P, R
ETS after age 18	2.3	0.9-6.2	1.2	0.5-2.8	0.8	0.4-1.8	1.9	0.7-5.2	
Morabia *et al.* (1998)	PREMENOPAUSAL				POSTMENOPAUSAL				
	ER- Cases		ER+ Cases		ER- Cases		ER+ Cases		
Smoking Status									A
Never	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	
Ever passive	4.2	0.9-19.0	1.7	0.7-4.0	3.4	1.0-12.1	1.8	1.0-3.2	
Morabia *et al.* (2000)	PREMENOPAUSAL				POSTMENOPAUSAL				
	NAT2-rapid		NAT2-slow		NAT2-rapid		NAT2-slow		
Smoking Status									A, E, FH
Never	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	
Ever passive	3.3	0.7-15.7	3.2	0.9-11.5	11.6	2.2-62.2	1.1	0.3-4.3	
Lilla *et al.* (2005)	SULT1A1*1/*1				SULT1A1*2				
	NAT2-rapid		NAT2-slow		NAT2-rapid		NAT2-slow		
Smoking Status									
Never	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent	A, AL, BF, BMI, E, FH, M, P
Ever passive	3.23	1.05-9.92	1.35	0.62-2.91	1.28	0.50-3.31	1.18	0.53-2.66	

Factors adjusted for: A = Age; AF = Age first childbirth; AL = Alcohol consumption; AM = Age menarche; BF = Breastfeeding; BMI = Body mass index; E = Education; FH = Family history breast; HB = History benign breast disease; M = Menopausal status; P = Parity; R = Race

Table 7.4.1L. Passive smoking and breast cancer risk: cohort studies

Cohort Study	Smoking Exposure	#Cases	Adjusted RR	95% CI	Factors Adjusted
Hirayama (1984)[a]	Never active No ETS		--	Ref	A, AF, AM, BMI, E, FH, HB, OC
Japan, 1966-1981	Spousal All	115	1.32	0.83-2.09	
Study size = 142,857					
Jee *et al.*, (1999)	Spousal Smoking Status				
Korea Medical Insurance Corp,	Non-smoker	DNS	1.0	Referent	A, RE, SES, SO, SV
1992-1997	Current	DNS	1.3	0.9-1.8	
Study Size=160,130	Current +30 yrs	DNS	1.7	1.0-2.8	
Total Cases=138	Ex-smoker	DNS	1.2	0.8-1.8	
Wartenberg *et al.* (2000)	Spousal Smoking Status (at baseline 1982):				
American Cancer	Never smoker	273	1.0	Referent	A, AF, AL, AM, AME, BMI, DF, DV,
Society CPS II	Current smoker	166	1.0	0.8-1.2	E, FH, HB, HRT, NSA, O, OC, R, SO
United States, 1982-1994	Former smoker*	230	1.0	0.8-1.2	
Study Size=146,488	ETS-Home	DNS	1.1	0.9-1.3	
Total Deaths=669	ETS-Work	DNS	0.8	0.6-1.0	
	ETS-Other Places	DNS	0.9	0.7-1.2	
Nishino *et al.* (2001)	Spousal	67	0.58	0.32-1.1	A, AF, AL, AM, BMI, DV, P
Egan *et al.* (2002)	Parental smoking				
Nurse's Health Study	Neither parent	472	1.00	Referent	A, AM, AF, AH, AL, AME, CAR, FH,
United States, 1982-1996	Mother Only	36	0.98	0.70-1.38	HB, HRT, M, P, WT18, WTA
Study Size = 78,206	Father Only	587	1.12	0.99-1.27	
Total Cases = 3,140	Both	127	0.92	0.76-1.13	
	Current Work or Home				
	None	184	1.00	Referent	
	Occasionally	611	1.16	0.98-1.36	
	Regularly, W or H	306	1.00	0.83-1.20	
	Regularly, W and H	57	0.90	0.67-1.22	

[a] From Wells (1998a) letter, Am J Epidemiol 147; 991-2. DNS = Data not presented in original publication.

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; PH = Physical activity; R = Race; RE = Residence; SES = Socioeconomic status; SO = Spousal Occupation; SV = Spousal vegetable intake; WT18 = Weight 18 years; WTA = Adult weight

Table 7.4.1L. Passive smoking and breast cancer risk: cohort studies

Cohort Study	Smoking Exposure	#Cases	Adjusted RR	95% CI	Factors Adjusted
Reynolds *et al.* (2004a)	Household				A,AF,AL,AM,BMI,FH,HRT,PH
California Teachers Study	**Full study**				
United States 1995-2000	Never	316	1.00	Referent	
	Childhood only	307	0.92	0.78-1.07	
	Adulthood only	211	0.94	0.79-1.12	
	Any	848	0.94	0.82-1.07	Excluding passive smokers from referent
	Pre-/perimenopausal				
	Never	78	1.00	Referent	
	Childhood only	96	0.93	0.69-1.26	
	Adulthood only	31	1.01	0.66-1.54	
	Any	179	0.93	0.71-1.44	Excluding passive smokers from referent
	Postmenopausal				
	Never	205	1.00	Referent	
	Childhood only	180	0.93	0.76-1.14	
	Adulthood only	161	0.88	0.71-1.08	
	Any	583	0.92	0.78-1.08	Excluding passive smokers from referent
Hanaoka et al., (2005)	**Full study**				A, AL, AM, BMI, E, FH, HB, HU, M, O, P
Japan Public Health Center	Never + no ETS	40	1.0	Referent	
Japan, 1990-1999	ETS	122	1.1	0.8-1.6	
	Premenopausal at baseline				
	Never + no ETS	9	1.0	Referent	
	ETS	68	2.6	1.3-5.2	
	Postmenopausal at baseline				
	Never + no ETS	31	1.0	Referent	
	ETS	52	0.6	0.4-1.0	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; PH = Physical activity; R = Race; RE = Residence; SES = Socioeconomic status; SO = Spousal Occupation; SV = Spousal vegetable intake; WT18 = Weight 18 years; WTA = Adult weight

Table 7.4.1M. Passive smoking and breast cancer risk: cohort studies which assessed dose-response

Cohort Study	Smoking Exposure		#Cases	Adjusted RR (95% CI)		Factors Adjusted
Wartenberg *et al.* (2000)	**Spousal – Amount** (at baseline 1982)					
American Cancer	Never smoker		217	1.0	(Referent)	A, AF, AL, AM, AME, BMI, DF, DV,
Society CPS II	Current/former smoker	<1	49	0.9	(0.6-1.2)	E, FH, HB, HRT, NSA, O, OC, R, SO
United States	(packs/day):	1	67	0.9	(0.7-1.1)	
1982-1994		> 1 to <2	43	1.1	(0.8-1.6)	
Study Size = 146,488		≥ 2	45	1.0	(0.7-1.3)	p trend=0.8
Total Deaths = 669	**Spousal – Duration** (at baseline 1982)					
	Years smoked, current	1-10	29	0.8	(0.6-1.2)	
(Lifelong never-smoking	or former smoker	11-20	31	0.7	(0.5-1.0)	
women married to current or		21-30	62	1.0	(0.7-1.3)	
former smokers)		≥ 31	82	1.1	(0.9-1.4)	p trend=0.7
	Spousal Pack-years	1-12	46	0.8	(0.6-1.2)	
		> 12-25	41	0.8	(0.6-1.1)	
		> 25-41	58	1.0	(0.8-1.4)	
		> 41	59	1.0	(0.8-1.4)	p trend=0.8
	Years smoked; current	1-10	DNS	DNS	(DNS)	
	smoker	11-20	DNS	2.5	(1.3-5.1)	
		21-30	DNS	1.1	(0.7-1.6)	
		>31	DNS	0.9	(0.6-1.2)	p trend=DNS
	Reported ETS exposures from all sources combined (at baseline 1982)					
	Daily Hours	1-hour	DNS	1.0	(0.8-1.2)	
		2- to 4-hour	DNS	1.0	(0.8-1.3)	
		5- to 8-hour	DNS	0.9	(0.7-1.2)	
		>9 hour	DNS	0.7	(0.4-1.3)	p trend=DNS
Egan *et al.* (2002)	Years lived w/ smoker:	< 5	646	1.00	(Referent)	A, AM, AF, AH, AL, AME, CAR, FH,
Nurse's Health Study		5-9	84	0.88	(0.69-1.09)	HB, HRT, M ,P, WT18, WTA
United States, 1982-1996		10-19	166	0.91	(0.77-1.08)	
Study Size=78,206		20-29	179	0.93	(0.79-1.10)	
Total Cases=3,140		30+	146	1.03	(0.86-1.24)	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; R = Race; SO = Spousal Occupation; WT18 = Weight 18 years; WTA = Adult weight. DNS = Data not presented in original publication.

Table 7.4.1M. Passive smoking and breast cancer risk: cohort studies which assessed dose-response

Cohort Study	Smoking Exposure		#Cases	Adjusted RR (95% CI)		Factors Adjusted
Hanaoka et al., (2005)	**Premenopausal**					A, AL, AM, BMI, E, FH, HB, M, O, OC,P,
Japan, 1990-1999	Work and/or public	~ none		1.0	(Referent)	Public health center
Total cases = 180		1-3 d/mo		0.6	(0.4-2.4)	
Premenopausal cases=68		> 3 d/mo		2.2	(1.4-3.7)	p trend=0.002

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AME = Age menopause; BMI = Body mass index; CAR = Carotenoid intake; DF = Dietary fat; DV = Dietary vegetable intake; E = Education; FH = Family history breast; HB = History benign breast disease; HRT = Hormone replacement therapy; M = Menopausal status; NSA = Number spontaneous abortions; O = Occupation; OC = Oral contraceptive use; P = Parity; R = Race; SO = Spousal Occupation; WT18 = Weight 18 years; WTA = Adult weight. DNS = Data not presented in original publication.

7.4.2. Stomach Cancer

7.4.2.1. Summary of Previous Findings

As discussed in the previous OEHHA report (Cal/EPA, 1997), the single mortality cohort of Hirayama (1984) reported unadjusted risk estimates for ETS exposure (nonsmoking women with smoking spouses) and stomach cancer. No association was observed. However, these associations with active smoking were not adjusted for dietary or other risk factors for stomach cancer. In summary, thus far there is no epidemiological evidence for an association between ETS exposure and stomach cancer, but research on this issue has been extremely limited.

7.4.2.2. Recent Epidemiological Data

Three primary studies investigating the relationship between passive smoking and stomach cancer were available for review (Jee *et al*., 1999; Nishino *et al.*, 2001; Mao *et al.*, 2002).

Jee et al., 1999. This study, described in Section 7.2.3, included stomach cancer incidence in a study of lung cancer among Korean women whose husbands smoked. In this study there was no association between exposure to spousal ETS and stomach cancer. Among spouses of current smokers, the risk of stomach cancer was 0.9 (95% CI 0.6; 1.2), and 1.0 (95% CI 0.7; 1.5) among spouses of ex-smokers after adjustment for husband's and wife's ages, SES, residency, husband's occupation, and husband's vegetable consumption.

Nishino et al., 2001. As previously described, the Japanese prospective cohort analyzed for several tobacco-related cancers, including cancer of the stomach among non-smoking women exposed via smoking spouses. Eighty-three cases of stomach cancer (57 among non-smokers) were identified in the cohort. No elevated risk was associated with spousal ETS exposure after either age-adjustment [RR 0.95 (95% CI 0.58-1.6)] or adjustment for other multiple factors including dietary [RR 0.98 (95% 0.59-1.6)].

Mao et al., 2002. A population-based Canadian case-control study assessed the stomach cancer risk associated with both active and passive smoking in eight Canadian provinces. Cases were obtained from population-based cancer registries between 1994 and 1997 (1,175 cases responded, 63%). Population controls were frequency matched as with the previously described breast cancer study (Johnson *et al.*, 2000). Mailed questionnaires were used to obtain a variety of demographic, economic, occupational, residential, dietary and smoking data. Active smoking risk estimates were adjusted for age, residence, education, social class, and dietary factors (meat, vegetables, fruit and juice intake).

Never-smoking males exposed to ETS had elevated stomach cancer risk (subsite cardia) associated with total ETS exposure (residential and occupational years exposed) which was statistically significant at the highest exposure duration [1-22 years: adjusted OR 3.5 (95% CI 0.7-17.3); 23-42: adjusted OR 2.8 (95% CI 0.5-14.2); $\geq$ 43: adjusted OR 5.8 (95% CI 1.2-27.5)], and which showed evidence of a trend with increasing exposure, p for trend 0.05. No increased risk was associated with distal stomach cancer. Only seventeen cases were reported in females, with no risk estimates reported.

7.4.2.3. Summary of ETS and Stomach Cancer

The single, well-designed population-based case-control study provides minimal evidence that ETS exposure may increase the risk of stomach cancer, particularly cancer of the cardia (Mao *et al.*, 2002). However, additional studies will be required to determine the association between ETS exposure and stomach cancer risk, particularly by subsite and sex.

7.4.3. Brain Tumors

7.4.3.1. ETS and Adult Brain Cancer Risk

7.4.3.1.1. Previous Findings

Three studies, one cohort (mortality) and two case-control studies, previously reviewed by OEHHA (Cal/EPA, 1997), presented limited evidence of a relationship between ETS exposure and brain tumors. The cohort study, which analyzed cancer mortality outcomes among nonsmoking women of smoking spouses, identified 34 deaths related to brain cancer, with an apparent significant dose response with the amount of husband's daily cigarette consumption (Hirayama 1984). The two case-control studies gave inconsistent results (Sandler *et al.*, 1985b; Ryan *et al.*, 1992): the one study specifically designed for brain tumors (meningiomas and gliomas) found a significant association between ETS and meningioma [RR 2.5 (95% 1.0-6.1)]; however, results are confused by a comparison group which potentially included active smokers. Therefore, the association between ETS exposure and adult brain malignancies remains inconclusive.

7.4.3.1.2. Recent Epidemiological Data

Only one new primary study was located (Hurley *et al*., 1996), however this study emphasized active smoking with only cursory treatment of the effects of ETS exposure. In addition, one published abstract reported a dose-related trend in brain cancer risk with ETS exposure in a Canadian case-control study; however, limited data were provided (KC Johnson; personal communication).

Hurley et al. (1996). This Australian case-control study was conducted within the Melbourne adult brain tumor study, a study designed to investigate glioma risk and occupational exposure to chemicals and electromagnetic radiation. Cases were 416 individuals with histologically confirmed glioma diagnosed between 1987 and 1991. There were 422 population controls matched by age and gender. Information relating to smoke exposure, diet, alcohol use, and demographics was collected by questionnaires followed by interviews. Risks were estimated by logistic regression analyses adjusted for age, gender and date of diagnosis or selection. There was no adjustment for diet or exposure to N-nitroso-containing compounds, possibly because they did not alter the results by more than 10%.

The risks associated with active smoking were generally elevated, especially for men, but the results appeared inconsistent with a causal role for smoke in glioma incidence (see Table 7.4.3A). For example, men who smoked for less than 10 years had a higher and significant risk for glioma (OR 2.49, 95% CI 1.25; 4.29) than did those who had smoked longer. Similarly, those who had started smoking after age 20, and so presumably had a shorter smoking history, had a higher risk (2.73, 95% CI 1.48; 5.02) than did those who started before age 20. When

smoking was measured as pack years, the highest risk was associated with the lowest number of years although none of these values was significant. The authors recognized that their results may be the result of chance, response bias or uncontrolled confounding. Indeed, the results suggest that systematic bias is a strong possibility. These results may also reflect an interaction between smoking and some unidentified environmental exposure.

Table 7.4.3A Active smoking and risk of glioma in adult men and women.

	All subjects		Women	Men
	Exposed cases/controls	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Never smoked		1.00	1.00	1.00
Ever smoked	242/232	1.29 (0.95; 1.75)	0.99 (0.62; 1.62)	1.64 (1.10; 2.45)
Pack years				
0		1.00	1.00	1.00
0-9	76-72	1.19 (0.79; 1.80)	0.89 (0.47; 1.70)	1.59 (0.91; 2.79)
9-24	63/81	1.01 (0.66; 1.54)	0.77 (0.37; 1.61)	1.20 (0.71; 2.04)
≥ 24	62/77	1.04 (0.66; 1.64)	1.06 (0.66; 1.71)	1.23 (0.71; 2.12)
Duration (yrs)				
Never		1.00	1.00	1.00
<10	54/43	1.37 (0.84; 2.24)	0.75 (0.35; 1.60)	2.49 (1.25; 4.29)
10-20	52/59	1.05 (0.66; 1.68)	1.10 (0.45; 2.68)	1.12 (0.64; 1.97)
≥ 20	117/128	1.25 (0.86; 1.83)	1.17 (0.63; 2.19)	1.48 (0.90; 2.42)
Start age (yr)				
Never		1.00	1.00	1.00
< 20	172/170	1.21 (0.85; 1.64)	1.17 (0.67; 2.08)	1.42 (0.93; 2.18)
>20	68/62	1.48 (0.80; 1.93)	0.78 (0.40; 1.52)	2.73 (1.48; 5.02)

In the context of ETS, there was no significant association reported between glioma and passive smoke exposure among nonsmokers as defined by living with a smoker (OR 0.97, 95% CI 0.61; 1.53). However, whereas the results for active smoking were presented for men and women separately and combined, with significant effects only seen for men, the results for passive smoking presumably represent both genders combined. It is thus not possible to tell whether passive smoking differentially affected men's risks as it appeared to do for active smoking. In addition, in the analysis of passive smoking, there is no indication whether any adjustments were made for possible confounding or consideration given to other sources of ETS exposure. While this study does not provide evidence for an association between ETS exposure and glioma, the results for active smoking are inconclusive.

7.4.3.2. ETS and Brain Cancer Risk in Children/Young Adults

7.4.3.2.1. Previous Findings

In the 1997 report, OEHHA reviewed a total of ten published studies examining the potential relationship between ETS exposure and the risk of developing childhood brain cancer. The ten studies varied in the method of case ascertainment, age of eligible cases (< 15 years, ≤ 18 years, <20 years, <25 years at time of diagnosis), availability of paternal smoking data (six of ten studies), and whether the study was specifically designed to identify potential risk factors for developing childhood brain cancer. Data from the ten studies did not support an association between childhood cancer and maternal smoking during or before pregnancy. Three population-

based (Preston-Martin *et al.*, 1982; John *et al.*, 1991; McCredie *et al.*, 1994) and one hospital based (Howe *et al.*, 1989) case-control studies found a small increased risk for brain tumors relative to paternal smoking, with two studies finding statistically significant associations (Preston-Martin *et al.*, 1982; McCredie *et al.*, 1994). The range of risk estimates for paternal smoking in these positive studies ranged from 1.5 (p=0.03) (Preston-Martin *et al.*, 1982) to 2.2 (95% CI 1.25-3.85) (McCredie *et al.*, 1994).

7.4.3.2.2. Recent Epidemiological Data

Table 7.4.3B summarizes results from twelve published studies reporting on childhood brain cancer risk and ETS exposure. The studies are described below.

Bunin et al., 1994. This U.S./Canada case-control study identified 155 cases of astrocytic glioma and 199 cases of primitive neuroectodermal tumor (PNET) through a pediatric oncology cooperative group, the Children's Cancer Group. Cases were diagnosed before age 6 in 1986 to 1989 and matched to population-based controls on race, age, and residential area. Data on maternal and paternal smoking (prior and during pregnancy) and maternal ETS exposure were collected via interview. No elevated risk was observed for either astrocytoma or PNET for either maternal (ever, during pregnancy or maternal ETS) or paternal smoking (ever or during pregnancy). All statistically non-significant risk estimates remained near unity; adjusted ORs ranged from 0.9-1.0 (Table 7.4.3B).

Cordier et al., 1994. This case-control study of childhood brain cancer investigated a variety of risk factors in children diagnosed prior to age 15 in Ile de France. Cases were derived from 13 hospitals and matched to population controls by year of birth. Interviews were conducted with the families of 75 of the possible 109 cases. Maternal smoking during pregnancy was associated with an elevated, statistically non-significant risk of childhood brain cancers (all histologies combined), adjusted for age, education, sex and maternal age [adjusted OR 1.6 (95% CI 0.7-3.5)]. Prenatal exposure to tobacco smoke, whether from maternal smoking, other household sources, or workplace smoke, was also associated with an elevated but not statistically significant risk [adjusted OR 1.5 (95% CI 0.8-2.8)]. The highest risk which was statistically significant was associated with postnatal, childhood exposure to tobacco smoke (maternal, household or other sources) [adjusted OR 2.3 (95% CI 1.1-4.6)] (Table 7.4.3B). No estimates or discussion on risk related to paternal smoking were provided. The authors reported that no dose-response of risk estimates based on duration of exposure or quantity of tobacco was found (no data presented).

Filippini et al., 1994. This case-control study across several Northern Italy provinces enrolled 91 of 103 primary brain cancer cases identified from hospital and other medical resources diagnosed between 1985 and 1988 in children under age 15. Population controls were matched on age, sex and residence. The comparison or unexposed group was defined as mothers that either never smoked or were ex-smokers at "time of conception" and had no ETS exposure either immediately prior to conception or during pregnancy. Ever-lifetime parental smoking was associated with a slightly elevated, but statistically non-significant, risk of childhood brain tumors after adjustment for parental education [maternal ever lifetime smoking OR 1.2 (95% CI 0.8-2.0); paternal ever lifetime smoking OR 1.3 (95% CI 0.7-2.2)]. Non-smoking mothers exposed to ETS during pregnancy had an elevated, but statistically nonsignificant risk of having a child diagnosed with a brain tumor [adjusted OR 2.0 (95% CI 1.0-4.0)]. However, the risk

estimate became significant for the highest exposure category. There was evidence of a dose-response [ORs of 1.7 (95% CI 0.8-3.8) and 2.2 (95% CI 1.1-4.6) for ≤ 2 hrs and > 2 hrs/day ETS exposure, respectively] (Table 7.4.3B).

Linet et al., 1996. This nested case-control Swedish study identified 570 incident childhood brain tumor cases through linkages of the Swedish Birth and Cancer registries. Population-based controls (five per case) matched on sex and age were selected from the Birth Registry (study years 1973-89). The majority of cases (98%) were diagnosed prior to age 15 with 10 cases diagnosed in adolescents ages 15 to 17. Unfortunately, maternal smoking status was only ascertained since 1983, therefore 466 cases and 2330 controls lacked smoking data. This left a total of 96 cases and 484 controls for which there were data on which to base an analysis of the effect of maternal smoking. No statistically significant risk was associated with maternal smoking for all brain tumors combined or for the individual tumor subgroups; however, the majority of cases had no data on maternal smoking.

Norman et al., 1996. This large, population-based case-control study identified incident brain cancer cases from three Surveillance, Epidemiology, and End Results Program (SEER) cancer registries in Los Angeles, Seattle and the San Francisco Bay Area, among children and young adults under age 20 between 1984 and 1991. No statistically significant association was found between the risk of childhood brain tumors (all histologies combined) and maternal or paternal smoking before pregnancy or with maternal smoking during pregnancy. An elevated but statistically non-significant risk of brain tumors was associated for paternal smoking alone during pregnancy [adjusted OR 1.2 (95% CI 0.90-1.5)] and for maternal smokers with additional exposure to ETS [adjusted OR 1.2 (95% CI 0.93-1.4)] (Table 7.4.3B). Similarly elevated, but non-significant risk estimates were reported for maternal ETS exposure among non-smoking mothers and/or smoking mothers after cases were stratified by age into cases diagnosed ≤ 5 years of age or > 5 years of age; adjusted ORs ranged from 1.1 (95% CI 0.76-1.5) to 1.3 (95% CI 0.87-1.9). Although the authors stated that effects of early childhood exposure to tobacco smoke were also explored, only one result was reported. No significant elevation in risk for brain tumors was found for children that lived for 6 months or more with a smoker [OR 0.93 (95% CI 0.74-1.17)].

Ji et al., 1997. As part of the population-based case control study in Shanghai, China, investigators evaluated the association between parental smoking and childhood brain cancer incidence. Cases diagnosed from 1981 through 1991 were ascertained from a population-based cancer registry among children under the age of 15. A total of 107 cases matched to population controls based on age, sex and local governmental sampling unit were included. Only paternal smoking was analyzed in this study.

Paternal smoking status (ever versus never) was associated with an elevated, but not statistically significant, risk for all childhood brain cancers combined [adjusted RR 1.4 (95% C.I. 0.6-3.2)] after adjustment for birth weight, income, paternal age, education and alcohol consumption. Adjusted risk estimates were highest for children of fathers that smoked for longer periods or more heavily during conception [adjusted RR 2.7 (95% C.I. 0.8-9.9), children of fathers smoking more than 5 pack-years before conception] (Table 7.4.3B). The level of paternal smoking after birth was not associated with an increased risk of childhood brain cancer. Additionally, as found in the study for all cancer sites combined, the risk was greatest in children diagnosed under age

5; cases in children ages 5 and older did not appear associated with paternal preconception smoking.

Sorahan et al. 1995; 1997a; 1997b. Three United Kingdom case-control studies of childhood cancer deaths in relation to reported parental tobacco consumption have been published from the Oxford Survey of Childhood Cancers (OSCC) (Sorahan *et al.*, 1995; Sorahan *et al.* 1997a; Sorahan *et al.*, 1997b). All three OSCC studies found no statistically significant association between maternal smoking (prior to or during pregnancy) and risk of childhood death due to tumors of the central nervous system (CNS) for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981, with risk estimates remaining near unity [RR range 0.9-1.1]. However, one of the studies identified a slightly higher, but statistically nonsignificant positive relationship between paternal smoking and childhood deaths due to tumors of the CNS [unadjusted OR 1.20 (95% CI 0.96-1.51)] (Sorahan *et al.* 1997a). The investigators also conducted a pooled analysis, consisting of 1,071 matched pairs total for CNS tumors. Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significant relative risk estimate [RR 1.30 (95% CI 1.06-1.59)] for tumors of the central nervous system from all three time periods combined (Sorahan *et al.*, 1997b). The newer study adjusted for several important confounders, including social class and paternal age, with little effect on the risk estimates (Sorahan *et al.*, 1997b) (Table 7.4.3B).

Sorahan et al., 2001. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) report included a reanalysis of 32 incident cases with maternal and 29 with paternal smoking data, among children under age 15 diagnosed with tumors of the central nervous system, 1980-1983 (Birch *et al.*, 1990; Sorahan *et al.*, 2001). Maternal and paternal smoking habits prior to conception were analyzed and presented separately, and the presented CNS-specific risk estimates were not adjusted for other factors. Daily levels of cigarette smoking (cigarettes/day) by either parent were not positively associated with increased risk of childhood CNS tumors (p-value for trend=0.67 and 0.71, for paternal and maternal smoking, respectively) (Table 7.4.3B).

Schuz et al., 1999. This population-based German case-control study interviewed 1,867 of 2,358 eligible incident childhood cancer cases identified through the German Childhood Cancer Registry (all sites combined), diagnosed among children under age 15 between 1992 and 1997. In the study, 399 cases of tumors of the central nervous system were included. Interview data included parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Data were presented independently for maternal smoking during pregnancy and paternal smoking before pregnancy (cigarettes/day). No association between parental smoking and risk of childhood brain tumors was found with statistically non-significant adjusted ORs ranging 0.8-1.1 (adjusted for urbanization and socioeconomic status based on income and parental education; Table 7.4.3B).

Filippini et al., 2002. A multi-country, multi-center study on childhood brain tumors organized by the International Agency for Research on Cancer (IARC) identified incident cases of cancer over a range of time periods (1980's and 1990's) in the U.S., Europe, Israel, Canada, and Australia. From the 1,640 eligible cases, 1,218 agreed to participate (74%) through maternal interview. Population controls were obtained at each study site by varying methods. Smoking questions included obtaining information on maternal smoking (before and during pregnancy),

paternal smoking (during pregnancy), other maternal ETS exposure (household or workplace), and childhood ETS exposure during year one. The overall risk for childhood brain cancer, all histological groups combined, was not significantly associated with either maternal or paternal smoking (before or during pregnancy) or with childhood ETS exposure after birth for the first year (adjusted for age, sex and study center). However, analysis by subtype did find elevated cancer risk for astroglioma with paternal smoking [adjusted OR 1.2 (95% CI 1.0-1.5)] and for primitive neuroectodermal tumor (PNET) with maternal ETS exposure [adjusted OR 1.3 (95% CI 1.0-1.7)]. Analysis stratified by age at diagnosis identified an increased overall cancer risk for children diagnosed under age 1 with paternal smoking during pregnancy [adjusted OR 1.7 (95% CI 1.0-2.9)]. However, overall no consistent association between childhood brain cancer and paternal smoking was observed. The occasional, scattered, slightly increased or decreased risks noted in certain subgroups was ascribed by the authors to multiple testing in the analysis.

7.4.3.3. Summary of ETS and Brain Cancer

In adults, the epidemiological evidence for an association between ETS exposure and risk of brain tumor remains weak and inadequately researched. More recent studies have focused on the potential association between ETS and childhood brain tumors. In children, recent studies or others not previously reviewed by OEHHA provide no substantial evidence for an association between maternal smoking and childhood brain tumors, with risk estimates generally near unity. Two European case-control studies reported more elevated, but nonetheless nonsignificant increases in risk, OR 1.6-1.7 for any maternal smoking (Cordier *et al.*, 1994; Filippini *et al.*, 1994). However, brain cancer risk was significantly elevated among children with any postnatal ETS exposure, OR 2.3 (95% CI 1.1-4.6) (Cordier *et al.*, 1994). Several studies indicated a slightly stronger association with paternal smoking and brain cancer than noted in the previous CAL/EPA (1997) report, although the association is still somewhat weak. The most recent and largest individual study (Filippini *et al.*, 2002) did not consistently observe statistically elevated brain cancer risk.

Paternal smoking was generally reported as ever active or ever smoking during pregnancy. Generally risk estimates were similar to or slightly higher than maternal smoking, but nonsignificant (Norman *et al.*, 1996; Ji *et al.*, 1997; Sorahan *et al.*, 1997a; Sorahan *et al.*, 1997b; Filippini *et al.*, 2002). However, the pooled estimate of risk from the OSCC studies (together the largest sample size of the studies reviewed), comparing paternal smokers versus paternal nonsmokers, was significant [RR 1.30 (95% CI 1.06-1.59)] for deaths from tumors of the central nervous system for all three time periods combined (Sorahan *et al.*, 1997b). One study also reported data mildly suggestive of a dose response (but without significant trend tests) for brain tumors and paternal smoking (Ji *et al.*, 1997). Overall, the generally positive, but inconsistent, associations reported between paternal smoking and childhood brain tumors, in combination with biologically plausible hypothesis, provide suggestive evidence of an association between ETS, or possibly pre-conceptual paternal smoking, and brain cancer in children.

Table 7.4.3B. Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother	Father
Bunin *et al.*, 1994	Astrocytoma:	Maternal smoking ever[a]	Paternal smoking ever
(Age <6)	86/82 (M), 86/82 (P)	1.1 (0.7-18.0)	1.1 (0.7-18.0)
		During pregnancy	During pregnancy
	64/63	1.0 (0.6-1.7)	1.0 (0.6-1.7)
		ETS during pregnancy	
	83/83	0.9 (0.6-1.5)	
	PNET	Maternal smoking ever[b]	Paternal smoking ever
	85/88	0.9 (0.6-1.5)	0.9 (0.6-1.5)
		During pregnancy	During pregnancy
	60/58	1.0 (0.6-1.7)	1.0 (0.6-1.7)
		ETS during pregnancy	
	79/81	0.9 (0.8-1.2)	
Cordier *et al.*, 1994		Maternal during pregnancy[c]	
(Age <15)	19/23	1.6 (0.7-3.5)	
		Any exposure pregnancy (mother, family, work)	
	51/70	1.5 (0.8-2.8)	
		Any exposure during childhood (mother, family, work)	
	41/51	2.3 (1.1-4.6)	
Filippini *et al.*, 1994		Maternal smoking lifetime[d]	Paternal smoking lifetime[d]
(Age <15)	90/304	1.2 (0.8-2.0)	1.3 (0.7-2.2)
			Paternal 3 month prior[d]
	90/300		1.3 (0.8-2.2)
		Maternal ETS conception[d]	
	38/123	Total 1.6 (0.8-3.3)	
	15/53	< 2 hr/day 1.5 (0.7-3.5)	
	23/70	> 2 hr/day 1.7 (0.8-3.7)	
		P trend = 0.08	
		Maternal smoking conception[d]	
	38/105	Total 1.9 (1.0-3.8)	
	32/87	1-10 cpd 2.0 (1.0-4.0)	
	6/18	>10 cpd 1.6 (0.5-4.8)	
		P trend = 0.36	
		Maternal ETS pregnancy[d]	
	57/155	Total 2.0 (1.0-4.0)	
	20/63	< 2 hr/day 1.7 (0.8-3.8)	
	37/92	> 2 hr/day 2.2 (1.1-4.6)	
		P trend=0.02	
		Maternal smoking pregnancy[d]	
	18/59	Total 1.6 (0.7-3.7)	
	14/48	1-10 cpd 1.6 (0.7-3.8)	
	4/11	>10 cpd 1.7 (0.4-6.6)	
		P trend=0.73	

PNET=Primitive neuroectodermal tumor. (M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls.

[a] ORs adjusted for income Table 2 Bunin *et al.* (1994).

[b] Unadjusted ORs Table 2 Bunin *et al.* (1994).

[c] ORs adjusted for child's age, sex and maternal age Table 4 Cordier *et al.* (1994).

[d] ORs adjusted for child's age, sex, paternal education Tables 4 to 6 Filippini *et al.* (1994).

Table 7.4.3B. Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother		Father
Linet *et al.*, 1996 (Age ≤ 17)	96/484	Maternal smoking[e]		
		Non-smoker	1.0 (Referent)	
		1-9 cpd	1.3 (0.7-2.2)	
		≥ 10 cpd	1.0 (0.5-2.1)	
Norman *et al.*, 1996 (Age <20)	540/801	Maternal smoking lifetime[f]		Paternal smoking lifetime[f]
		Total	0.82 (0.64-1.04)	1.1 (0.84-1.3)
		1-10 cpd	0.84 (0.63-1.1)	1.2 (0.86-1.7)
		>10 cpd	0.75 (0.54-1.03)	0.98 (0.72-1.3)
		Maternal smoking pregnancy[f]		Paternal smoking pregnancy[f]
		Active	0.98 (0.72-1.3)	1.2 (0.90-1.5)
		Active/Passive	1.2 (0.93-1.4)	DNS
Ji *et al.* , 1997 (Age <15)	107/107			Paternal Smoking:
		Ever Active[g]		1.4 (0.6-3.2)
		Duration (years)[g]:	< 10	0.8 (0.2-3.8)
			10-14	1.3 (0.4-4.1)
			≥ 15	3.4 (0.9-12.5)
				P trend = 0.10
		Pack-year prior to conception[g]	≤ 2	1.5 (0.5-4.4)
			> 2 - < 5	1.7 (0.5-5.8)
			≥ 5	2.7 (0.8-9.9)
				P trend = 0.14
		Pack-year after birth[g]	≤ 2	1.3 (0.4-3.7)
			> 2 - < 5	1.8 (0.6-5.2)
			≥ 5	1.0 (0.3-3.3)
				P trend = 0.96
Sorahan *et al.*, 1995; 1997a and b (Deaths, age < 15)		Maternal smoking at interview Increase risk by level		Paternal smoking at interview Increase risk by level
1953-1955 (1997a)	229/229	1.04 (0.81-1.35)[h]		1.20 (0.96-1.51)[h]
1971-1976 (1997b)	410/410	1.07 (0.95-1.19)[i]		1.02 (0.93-1.11)[i]
1977-1981 (1995)	312/312 (M), 299/299 (P)	1.06 (0.94-1.20)[j]		1.09 (0.95-1.20)[j]
Pooled Estimate for 3 time periods (1997b)	1043/1058(M), 1016/1035 (P)	1.01 (0.84-1.23)[k]		1.30 (1.06-1.59)

(M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls.

[e] ORs adjusted for child's age and sex Table 2 Linet *et al.* (1996).

[f] ORs adjusted for child's age, sex and race Table 3 Norman *et al.* (1996).

[g] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

[h] Unadjusted RR represents change risk one categorical level of smoking, maternal/paternal daily smoking analyzed simultaneously, Table 2 Sorahan *et al.* (1997a).

[i] Table 2 Sorahan *et al.* (1997b), unadjusted RR estimate change one level daily consumption.

[j] Table 4 Sorahan *et al.* (1995) unadjusted RR estimate change one level daily consumption.

[k] ORs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b)

Table 7.4.3B. Brain Tumors in Children and Exposure to Parent's Smoking

Study (Age of Subjects)	# Cases/ Controls	OR for Smoking Habits of Mother		Father
Schuz *et al.*, 1999	399/2588	Maternal during pregnancy[l]		Paternal before pregnancy[l]
(Age <15)		1-10 cpd	0.8 (0.6-1.1)	0.8 (0.5-1.2)
		11-20 cpd	1.6 (0.9-2.8)	1.1 (0.8-1.4)
		>20 cpd	0.8 (0.2-3.9)	1.0 (0.7-1.4)
Filippini *et al.*, 2002		Maternal ETS		Paternal before pregnancy:
(Age ≤ 19)	345/1,190 (P)	1.3 (1.0-2.9) PNET		1.2 (1.0-1.5)
				astroglial diagnosis under 1 yr of age 1.7 (1.0-2.9)
Sorahan *et al.*, 2001		Maternal at conception[m]		Paternal at conception
(Age < 15)	72/72 (M)	<10 cpd	6.56 (1.36-31.73)	0.51 (0.09-2.97)
	66/65 (P)	10-19	1.28 (0.55-3.03)	1.25 (0.42-3.72)
		20-29	1.30 (0.52-3.22)	0.21 (0.21-1.33)
		30-39	NA	0.15 (0.01-1.54)
		≥ 40 cpd	NA	0.64 (0.08-4.79)
			P trend=0.71	*P* trend=0.67

[l] ORs adjusted for age, sex, and socioeconomic status Table 4 Schuz *et al.* (1999).
[m] Unadjusted ORs presented in Table 3 of Sorahan *et al.* (2001) for GP controls
(M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls. PNET=Primitive neuroectodermal tumor.

7.4.4. Leukemia

7.4.4.1. Active Smoking and Leukemia

Previously, OEHHA reported evidence that cigarette smoking may be related to an increased risk of leukemia. Several prospective cohorts have reported an increased risk of various magnitude and statistical significance, for either all leukemia combined or for selected subtypes, while other studies including several case-control studies found no elevated risk (Cal/EPA, 1997). No new primary studies were located for this update.

7.4.4.2. ETS and the Risk of Leukemia in Adults

7.4.4.2.1. Previous Findings

The OEHHA report (Cal/EPA, 1997) noted that the evidence was insufficient to evaluate an association between ETS exposure and adult leukemia, and cited a single study examining the association between ETS exposure and adult onset leukemia (Sandler *et al.*, 1985a). This one study reported an elevated, non-significant risk for all hematopoietic malignancies combined among nonsmoking women exposed as children to parental smoking (maternal and paternal). No estimates related to other potential sources of ETS, including spouses or workplace, were reported.

7.4.4.2.2. Recent Epidemiological Data

No new primary studies were located.

7.4.4.3. ETS and the Risk of Leukemia in Children

7.4.4.3.1. Previous Findings

In the 1997 report, OEHHA reviewed a total of eight published studies examining the potential relationship between ETS exposure and the risk of developing leukemia. The epidemiological evidence for parental smoking and risk of childhood leukemia was considered inconclusive and often conflicting. No association was observed in the one cohort study reviewed (Pershagen *et al.*, 1992). Two of seven case-control studies identified a significant increase in leukemia risk with maternal smoking (Stjernfeldt *et al.*, 1986a; Stjernfeldt *et al.*, 1986b; John *et al.*, 1991). The case control studies varied in the type of cases enrolled (acute lymphocytic, non-acute lymphocytic, acute myeloid, or all leukemias combined), the age of cases and other potential risk factors. In summary, OEHHA considered the evidence insufficient to assess the association between ETS exposure and leukemia in children/adolescents. (Cal/EPA, 1997).

7.4.4.3.2. Recent Epidemiological Data

Table 7.4.4A summarizes data from the ten studies reporting on childhood leukemia risk associated with ETS exposure.

Klebanoff et al., 1996. In the previously described United States cohort analyzed by Klebanoff *et al.* (1996), a subset analysis was conducted for leukemia risk (17 of 51 reported childhood cases ages 8 or under). Data to determine the proportion of lymphoblastic cases were not available. In this cohort, the children of smoking mothers were not at increased risk of developing leukemia (all types combined) [adjusted RR 0.82 (95% CI 0.31-2.11)]. No data on

paternal or other passive smoking exposure were available. Limited covariate analysis was presented, but did not alter the risk estimates to any substantial degree.

Shu et al., 1996. Data from the Children's Cancer Group (CCG) case-control study, a cooperative clinical trials group within the U.S and Canada, evaluated the relationship between infant leukemia risk and parental alcohol consumption and/or cigarette smoking during pregnancy or during the month prior to it. Three hundred two leukemia cases (203 acute lymphoid leukemias [ALLs], 88 acute myeloid leukemias [AMLs] and 11 other leukemia types) were diagnosed in children at 18 months of age or younger between 1983 and 1988, and matched to 558 controls by residence and year of birth. Maternal and paternal smoking data were collected via telephone interview. Maternal smoking during pregnancy (versus nonsmoking mothers) was negatively associated with infant leukemia risk [total leukemia adjusted OR 0.66 (95% CI 0.46-0.94) after adjustment for sex, maternal education and alcohol consumption], as well as AML separately [OR 0.45 (95% CI 0.21-0.96)]. Paternal smoking one month prior to pregnancy was related to a statistically significant elevated risk of ALL [adjusted OR 1.56 (95% CI 1.03-2.36)], while paternal smoking during pregnancy was associated with an elevated but non-significant risk of ALL [adjusted OR 1.45 (95% CI 0.95 -2.19) after adjustment for sex, paternal age, education, and maternal alcohol consumption)]. The risk of ALL did not increase with increasing paternal cigarette consumption either one month prior to or during pregnancy (p for trend = 0.12). Paternal smoking was not associated with the risk of AML [adjusted ORs 0.75 (95% CI 0.35-1.62) and 0.82 (95% CI 0.38-1.78), one month prior to and during pregnancy, respectively]. The study observed no statistical interaction between maternal and paternal alcohol consumption and smoking.

Ji et al., 1997. As part of the population-based case control study in Shanghai, China, the association between parental smoking and the risk of childhood acute leukemia was evaluated. As described previously, cases diagnosed from 1981 through 1991 were ascertained from a population-based cancer registry among children under the age of 15. A total of 166 cases of acute leukemia (114 ALL and 52 AML) were matched to population controls based on age, sex and local governmental sampling unit. Only paternal smoking was analyzed in this study. Paternal preconceptual versus postconceptual and postnatal smoking effects were derived in several ways by parsing out the window of paternal smoking effect as follows: 1. 13% of control fathers and 12% of case fathers began smoking after the birth of the index child. Paternal smoking that began after the birth of the index child was not associated with an increased risk of childhood cancers**.** 2**.** Increased levels of smoking (40% of fathers who smoked) were not related to an increase in cancer. 3. Preconceptual smoking was assessed in some detail. It was only associated with an increase in cancer for fathers with at least 5 years preconceptual exposure. Risk increased with increasing preconceptual exposure as detailed by increased duration or total pack years. 4. Childhood cancer diagnosed after 5 yrs of age was not linked to paternal preconceptual smoking (etiologically probably a different group of cancers even though histologically the same). 5**.** There was no assessment of any effect of maternal exposure to passive smoke in this study. Again though, the effect was only noted with a substantial number of prenatal years of paternal smoking. This is strengthened by in vitro evidence of DNA damage in sperm cells and mutations in germ cells.

Paternal smoking status (ever versus never) was positively associated, although not statistically significantly, with increased risk for all childhood acute leukemias [adjusted OR 1.3 (95% CI

0.7-2.4), adjusted for birth weight, income, paternal age, education and alcohol consumption)]. As found in the analysis for all sites combined, adjusted risk estimates were highest among fathers that smoked for longer periods or more heavily during conception, with significantly elevated adjusted risks in the highest exposure category for acute leukemia [OR 2.4 (95% CI 1.1-5.6)], and for ALL [OR 3.8 (95% CI 1.3-12.3) among children of fathers smoking more than 5 pack-years before conception]. For AML the association was positive but not statistically significant [OR 2.3 (95% CI 0.4-14.8)]. A significant trend between increasing acute leukemia risk and increasing cumulative paternal preconception smoking (pack-years before conception) was observed for acute leukemia (ALL and AML combined) (P=0.02), and ALL (P=0.01). The level of paternal smoking after birth was not associated with an increased risk of childhood acute leukemia (combined, ALL or AML separately).

Sorahan et al. 1995; 1997a; 1997b. Three United Kingdom case-control studies of childhood cancer deaths in relation to reported parental tobacco consumption have been published from the Oxford Survey of Childhood Cancers (OSCC). All three OSCC studies found no statistically significant association between maternal smoking (prior to or during pregnancy) and risk of childhood death due to leukemia for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981, with risk estimates remaining near unity. However, the relative risk of leukemia was significantly elevated in association with prenatal paternal smoking for acute lymphocytic (ALL) [OR 1.16 (95% CI 1.06-1.27)] but not myeloid leukemia [OR 1.02 (95% CI 0.89-1.16)], for deaths occurring 1977-1981 (Sorahan *et al.*, 1995). By comparison the opposite result, significant risk for AML but not ALL-related deaths, was reported for 1971-1976 [myeloid leukemia OR 1.27 (95% CI 1.10-1.47) and ALL OR 1.07 (95% CI 0.99-1.16] (Sorahan *et al.*, 1997b), although statistical significance is almost reached for ALL. In the earliest time period, 1953-1955, the association between paternal smoking and leukemia risk remained nonsignificant for both ALL [OR 1.08 (95% CI 0.91-1.27)] and myeloid leukemia [OR 0.98 (95% CI 0.73-1.32)]. In the final mortality analysis, a pooled analysis was conducted, consisting of 2,364 matched pairs total for all leukemia combined (ALL and myeloid leukemia were not reported separately). Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significantly elevated risk estimate for leukemia [adjusted OR 1.20 (95% CI 1.05-1.37)] for all three time periods combined (Sorahan *et al.*, 1997b). The estimate for maternal smoking remained near unity [adjusted OR 1.02 (95% CI 0.90-1.16)] (Sorahan *et al.*, 1997b).

Brondum et al., 1999. Another study from the Children's Cancer Group (CCG) utilized information on 1,842 ALL cases and 517 AML patients, diagnosed between January 1, 1989 and June 15, 1993. ALL cases were aged 15 years or younger, while AML patients were under age 18. Population-based controls (random digit dialing) were matched to cases by age, race, and residence (telephone area code). Maternal and paternal smoking data were collected via telephone interview – current smoking, ever smoking, smoking during month prior to pregnancy, during pregnancy, or after pregnancy. ALL and AML were analyzed separately.

The risk of leukemia (ALL or AML) was not statistically associated with maternal or paternal current smoking or ever smoking. The risk of ALL was not associated with paternal smoking (ever smoked) [adjusted OR 1.04 (95% CI 0.90-1.20)], or maternal smoking (ever smoked) [adjusted OR 1.04 (95% CI 0.91-1.19], after adjustment for income, race and education. Similar results were reported for AML: paternal ever smoking [adjusted OR 0.88 (95% CI 0.67-1.16)],

and maternal ever smoking [adjusted OR 0.95 (95% CI 0.74-1.22)]. Evaluating parental smoking by the time periods either parent smoked (the month prior to pregnancy, during pregnancy, or for the month prior to and during pregnancy combined), did not substantially alter risk estimates. The highest risk estimates were observed for ALL and paternal smoking [<10 cigarettes/day (lifetime), OR 1.16 (95% CI 0.88-1.51); <10 years smoked, OR 1.12 (95% CI 0.91-1.38); and, 10-<20 years smoked, OR 1.22 (95% CI 1.00-1.47)]. However, no significant trends for increasing risk of ALL with paternal lifetime daily cigarette consumption, years smoked, or pack-years were identified. In the case of AML, estimates for parental smoking (maternal or paternal) and risk of AML remained consistently below 1.0 for the various exposure periods. The adjusted ORs for both ALL and AML were also not statistically elevated when total parental smoking was evaluated (neither ever smoked, both parents ever smoked, father only ever smoked, mother only ever smoked), except in the cases of AML homes where only the mother had ever smoked [OR 1.78 (95% CI 1.15-2.75)]. The authors report (no data presented) that the elevated ORs were observed regardless of age group, morphologic subgroup, and exposure periods (prior to pregnancy, individual trimesters). The risk estimate with maternal (not father) ever smoking for one AML morphologic subgroup, M0-M2/granulocytic sarcoma, was substantially elevated [OR 2.69 (95% CI 1.04-6.95)].

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 755 acute leukemia cases (650 ALL and 105 ANLL cases) were included among children under age 15. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Analyses were conducted for acute non-lymphocytic leukemias (ANLL) and for 3 immunological subtypes of ALL (common ALL, pre-beta ALL, and t-ALL). For "common" ALL (450 cases), a slightly increased risk with increasing number of cigarettes per day (maternal smoking) was observed [1-10 cig/day: OR 1.1 (95% CI 0.9-1.4); 11-20 cig/day: OR 1.2 (95% CI 0.8-2.0); 20+ cig/day: OR 2.1 (95% CI 0.7-6.3)]. Paternal smoking the 3 months prior to conception was not associated with childhood leukemia risk, with the heaviest paternal smoking category (>20 cigarettes/day) associated with an OR 1.1 (95% CI 0.8-1.5) for common-ALL.

Infante-Rivard et al, (2000) conducted a case-control study based out of several major cancer treatment facilities enrolled the families of children diagnosed between 1980 and 1993 (study initiated in 1989) in Quebec, Canada. Four hundred and ninety-one incident cases (510 eligible) of acute lymphoblastic leukemia (ALL) in children under age 10 were enrolled. Population controls (493 of 588 eligible) were matched by age, sex and region of residence at time of diagnosis. Additionally, this study investigated the relationship or interaction between specific genetic polymorphisms of a primary metabolic cytochrome P450, the CYP1A1 (3 different alleles analyzed), maternal smoking and ALL risk (genotyping available on 158 cases). Maternal and paternal smoking habits were obtained via telephone interview. A small increased ALL risk which was not statistically significant was associated with maternal smoking during the later trimesters [adjusted OR 1.2 (95% CI 0.8-1.6), second and third trimester]. No association was observed for either maternal or paternal smoking between birth and date of diagnosis. In the case-only genotype analysis, nonsignificant increases in ALL risk for maternal smoking (reported as interaction odds ratios) were observed for two alleles, CYP1A1*4 and CYP1A1*2A. A third allele, CYP1A1*2B, appeared protective (Table 7.4.4B). Although the small sample size (when stratified by genotype) limits broad interpretation of the genotype findings, the study

found some evidence that variants of CYP1A1 could modify even the small risk of ALL associated with parental smoking in this study.

A later study by the same group, although lacking exposure data on tobacco smoking, further demonstrated a role for genetic polymorphisms of metabolic enzymes in the modification of risk in childhood ALL (Krajinovic *et al.*, 2002). This study investigated whether polymorphisms in the genes encoding for three other enzymes involved in the xenobiotic biotransformation, CYP2E1, MPO and NQO1, were additional risk-modifying factors in childhood ALL. This case-control study included 174 patients of French-Canadian origin identified from a Montreal hospital between August 1988 and September 1998 (median age 5.2). Three hundred and thirty seven controls were obtained from an institutional DNA bank. Carriers of one variant CYP2E1 (CYP2E1*5) were at significantly increased risk for ALL [OR 2.8 (95% CI 1.2-6.4), adjusted for sex and age)]. NQO1 (NQO1*2 and *3) contributed to a statistically significant increased ALL risk [OR 1.7 (95% CI 1.2-23.4)]. No association was identified for MPO alone, but wild type MPO, in combination with specific CYP2E1 and NQO1 variants, elevated the risk of ALL further [OR 5.4 (95% CI 1.2-23.4)], suggesting a potential combined effect.

Sorahan et al., 2001. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) report included a reanalysis on 85 ALL cases with maternal smoking data and 57 ALL cases with paternal smoking data diagnosed among children under age 15 between 1980 and 1983 (Birch *et al.*, 1990; Sorahan *et al.*, 2001). Maternal and paternal smoking habits were analyzed and presented separately by dose level (< 10 cig/day, 10-19 cig/day, 20-29 cig/day, 30-39 cig/day, > 40 cig/day). ALL-specific risk estimates for paternal smoking increased with increasing dose level [1-10 cig/day: OR 0.99 (95% CI 0.35-2.85); 10-19 cig/day: OR 1.34 (95% CI 0.62-2.91); 20-29 cig/day: OR 1.32 (95% CI 0.72-2.45); 30-39 cig/day: OR 2.33 (95% CI 0.71-7.63); 40 cig/day: OR 5.29 (95% CI 1.31-21.30), p for trend=0.06)]. At the highest exposure, the OR was statistically significant. This is consistent with Ji *et al.* (1997). Maternal smoking did not show a similar pattern (P for trend 0.56) (Table 7.4.4A).

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Klebanoff *et al.*, 1996 (Age < 9)	17 Cohort study (All types)	During/Current at Diagnosis	0.82 (0.31-2.11)[a]	Not available
Shu *et al.*, 1996 (Age ≤ 18 months)	302/558 (All types)	Month prior	0.71 (0.51-1.01)[b]	1.28 (0.90-1.81)[b]
		During Pregnancy	0.66 (0.46-0.94)	1.23 (0.86-1.75)
		1-10 cpd[c]	0.66 (0.41-1.04)	1.39 (0.69-2.82)
		11-20 cpd	0.64 (0.39-1.06)	1.15 (0.74-1.80)
		> 20 cpd	0.62 (0.22-1.79)	1.36 (0.81-2.28)
			p trend=0.03	p trend=0.23
	203/558 (ALL[d])	Month prior	0.84 (0.51-1.28)	1.56 (1.03-2.36)
		During Pregnancy	0.78 (0.51-1.18)	1.45 (0.95-2.19)
		1-10 cpd	0.78 (0.45-1.32)	2.40 (1.00-5.72)
		11-20 cpd	0.79 (0.44-1.42)	1.33 (0.79-2.34)
		> 20 cpd	0.48 (0.12-1.90)	1.51 (0.82-2.77)
			p trend=0.18	p trend=0.12
	88/558 (AML[d])	Month prior	0.48 (0.22-1.05)	0.75 (0.35-1.62)
		During Pregnancy	0.45 (0.21-0.96)	0.82 (0.38-1.78)
		1-10 cpd	0.46 (0.16-1.31)	0.42 (0.09-1.95)
		11-20 cpd	0.41 (0.15-1.13)	0.73 (0.27-1.94)
		> 20 cpd	0.69 (0.08-5.78)	1.29 (0.44-3.74)
			p trend=0.07	p trend=0.98

[a] RR (Proportional hazards ratio) no adjustment for other factors reported in text of Klebanoff *et al* (1996).
[b] ORs adjusted for maternal alcohol, maternal/paternal education, maternal/paternal age and sex from Tables 4 and 5 in Shu *et al.* (1996).
[c] cpd=cigarettes/day
[d] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Ji *et al.*, 1997 (Age <15)	166/166 (Acute Leukemias, All types)	Ever Active	Not available	1.3 (0.7-2.4)[e]
		Duration (years):		
		< 10	Not available	0.9 (0.3-2.3)
		10-14	Not available	1.0 (0.5-2.2)
		≥ 15	Not available	1.7 (0.8-3.7)
				p trend=0.23
		Pack-year prior conception		
		≤ 2	Not available	0.7 (0.3-1.8)
		> 2 to < 5	Not available	1.0 (0.4-2.1)
		≥ 5	Not available	2.4 (1.1-5.6)
				p trend=0.02
		Pack-year after birth		
		≤ 2	Not available	1.3 (0.6-2.6)[c]
		> 2 to < 5	Not available	1.6 (0.7-3.5)
		≥ 5	Not available	1.0 (0.4-2.4)
				p trend=0.94
	114/114 (ALL[f])	Pack-year prior conception		
		≤ 2	Not available	0.8 (0.2-2.5)[g]
		> 2 to < 5	Not available	1.0 (0.4-2.7)
		≥ 5	Not available	3.8 (1.3-12.3)
				P trend=0.01
		Pack-year after birth		
		≤ 2	Not available	1.1 (0.4-2.8)
		> 2 to < 5	Not available	1.8 (0.6-5.2)
		≥ 5	Not available	1.8 (0.6-5.5)
				P trend=0.33
	52/52 (AML)	Pack-year prior conception		
		≤ 2	Not available	0.9 (0.1-7.3)[g]
		> 2 to < 5	Not available	0.6 (0.1-3.1)
		≥ 5	Not available	2.3 (0.4-14.8)
				P trend=0.36
		Pack-year after birth		
		≤ 2	Not available	5.0 (0.8-32.5)
		> 2 to < 5	Not available	6.1 (0.8-45.1)
		≥ 5	Not available	0.5 (0.1-2.7)
				P trend=0.24

[e] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).
[f] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia
[g] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Sorahan *et al.*, 1995; 1997a; 1997b				
(Deaths, Age < 15)				
1953-1955 (1997a)	367/367 (ALL[j])		1.24 (1.01-1.52)[h]	1.08 (0.91-1.27)[h]
	115/115 (AML)		1.20 (0.85-1.68)[h]	0.98 (0.73-1.32)[h]
	27/27 (Monocytic)		1.21 (0.58-2.54)[h]	1.10 (0.61-2.01)[h]
	216/216 (Other/Unspecified)		1.18 (0.91-1.55)[h]	1.14 (0.93-1.39)[h]
1971-1976 (1997b)	573/573 (ALL)		0.98 (0.89-1.07)[i]	1.07 (0.99-1.16)[i]
	190/190 (AML)		1.00 (0.83-1.20)[i]	1.27 (1.10-1.47)[i]
	25/25 (Monocytic)		0.66 (0.36-1.19)[i]	0.84 (0.56-1.26)[i]
	47/47 (Other/Unspecified)		0.91 (0.67-1.24)[i]	0.99 (0.75-1.30)[i]
1977-1981 (1995)	400/400 (M[j]) (ALL)		0.94 (0.83-1.05)[k]	
	371/371 (P)			1.16 (1.06-1.27)[k]
	151/151 (M) (AML)		0.93 (0.79-1.10)[k]	
	147/147 (P)			1.02 (0.89-1.16)[k]
	22/22 (M) (Other/Unspecified)		1.23 (0.69-2.20)[k]	
	19/19 (P)			0.66 (0.44-0.99)[k]
Pooled Estimate - for 3 time periods (1997b)	2312/2317 (M) (All leukemias)		1.02 (0.90-1.16)[l]	
	2254/2281 (P)			1.20 (1.05-1.37)[l]

[h] Unadjusted RR represents change risk one categorical level of smoking, maternal/paternal daily smoking analyzed simultaneously, Table 2 Sorahan *et al.* (1997a).
[i] Table 2 Sorahan *et al.* (1997b), unadjusted RR estimate change one level daily consumption.
[j] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia (M)=Maternal exposed; (P)= Paternal exposed.
[k] Table 4 Sorahan *et al.* (1995) unadjusted RR estimate change one level daily consumption.
[l] ORs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b).

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Brondum *et al.*, 1999	Total	Current	1.02 (0.87-1.19) [m]	1.06 (0.90-1.25) [m]
(Age <15 ALL[n])	1914/1987 (ALL)	Ever	1.04 (0.91-1.19)	1.04 (0.90-1.20)
		Lifetime daily		
	1842 (M)	< 10 cpd	1.02 (0.83-1.26)	1.16 (0.88-1.51)
	1618 (P)	10-19 cpd	1.04 (0.86-1.26)	1.04 (0.83-1.31)
		20+ cpd	1.04 (0.87-1.26)	1.06 (0.88-1.26)
			p trend=0.59	p trend=0.59
		Lifetime duration		
		< 10 yrs	1.16 (0.98-1.38)	1.12 (0.91-1.38)
		10-19 yrs	1.03 (0.86-1.22)	1.22 (1.00-1.47)
		20+ yrs	0.66 (0.49-0.93)	0.91 (0.72-1.14)
			p trend=0.27	p trend=0.79
		During Pregnancy	1.06 (0.91-1.23)	1.07 (0.91-1.25)
		Both parents ever smoked	1.09 (0.91-1.30)	
		Father only ever smoked		1.04 (0.86-1.26)
		Mother only	1.10 (0.88-1.38)	
(Age < 17 AML)	Total	Current	0.97 (0.73-1.30)[m]	0.91 (0.67-1.24)[m]
	530/612 (AML)	Ever	0.95 (0.74-1.22)	0.88 (0.67-1.16)
		Lifetime daily		
	517 (M)	< 10 cpd	1.25 (0.88-1.76)	1.04 (0.62-1.74)
	450 (P)	10-19 cpd	0.87 (0.61-1.24)	0.92 (0.61-1.37)
		20+ yrs	0.73 (0.30-1.07)	0.81 (0.58-1.14)
			P trend=0.13	P trend=0.22
		Lifetime duration		
		< 10 yrs	1.02 (0.75-1.41)	1.06 (0.71-1.58)
		10-19 yrs	0.83 (0.58-1.18)	0.98 (0.69-1.45)
		20+ yrs	1.05 (0.64-1.70)	0.65 (0.44-0.96)
			P trend=0.66	P trend=0.06
		During Pregnancy	0.89 (0.66-1.20)	0.88 (0.65-1.19)
		Both parents ever smoked	0.85 (0.59-1.22)	
		Father only ever smoked		1.32 (0.91-1.93)
		Mother only	1.78 (1.15-2.75)	

[m] ORs adjusted for annual income, parental race and education Tables 4 and 5 Brondum *et al.* (1999).
[n] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia (M)=Maternal exposed cases/controls, (P)= Paternal exposed cases/controls, cpd=cigarettes/day

Table 7.4.4A Maternal or Parental Smoking and Childhood Leukemia

Study (Age of Subjects)	# Cases/ # Controls (Type of Leukemia)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Schuz *et al.*, 1999	982/982 (M[o])	During pregnancy		
(Age <15)		1-10 cpd	0.8 (0.6-1.1) [p]	Not available
	(Acute	11-20 cpd	0.5 (0.3-0.9)	Not available
	leukemias)	> 20 cpd	1.3 (0.4-4.7)	Not available
	955/955 (P)	Before pregnancy		
		1-10 cpd	Not available	1.1 (0.8-1.5) [p]
		11-20 cpd	Not available	1.0 (0.8-1.2)
		> 20 cpd	Not available	0.9 (0.7-1.2)
Infante-Rivard *et al.*, 2000				
(Age <10)	491/491 (M)	During Pregnancy:		
	486/486 (P)	1st Trimester:		
	(ALL)	1-20 cpd	1.1 (0.8-1.6) [q]	Not available
		20+ cpd	1.0 (0.7-1.6)	Not available
		2nd Trimester:		
		1-20 cpd	1.2 (0.8-1.6)	Not available
		20+ cpd	1.2 (0.7-1.9)	Not available
		3rd Trimester:		
		1-20 cpd	1.2 (0.8-1.6)	Not available
		20+ cpd	1.2 (0.8-2.0)	Not available
		Postnatal < Diagnosis		
		1-20 cpd	1.0 (0.7-1.4)	1.0 (0.7-1.4)
		20+ cpd	1.0 (0.6-1.3)	1.0 (0.7-1.3)
Sorahan *et al.*, 2001		At conception		
(Age < 15)	140/142 (M)	< 10 cpd	1.34 (0.46-3.87)[r]	0.99 (0.35-2.85)[r]
	139/132 (P)	10-19	1.11 (0.59-2.08)	1.34 (0.62-2.91)
	(ALL)	20-29	0.98 (0.51-1.85)	1.32 (0.72-2.45)
		30-39	0.26 (0.03-2.38)	2.33 (0.71-7.63)
		≥ 40 cpd	(30+ max category)	5.29 (1.31-21.30)
			p trend=0.56	p trend=0.06

[o] ALL=Acute lymphocytic leukemia, AML=Acute myeloid leukemia (M)=Maternal exposed cases/controls, (P)= Paternal exposed cases/controls, cpd=cigarettes/day

[p] ORs adjusted for age, sex, and socioeconomic status Table 3 Schuz *et al.* (1999).

[q] ORs adjusted for age, sex, maternal age and education Table 2 Infante-Rivard *et al.* (2000).

[r] Unadjusted ORs presented in Tables 1 and 2 of Sorahan *et al.* (2001) for GP controls.

Table 7.4.4B Maternal Smoking and CYP1A1 Allelic Variants in Childhood Leukemia*

Smoking Habits (cigarettes/day)	# Cases/ Controls	OR (95% CI) CYP1A1*2A	# Cases/ Controls	OR (95% CI) CYP1A1*2B	# Cases/ Controls	OR (95% CI) CYP1A1*4
1st Trimester:						
1-20 cpd	7/37	1.0 (0.4-2.9)	1/44	0.1 (0.01-0.9)	2/43	1.1 (0.2-6.4)
20+ cpd	6/17	2.1 (0.7-6.6)	2/21	0.5 (0.1-2.4)	2/21	1.0 (0.3-11.7)
2nd Trimester:						
1-20 cpd	5/42	0.5 (0.2-1.6)	2/46	0.2 (0.1-1.1)	3/45	2.2 (0.4-11.8)
20+ cpd	5/9	2.8 (0.8-9.7)	1/13	0.4 (0.1-3.7)	2/12	5.3 (0.8-36.8)
3rd Trimester:						
1-20 cpd	5/41	0.6 (0.2-1.7)	2/45	0.3 (0.1-1.2)	3/44	2.3 (0.4-12.2)
20+ cpd	5/9	2.8 (0.8-9.8)	1/31	0.4 (0.1-3.7)	2/12	5.4 (0.8-37.3)

* Acute lymphocytic leukemia. Interaction ORs adjusted for age and sex of child. Table 3 Infante-Rivard *et al.* (2000)

7.4.4.4. Summary of ETS and Leukemia

In adults, no additional studies investigating the association between ETS exposure and hematopoietic tumors were available for review. The 1997 Cal/EPA document noted that the evidence was insufficient to assess potential associations with childhood leukemia from the studies available at that time. In general, the subsequent studies have not found an association with maternal smoking. There is strengthened (though not conclusive) evidence of an association with paternal preconceptional smoking. Thus, evidence to date is suggestive of an association between preconceptional paternal smoking and leukemia risk, but not postconceptional ETS exposure. The observed associations may be the result of heritable germ cell mutations.

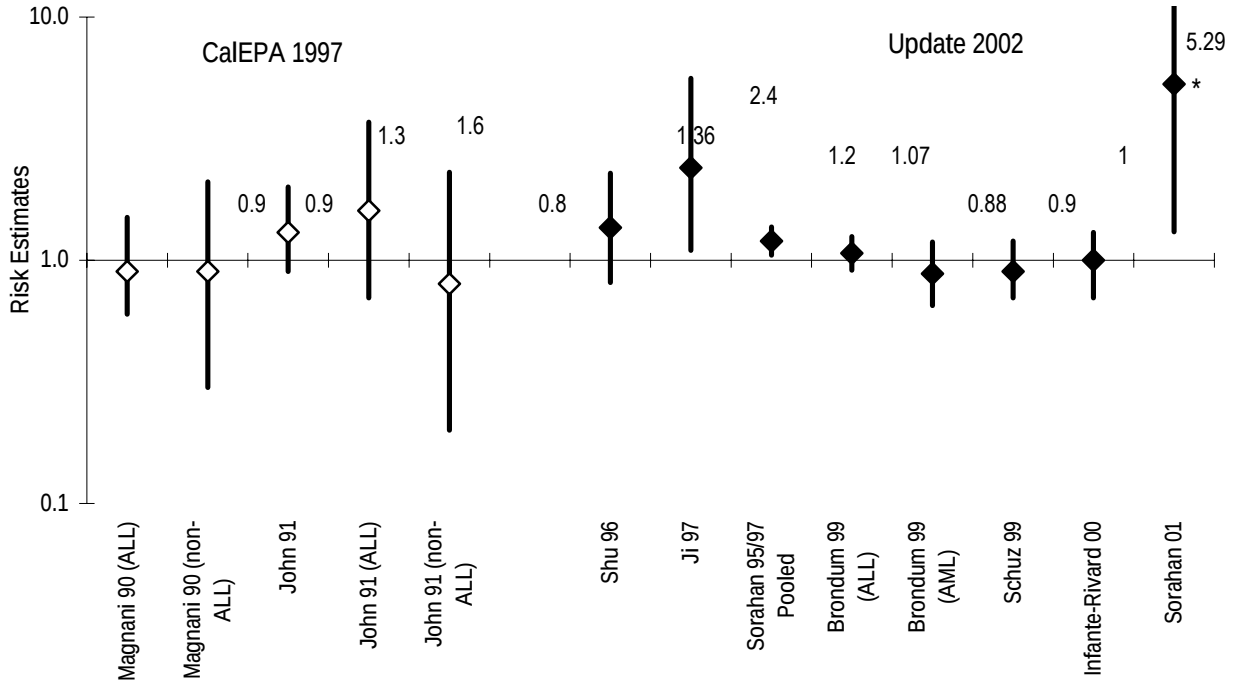
In the studies investigating parental smoking and overall childhood cancer, several included analysis of leukemia risk associated with parental smoking (Sorahan *et al.*, 1995; Klebanoff *et al.*, 1996; Ji *et al.*, 1997; Sorahan *et al.*, 1997a; Sorahan *et al.*, 1997b; Schuz *et al.*, 1999; Sorahan *et al.*, 2001) while others focused only on childhood leukemia (Shu *et al.*, 1996; Brondum *et al.*, 1999; Infante-Rivard *et al.*, 2000). Recent study results on the relationship between parental smoking and leukemia remain mixed, with leukemia risks associated with maternal smoking generally null (Klebanoff *et al.*, 1996; Shu *et al.*, 1996; Sorahan *et al.*, 1995; Sorahan *et al.*, 1997b; Infante-Rivard *et al.*, 2000; Sorahan *et al.*, 2001), in contrast to the several positive, but weak associations reported for paternal smoking (Ji *et al.*, 1997; Sorahan *et al.* 1997b; Sorahan *et al.*, 2001). However, other studies also reported no association between paternal smoking and leukemia (Brondum *et al.*, 1999; Schuz *et al.*, 1999; Infante-Rivard *et al.*, 2000).

Two studies presented evidence suggestive of a dose-response between paternal smoking and ALL, with pack-years prior to conception (Ji *et al.*, 1997) or with daily cigarette consumption at conception (Sorahan *et al.*, 2001). Both studies were based on cases under age 15, however, the results presented in the U.K. study were unadjusted (Sorahan *et al.*, 2001). Ji *et al.* (1997) found the highest risk estimates for both ALL [adjusted OR 3.8] and AML [adjusted OR 2.3] with increasing pack-years prior to conception. Additionally, the case-control study on infants ≤ 18

months (Shu *et al.*, 1996) also was suggestive of a dose-response between ALL risk and daily paternal cigarette consumption (P for trend 0.12), with a significant adjusted OR 1.56 (95% CI 1.03-2.36) associated with smoking one month prior to conception. However in the majority of studies, risks associated with paternal smoking (ever active) remained below 1.2 (Figure 7.4.6 below). The associations seen in Ji *et al.* (1997) and Sorahan *et al.* (2001) relate to active smoking prior to conception and not necessarily exposure of the developing fetus to ETS.

Similar to earlier discussion on the overall childhood cancer risk and ETS related risks, the studies reporting results for leukemia varied in study design (particularly age of study population), definition of ETS exposure (binomial, daily dose, cumulative dose, maternal or paternal or both) and timing of exposure (ever active, during conception, during pregnancy, postnatally), making comparison of results across studies difficult. Age-specific incidence patterns in leukemia vary substantially by age and race/ethnicity. Although ALL remains the most frequently diagnosed malignancy in children under age 15, the childhood and adolescent incidence peaks before age 4 (Campleman *et al.*, 1999; Ries *et al.*, 1999), with rates in California highest among Hispanics and non-Hispanic whites (Campleman *et al.*, 1999). In contrast to earlier studies previously reviewed by OEHHA, these more recent studies distinguished between ALL and non-ALL cases and the majority adjusted for at least some other potential confounders including social class, income, race and/or education.

Figure 7.4.6. Paternal smoking and risk of childhood leukemia.*



*NOTE: Studies reviewed in Cal/EPA 1997 and Update 2002 used a variety of exposure measurements. ALL = acute lymphocytic leukemia. AML = acute myeloid leukemia. Sorahan *et al.* (2001) provides an unadjusted risk estimate.

7.4.5. Lymphomas and Non-Hodgkin's Lymphoma

7.4.5.1. ETS and Lymphoma Risk

7.4.5.1.1. Previous Findings

Previously, OEHHA summarized six reports with at least some examination of the relationship between ETS exposures and childhood lymphomas, whether Hodgkin's Disease, non-Hodgkin's lymphoma (NHL) or all lymphomas combined (Cal/EPA, 1997). Several studies found elevated but statistically non-significant increased risk for either all lymphomas or NHL with maternal smoking, but small case numbers limited dose specific estimates. In summary, OEHHA found the data insufficient to assess potential associations between ETS exposure and lymphoma risk.

7.4.5.1.2. Recent Epidemiological Data

Table 7.4.5A summarizes data from the six studies reporting estimates of lymphoma risk associated with ETS exposure.

Ji et al., 1997. As part of the case-control study discussed earlier, a subset of 87 childhood lymphoma cases (72 non-Hodgkin's lymphoma) was analyzed. Lymphoma risk among children of fathers that ever smoked was elevated with adjusted OR 4.0 (95% CI 1.3-12.5). The risks were highest for children with fathers who smoked more than 5 pack-years before conception [adjusted OR 4.5 (95% CI 1.2-16.8)], or greater than 10 pack-years [OR 5.7 (1.3-26.0)]. Some evidence for a dose-response between duration of paternal smoking and childhood lymphoma risk was observed for active-smoking in years [p for trend 0.05; < 10 years: OR 1.3 (95% CI 0.2-7.0); 10 to 14 years: OR 3.4 (95% CI 0.9-12.7); > 15 years: OR 3.5 (95% CI 0.9-13.7)], and for pack-years, p for trend 0.03; < 5 pack-years: OR 2.8 (95% CI 0.6-12.8); >5 to <10 pack-years: OR 1.3 (95% CI 0.3-5.5); > 10 pack-years: OR 5.7 (95% CI 1.3-26.0)]. The increase in lymphoma risk with increasing cumulative paternal preconception cigarette smoking was marginally significant [p for trend 0.07; < 2 pack-years: OR 3.1 (95% CI 0.8-11.4); >2 to <5 pack-years: OR 1.8 (95% CI 0.4-7.8); > 5 pack-years: OR 4.5 (95% CI 1.2-16.8)]. Additionally, levels of paternal smoking after birth were also associated with increased lymphoma risk [p for trend 0.08; < 2 pack-years: OR 3.9 (95% CI 0.9-16.0); >2 to <5 pack-years: OR 2.7 (95% CI 0.8-9.6); > 5 pack-years: OR 5.0 (95% CI 1.2-22.4), estimates adjusted for birth weight, income, paternal age, education and alcohol consumption].

Sorahan et al., 1995; 1997a; 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed lymphoma risk relative to maternal smoking (prior to or during pregnancy) utilizing childhood deaths due to lymphoma for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. In the final mortality analysis, a pooled analysis was conducted, consisting of 503 matched pairs total for all lymphoma combined (risks for NHL and Hodgkin's Disease were not reported separately). Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significantly elevated risk estimate [adjusted RR 1.67 (95% CI 1.23-2.26)] for lymphoma from all three time periods combined (Sorahan *et al.*, 1997b). The estimate for maternal smoking remained near unity [adjusted OR 0.96 (95% CI 0.73-1.27)] (Sorahan *et al.*, 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 234 cases of non-Hodgkin's lymphoma (NHL) among children under age 15 were

included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Risk of NHL was positively associated with heavy maternal smoking during pregnancy, > 20 cigarettes per day [adjusted OR 5.2 (95% CI 1.2-22.4)] and light paternal smoking prior to pregnancy, 1-10 cigarettes per day [adjusted OR 1.6 (95% CI 1.0-2.5)]. Risk estimates associated with either lower maternal smoking (1-10 or 11-20 cigarettes/day) or higher paternal smoking (11-20 or >20 cigarettes/day), ranged between 1.0 and 1.3 and were not statistically significant (adjusted for urbanization and socioeconomic status) (see Table 7.4.5A).

Sorahan et al., 2001. The Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) report included a reanalysis on reticuloendothelial malignancies (excluding ALL), for 95 cases with maternal and 85 cases with paternal smoking data (parental smoking analyzed separately). For paternal smoking at conception, elevated risk estimates were observed for four of five exposure strata of cigarettes/day [< 10 cpd: OR 1.32 (95% CI 0.32-5.51); 10-19 cpd: OR 2.65 (95% CI 0.83-8.46); 20-29 cpd: OR 3.69 (95% CI 1.49-9.15); 30-39 cpd: OR 0.29 (95% CI 0.03-2.56); 40+ cpd: OR 1.20 (95% CI 0.29-5.50), p for trend 0.35)]. The majority of exposed cases, 50 of 56, were categorized under <30 cigarettes/day. Elevated risks were also associated with maternal smoking prior to pregnancy [< 10 cpd: OR 1.20 (95% CI 0.41-3.47); 10-19 cpd: OR 2.81 (95% CI 1.07-7.39); 20-29 cpd: OR 1.38 (95% CI 0.58-5.50), p for trend 0.36].

7.4.5.1.3. Nonhuman Epidemiology

Bertone et al., 2002. This was a case control study of the association between ETS exposure and malignant lymphoma in pet cats. Malignant lymphoma occurs commonly in domestic cats and is histologically similar to that in humans. In recent years, with the reduction in the role of feline leukemia virus due to vaccination, other environmental causes have been entertained. Pet dogs and cats have been considered as potential sentinels for environmental health hazards in humans.

Cats diagnosed with biopsy-confirmed malignant lymphoma were compared with cats diagnosed with renal disease. Characteristics of the animals, including breed, age, hair length, reproductive status and general medical history were collected along with data on the animals' diets, time spent in and out of doors, exposure to flea control products, and housing. Exposure to ETS for the two years prior to diagnosis was assessed by questionnaire and included type and quantity of tobacco products used, number of years the cat lived with smokers, number of household smokers, and average number of cigarettes smoked per day.

Multivariate analysis revealed that, compared with cats having no ETS exposure, cats with any exposure to ETS showed a significantly elevated risk of malignant lymphoma (RR 2.4, 95% CI 1.2; 4.5). There was also evidence of dose dependence based on years of exposure (trend p = 0.003), number of household smokers (trend p = 0.005), number of cigarettes smoked per day (trend p= 0.006), and ETS exposure index (years of ETS exposure times number of cigarettes smoked per day; trend p = 0.008).

Since no biochemical measures of ETS were made, it is difficult to quantify the effective doses the cats received. An attempt to mitigate possible misclassification of ETS exposure levels was made by including information on house size and time spent out of doors in the multivariate analysis. Neither of these factors altered the risk estimates. Misclassification of exposure in this study is likely to be nondifferential and would be expected to bias towards the null. The

apparent elevated risk and its dose-dependent nature strongly support a role for ETS in malignant lymphoma in these animals.

Table 7.4.5A Maternal or Paternal Smoking and Risk of Lymphoma in Children

Study (Age of Subjects)	# Cases/ # Controls (Type of lymphoma)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Ji *et al.* (1997) (Age <15)	87/87 (All lymphomas)	Ever active smoker	Not available	4.0 (1.3-12.5)[a]
		Age initiated smoking		
		≥ 25	Not available	4.3 (1.0-17.9)[a]
		20 to 24	Not available	1.9 (0.5-7.3)
		< 20	Not available	5.6 (1.5-21.2)
				p trend=0.92
		Cigarettes per day		
		< 10	Not available	3.4 (0.8-14.0)[a]
		10 to 14	Not available	1.1 (0.3-4.8)
		≥ 15	Not available	3.8 (0.9-16.5)
				p trend=0.09
		Duration years		
		≤ 10	Not available	1.3 (0.2-7.0)[a]
		> 10 to 14	Not available	3.4 (0.9-12.7)
		≥ 15	Not available	3.5 (0.9-13.7)
				p trend=0.05
		Duration pack-years		
		≤ 5	Not available	2.8 (0.6-12.8)[a]
		> 5 to < 10	Not available	1.3 (0.3-5.5)
		≥ 10	Not available	5.7 (1.3-26.0)
				p trend=0.03
		Pack-year prior conception		
		≤ 2	Not available	3.1 (0.8-11.4)[a]
		> 2 to <5	Not available	1.8 (0.4-7.8)
		≥ 5	Not available	4.5 (1.2-16.8)
				p trend=0.07
		Pack-year after birth		
		≤ 2	Not available	3.9 (0.9-16.0)[a]
		> 2 to <5	Not available	2.7 (0.8-9.6)
		≥ 5	Not available	5.0 (1.2-22.4)
				p trend=0.08

[a] ORs adjusted for birth weight, parental age, alcohol consumption, education and income Tables 2 and 3 Ji *et al.* (1997).

Table 7.4.5A Maternal or Paternal Smoking and Risk of Lymphoma in Children

Study (Age of Subjects)	# Cases/ # Controls (Type of lymphoma)	Smoking Habits (cigarettes/day)	OR (95% CI) Maternal Smoking	OR (95% CI) Paternal Smoking
Sorahan *et al.*, 1995, 1997a and b (Deaths, Age < 15)		Current at interview (after death)		
1953-1955 (1997a)	125/125 (All Lymphomas)		0.79 (0.55-1.14) [b]	1.37 (1.02-1.83) [b]
1971-1976 (1997b)	165/165 (All Lymphomas)		1.05 (0.89-1.23) [c]	1.07 (0.92-1.23) [c]
1977-1981 (1995)	139/139 (All Lymphomas)		0.98 (0.83-1.17) [d]	1.14 (0.99-1.31) [d]
Pooled Estimate for 3 time periods (1997b)	486/493 (M[e]) (All Lymphomas) 476/477 (P) (All Lymphomas)		0.96 (0.73-1.27) [f]	1.67 (1.23-2.26) [f]
Schuz *et al.*, 1999 (Age <15)	228/2571 (M) 221/2540 (P) (NHL)	During pregnancy		
		1-10	1.3 (0.9-1.9)[g]	Not available
		11-20	1.0 (0.4-2.5)	Not available
		> 20	5.2 (1.2-22.4)	Not available
		Before pregnancy		
		1-10	Not available	1.6 (1.0-2.5)[g]
		11-20	Not available	1.1 (0.7-1.6)
		> 20	Not available	1.1 (0.7-1.8)
Sorahan *et al.*, 2001 (Age < 15)		At conception		
	95/91 (M)	< 10	1.20 (0.41-3.47)[h]	1.32 (0.32-5.51) [h]
	85/86 (P)	10-19	2.81 (1.07-7.39)	2.65 (0.83-8.46)
	(Other RES)	20-29	1.38 (0.58-3.26)	3.69 (1.49-9.15)
		30-39	(20-29 max)	0.29 (0.03-2.56)
		≥ 40		1.20 (0.29-5.05)
			p trend=0.36	p trend=0.35

[b] Unadjusted RR represents risk with change of one categorical level of smoking, maternal/paternal daily smoking analyzed simultaneously, Table 2 Sorahan *et al.* (1997a).
[c] Table 2 Sorahan *et al.* (1997b), unadjusted RR estimate change in one level of daily consumption.
[d] Table 4 Sorahan *et al.* (1995) unadjusted RR estimates associated with change of one level daily consumption.
[e] (M)=Maternal exposed cases/controls. (P)=Paternal exposed cases/controls. NHL=Non-Hodgkins Lymphoma, RES=other reticuloendothelial neoplasms (excludes ALL).
[f] ORs adjusted for social class, paternal/maternal age, birth order, and obstetric radiography Table 5 Sorahan *et al.* (1997b).
[g] ORs adjusted for age, sex, and socioeconomic status Table 4 Schuz *et al.* (1999).
[h] Unadjusted ORs presented in Table 3 of Sorahan *et al.* (2001) for General Practitioner controls.

7.4.5.2. Summary of ETS and Lymphoma

In summary, the more recent data on ETS exposure and risk of lymphomas and NHL remain inconclusive for adults, primarily due to a lack of investigations. The evidence is strongly suggestive of a relationship with childhood lymphomas (all combined) or NHL. Although small increased risks were reported in some previously reviewed studies (Cal/EPA, 1997), results were inconsistent and based on small numbers. However, in these recently published childhood studies, although largely reporting risk for all lymphomas combined, paternal smoking was significantly associated with overall lymphoma risk (Ji *et al.*, 1997; Sorahan *et al.*, 1997b) with some evidence for a dose-response trend in duration years or pack-years including prior to conception (Ji *et al.*, 1997). More studies on specific lymphoma cell types with more thorough exposure assessment and inclusion of older adolescents at higher risk of lymphomas will help elucidate this potential relationship.

7.4.6. Other Rare Childhood Cancers

7.4.6.1. ETS and Neuroblastoma

7.4.6.1.1. Previous Findings

The previous OEHHA report cited a single case-control study based on 104 of 139 (74.8% response) incident cases from a pediatric cancer registry diagnosed between 1970 and 1979 (Kramer *et al.*, 1987). Parental smoking prior to pregnancy was determined via interview following diagnosis. An elevated, but not statistically significant, risk was observed for maternal smoking during pregnancy [OR 1.26 (90% C.I. 0.76-2.09)] or prior to conception (OR 1.26). Similar results were observed for paternal smoking prior to birth [OR 1.60 (90% C.I. 0.94-2.74)].

7.4.6.1.2. Recent Epidemiological Data

Four case control studies, including the three OSCC reports, investigated the association between neuroblastoma and ETS exposure. The series of studies by Sorahan provide some evidence suggestive of an association between paternal smoking and neuroblastomas. The smaller Schuz study did not support this.

Sorahan et al., 1995; 1997a; 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed for paternal smoking (prior to or during pregnancy) and risk of childhood death due to neuroblastoma for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. Risk estimates varied by time period, ranging between OR 0.93-1.04 for maternal smoking, and OR 1.00-1.48 for paternal smoking. The only significant elevation in risk reported was for paternal smoking and neuroblastoma deaths reported 1953 to 1955 [OR 1.48 (95% 1.09-2.02)]. In the final mortality analysis, a pooled analysis was conducted, consisting of 472 matched pairs total for neuroblastoma diagnosed during all three time periods. Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave a significantly elevated risk estimate [adjusted OR 2.02 (95% CI 1.45-2.82)] for neuroblastoma from all three time periods combined (Sorahan *et al.* 1997b). The estimate for maternal smoking remained near unity [adjusted OR 0.95 (95% CI 0.71-1.26)] (Sorahan *et al.*, 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 160 cases of neuroblastoma among children were included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Risk of neuroblastoma was weakly associated with light maternal smoking during pregnancy [1-10 cigarettes/day: adjusted OR 1.5 (95% CI 1.0-2.2), based on 39 cases]. Risk estimates at higher smoking strata were inconsistent (i.e., at 11-20 and > 20 cigarettes/day, ORs 0.6 and 2.5, respectively), but were each based on only three cases. Paternal smoking was not significantly associated with an increased neuroblastoma risk [adjusted ORs range 0.6-1.2].

7.4.6.2. Wilms' Tumor of the Kidney

7.4.6.2.1. Previous Findings

The Cal/EPA (1997) report summarized four studies examining the role of ETS and Wilms' tumor, only one of which was designed specifically to identify risk factors for Wilms' tumor (Bunin *et al.*, 1987). This one hospital based case-control study reported no association with maternal smoking during pregnancy, however no risk estimates were presented. The three other case-control studies presented suggestive, but inconsistent and statistically nonsignificant risk estimates, between maternal smoking and the risk of Wilms' tumor (Stjernfeldt *et al.*, 1986a;b; McKinney and Stiller, 1986; Buckley *et al.*, 1986).

7.4.6.2.2. Recent Epidemiological Data

Several of the previously described studies presented limited data on the potential association between ETS and Wilms' tumor (Schuz *et al.*, 1999; Sorahan *et al.*, 1995; Sorahan *et al.* 1997a;b). These studies do not provide adequate evidence of any association between parental smoking and childhood cancers of the kidney.

Sorahan et al., 1995, 1997a, 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed for paternal smoking (prior to or during pregnancy) and risk of childhood death due to Wilms' tumor for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. In the final mortality analysis, a pooled analysis was conducted, consisting of 278 matched pairs for Wilms' tumor diagnosed during all three time periods. Site-specific pooled estimates of risk comparing paternal smokers versus paternal nonsmokers gave an elevated but non-significant risk estimate [adjusted OR 1.27 (95% CI 0.85-1.92)] for Wilms' tumor from all three time periods combined (Sorahan *et al.*, 1997b). The estimate for maternal smoking was significantly negatively associated with Wilms' tumor [adjusted OR 0.67 (95% CI 0.46-0.99)] (Sorahan *et al.*, 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 147 cases of nephroblastoma among children under age 15 were included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. Risk of nephroblastoma was not associated with either maternal smoking during pregnancy [(1-10 cigarettes/day: OR 0.9 (95% CI 0.5-1.4); 11-20 cigarettes/day: OR 1.2 (95% CI 0.5-3.0)] or paternal smoking prior to pregnancy [1-10 cigarettes/day: OR 0.8 (95% CI 0.4-1.4); 11-20 cigarettes/day: OR 0.8 (95% CI 0.5-1.3); >20 cigarettes/day: OR 0.9 (95% CI 0.5-1.6)].

7.4.6.3. Germ Cell Tumors

7.4.6.3.1. Previous Findings

The Cal/EPA (1997) report briefly mentioned a single study that analyzed the association between germ cell tumors (41 cases) and paternal smoking within a larger case control study (555 cases) (McKinney and Stiller, 1986). No difference was observed for either maternal or paternal smoking habits between cases and controls.

7.4.6.3.2. Recent Epidemiological Data

One additional primary case-control study (described previously) provides no evidence for an association between ETS and germ-cell malignancies (Shu *et al.*, 1995).

Shu et al., 1995. A case-control study of childhood malignant germ-cell tumors, 105 cases and 639 population controls, was derived from the Children's Cancer Group (U.S. and Canada) to analyze a variety of potential risk factors for germ-cell malignancies. Cases were diagnosed in children under age 15 with a variety of germ–cell malignancies (34 percent ovarian, 23 percent testicular, and 43 percent extra-gonadal). Mothers of cases were less likely than controls to have smoked, with an adjusted OR for risk of germ-cell tumors of 0.6 (95% CI 0.3-1.0) for ever smoking 3 months prior to or during pregnancy (adjusted for age, sex, gestational age, parity, maternal education). No relationship was observed between paternal smoking and risk of germ-cell tumors.

7.4.6.4. Bone and Soft-Tissue Sarcomas

7.4.6.4.1. Previous Findings

The previous OEHHA report (Cal/EPA, 1997) summarized results from three case-control studies; two specifically addressed rhabdomyosarcoma (Grufferman *et al.*, 1982; Magnani *et al.*, 1989) while the other analyzed soft tissue and bone sarcomas from a larger study (McKinney and Stiller, 1986). The association between maternal smoking and the risk of soft tissue sarcomas or bone sarcomas was elevated, but not significantly, in one study (McKinney and Stiller, 1986). The other two studies did not observe increased risk for either rhabdomyosarcoma specifically or all other soft tissue sarcomas combined. However, one study did report a statistically significant elevated risk for rhabdomyosarcoma for paternal smoking [RR 3.9 (95% C.I. 1.5-9.6)], even after adjusting for income, education and paternal occupations [RR 2.8, p = 0.07].

7.4.6.4.2. Recent Epidemiological Data

Two case-control studies, including three reports from the OSCC mortality study, described previously, reported limited risk estimates for ETS exposure and the potential association with bone or soft-tissue sarcomas (Schuz *et al.*, 1999; Sorahan *et al.* 1995, Sorahan *et al.* 1997a; b). These studies do not provide sufficient evidence of an association between parental smoking and bone or soft tissue sarcomas.

Sorahan et al., 1995, 1997a, 1997b. As described previously, three Oxford Survey of Childhood Cancers (OSCC) studies also analyzed for paternal smoking (prior to or during pregnancy) and risk of childhood death due to bone sarcomas for the three time periods, 1953 to 1955, 1971 to 1976, and 1977 to 1981. In the final mortality analysis, a pooled analysis was conducted, consisting of 232 matched pairs for bone sarcomas diagnosed during all three time periods. Site-

specific pooled estimates of risk comparing parental smokers versus parental nonsmokers gave elevated non-significant risk estimates [RR 1.24 (95% CI 0.80-1.93) and 1.31 (95% CI 0.87-2.00)] for paternal and maternal smoking, respectively (Sorahan *et al.* 1997b).

Schuz et al., 1999. In the population-based case-control study of Schuz *et al.* (1999) described previously, 97 cases of bone sarcomas and 137 cases of soft tissue sarcomas reported among children under age 15 were included in the analysis. Interview data obtained parental smoking status (maternal and paternal) as cigarettes per day prior to pregnancy, during pregnancy, and 3 months following birth. No elevated risk estimates were reported for either maternal or paternal smoking.

7.4.6.5. Summary of ETS and Other Rare Childhood Cancers

The epidemiological evidence on the association between ETS exposure and other rare childhood cancers remains inconclusive. Many studies included cases in children under age 15, unfortunately excluding older adolescents, ages 16 to 19, that have higher age-specific incidence of several important histological types of sarcomas and germ-cell tumors (Campleman *et al.*, 1999; Ries *et al.*, 1999). However, the population-based nature of the studies does provide limited evidence suggesting a potential for a positive association between ETS and bone or soft tissue sarcomas, neuroblastoma or Wilms' tumor. Not surprisingly, given that these are rare events, small case numbers limit the ability to observe a statistically significant effect. Therefore, it is important to evaluate these studies in terms of the collective evidence, the direction of the risk estimates from individual studies, and possible biases (*i.e.*, confounding by social class, or other exposures) in explaining the findings. Future studies will require data collection on and control of other potential risk factors.

7.5. Chapter Summary and Conclusions

To summarize, the body of evidence supports that ETS exposure is causally associated with cancers of the lung and the nasal sinus. Epidemiologic studies, supported by animal data, provide evidence consistent with a causal association between ETS exposure and breast cancer in younger primarily premenopausal women. The evidence is suggestive of a causal association between ETS exposure and cervical cancer, nasopharyngeal cancer, and "all cancers" for adults and children (paternal smoking only). The evidence suggests an association between paternal smoking and childhood brain tumors and lymphoma; it is not possible at this point to separate the direct effects of pre-conceptual paternal smoking on the sperm from the effects of postnatal ETS exposure of the child for these two endpoints. Evidence is suggestive of an association between pre-conceptual paternal smoking, but not postnatal ETS, and childhood leukemia. Finally, currently there is insufficient evidence to assess potential associations between ETS exposure and cancers of the bladder, stomach, brain, hematopoietic system and lymphatic system in adults, and rare childhood cancers; thus the evidence are inconclusive for these cancers.

Appendix 7A

7.ApA.1 Primary Studies of Active Smoking and Breast Cancer Risk

A review of recent studies evaluating the association between active smoking and breast cancer is presented here as background, to aid in understanding the discussion on passive smoking risk, and for completeness in updating the previous document (Cal/EPA, 1997). This is not an attempt to provide an exhaustive review on the subject. As summarized below, 5 recent cohort and 14 case-control studies (primary studies) reported on the association of active smoking with breast cancer since the previous OEHHA document. In addition, the study by Morabia *et al*. (1996) is included below as it is an important study of active smoking and breast cancer reviewed in the 1997 report.

Morabia et al. (1996) examined the relationship of breast cancer with active and passive smoking among Swiss women in a population-based case control study. Cases (n = 244) were women <75 years old with a first diagnosis of invasive breast cancer in 1992-1993, while population controls (n = 1,032) were 30-74 years of age. Data were collected by interview with questions covering the major known or postulated risk factors for breast cancer as well as smoking history. Smoke exposure data were recorded year by year from age ten to the date of the interview, and included both passive and active exposures, duration of exposures (hours per day) and intensities (cigarettes per day). In this study, passive exposure was defined as having been exposed to ETS for at least one hour per day for at least 12 consecutive months. Women recruited during the second year of the study also completed a semiquantitative food frequency questionnaire to control for possible dietary confounders. Multivariate analyses were adjusted for age, education, BMI, age at menarche, age at first live birth, oral contraceptive use, history of familial breast cancer and cancer biopsy. Dietary data were available for 150 cases and 336 controls, and were used to adjust the multivariate analyses of the whole group (n = 1,276) for alcohol and saturated fat intake.

As shown in Table 7.ApA.1, both active and passive smoke exposure were associated with an increased risk of breast cancer that was statistically significant for all cases except ever active smoking of 1-9 cpd when compared to controls who were neither actively nor passively exposed. The fourth column of the table shows that the estimated risks for active smoking become non-significant when the control group included both non-exposed individuals and those exposed to ETS. Inclusion of ETS-exposed individuals in some studies of active smoking and breast cancer may explain their failure to find an association.

Table 7.ApA.1. Breast cancer risk associated with active and passive smoking

Exposure	Multivariate *vs*. unexposed	+ dietary adj. *vs* unexposed	*vs*. unexposed with passive exposure
Active 1-9 cpd	2.4 (1.3; 4.4)	2.2 (1.0; 4.4)	1.2 (0.8; 2.0)
10-19 cpd	3.6 (2.0; 6.2)	2.7 (1.4; 5.4)	1.7 (1.1; 2.5)
≥ 20 cpd	3.7 (2.1; 6.7)	4.6 (2.2; 9.7)	1.9 (1.2; 2.9)
Ever passive	2.3 (1.5; 3.7)	3.2 (1.7; 5.9)	

(from Morabia *et al.*, 1996)

A strength of this study's design was its ability to quantify potential selection, recall and detection biases. Selection bias was assessed by collecting smoking status on non-participants; the authors indicated there was some *"slightly conservative selection bias* (that) *may be due to a small number of current smokers among nonparticipating controls being reluctant to tell their true smoking status."* Interviewers were blind to the interviewees' case-control status. No evidence for differential recall between controls and cases was found based on questions regarding attitudes towards ETS exposure. This study thus supports an association of both passive and active smoking with breast cancer.

Millikan et al. 1998. An ongoing population-based case-control study (498 cases and 473 controls), the Carolina Breast Cancer Study (CNCS), examined the effects of active smoking on breast cancer risk and modification by genetic variation of N-acetylation metabolism (NAT). Risk estimates were adjusted for age, race, reproductive factors, alcohol, and family history of breast cancer. No association was observed between breast cancer and current active smoking versus never smokers in all or stratified by menopausal status (see Table 7.ApA.5). However, elevation in postmenopausal breast cancer risk was associated with former smoking [OR 1.5 95% CI 1.0-2.4], with risks highest among women smoking in the past 3 years [OR 3.4 (95% CI 1.4-8.1], versus those who had quit smoking 4-9 years previously [OR 3.0 (95% CI 1.3-6.7], or 10-19 years previously [OR 0.6 (95% CI 0.3-1.4)] (Table 7.ApA.6). Neither NAT1 or NAT2 genotype were individually associated with breast cancer risk, but some evidence suggested a modification of smoking effects among postmenopausal ex-smokers, particularly those that quit in the past 3 years (see Table 7.ApA.7). The reported odds ratios for active smoking are compared to non-smokers rather than non-smokers without ETS exposure, though the authors note, *"when we excluded women with exposure to ETS from the referent group, ORs for active smoking were unchanged or slightly attenuated."*

Lash and Aschengrau 1999. A U.S. case-control study identified 334 incident cases of breast cancer from 1983 to 1986 among residents of five Massachusetts communities. Ever active smokers had an elevated risk of breast cancer when compared to nonsmokers (no active or passive exposure) [adjusted OR 2.0 (95% CI 1.1-3.6)] (Table 7.ApA.5). The association with active smoking varied significantly by whether women smoked prior to first pregnancy, with higher risk among those smoking before versus after first pregnancy [adjusted OR 5.6 (95% CI 1.5-21) and OR 2.1 (95% CI 1.1-4.0), respectively]. No dose response was observed for cigarettes per day, however, only 16 cases reported smoking greater than 20 cigarettes per day. Similarly, no trend was observed by years smoking (Table 7.Ap.A.6). This study did not report results separately by menopausal status as 90% of the cases were in postmenopausal women. A limitation of the study was lack of control for socioeconomic status. Since breast cancer is associated with higher SES, and higher SES is associated with lower smoking, the odds ratios for smoking may have been biased to be too low.

Delfino et al., 2000. A U.S. case-control study recruited women with suspicious breast masses detected either clinically or by mammography. Passive exposure evaluation was limited to the residential setting. One hundred and thirteen cases of breast cancer and 278 controls with benign breast disease were enrolled. Since benign breast disease may share risk factors with breast cancer cases, including smoking, three analyses with varying control groups based on histopathology were conducted, all controls (n=278), low-risk controls (107), and high-risk

controls (148). Additional analysis included genotyping of N-acetyltransferase 2 (NAT2) to determine any modification by variation of NAT2 genetic polymorphisms on breast cancer risk.

Utilizing all controls, no significant increase in breast cancer risk was found among current or former active smokers compared to the reference non-exposed women (no active or passive smoking). No association was seen with either duration or quantity of cigarettes smoked per day (Table 7.ApA.5) or NAT2 status. Limitations of the study include lack of adjustment for socioeconomic status and alcohol consumption, which are risk factors for breast cancer and associated with smoking, and limited sample size in sub-strata.

Johnson et al., 2000. A population-based case-control study utilized data from the Canadian National Enhanced Cancer Surveillance System including 805 premenopausal and 1,512 postmenopausal women with incident primary breast cancer cases. Among premenopausal women, ever smokers (current and ex-smokers) compared to nonsmokers who were not regularly exposed to ETS, a significantly elevated breast cancer risk was identified [adjusted OR 2.3 (95% CI 1.2-4.5)]. ORs were adjusted for alcohol, education, age, age at first childbirth, adult height, age at menarche, BMI, parity, physical activity and residence. Postmenopausal women ever smokers had an adjusted OR 1.5 (95% CI 1.0-2.3). For ever smokers, the premenopausal risk estimates were higher when childhood exposures to passive smoke (under age 20) were also included [adjusted current smoker, OR 2.1 (95% CI 1.0-4.4), and ex-smoker, OR 2.6 (95% 1.3-5.3)] (Table 7.ApA.5). Postmenopausal breast cancer risk among current smokers also increased when childhood ETS exposure was included [OR 1.8 (95% CI 1.1-2.9)]. Among postmenopausal women, statistically significant dose-response relationships were observed between breast cancer risk and years smoking (P for trend 0.003), or total pack-years (P for trend 0.01) (Table 7.ApA.6).

These authors also examined breast cancer risk associated years of smoking before a first full-term pregnancy among parous women, and total lifetime smoking among nulliparous women. Premenopausal analyses were limited by small numbers of women smoking more than 30 years and no patterns of increased risk were observed. For postmenopausal parous women, no increase in risk was observed for less than 30 years of smoking, but 30 or more years of smoking were associated with a risk factor adjusted OR of 1.36 (95% CI 1.11-1.67). For parous women who had smoked at least 30 pack-years, smoking before pregnancy for 1-4, 5-7 and 8 or more years, were associated with breast cancer, with OR's of 1.19, 1.26 and 1.88 (95% CI 1.23-2.87), respectively. Nulliparous women with 30 years of smoking or more had an OR of 2.43 (95% CI 1.25-4.72). This analysis is without removing passive smokers from the referent non-exposed category.

These data suggest that women smoking for many years, especially before a first full-term pregnancy, have increased postmenopausal breast cancer risk (Johnson *et al.*, 2003). Among postmenopausal women a dose-response relationship between breast cancer risk and increasing years of active smoking, increasing pack-years and decreasing years since cessation was observed. This study's strengths include the population-based design, the ability to analyze risk separately for pre- and postmenopausal women, the lifetime passive and active smoking assessment, and the ability to control for other risk factors, including alcohol consumption, education, reproductive factors and physical activity. A limitation of the study was lack of

consideration of time-since-first-exposure in the dose-response analyses (years of smoking and pack-years).

Rookus et al. (2000) analyzed data from a Dutch population-based case-control study (n = 918) of breast cancer and oral contraceptives, in which lifetime histories of active and passive smokers were collected by interview. Passive smokers were defined as lifetime non-smokers with at least 20 years daily domestic or occupational exposure to ETS, or with exposure to someone smoking daily in their bedroom for more than one year. ORs were adjusted for lifetime physical activity level and other potential confounders. When passive smokers were included in the reference group of never smokers, the ORs for current and ex-smokers were 1.0 (95% CI: 0.8-1.3) and 1.3 (95% CI: 1.0-1.6), respectively. However, compared to non-exposed controls, the risks for current smokers and ex-smokers were higher (OR: 1.2, 95% CI:0.8-1.6 and 1.4, 95% CI: 1.0-2.0, respectively). This study is of interest because it directly addresses the concern that many studies may miss the effect of active smoking if passive smoking is inadequately measured and controlled for and because ETS exposure from both domestic and occupational situations was measured.

Marcus et al. 2000. A population-based case-control study, the Carolina Breast Cancer Study, analyzed data from 864 incident breast cancer cases to evaluate the relationship between adolescent exposure to active or passive smoking and breast cancer risk. After adjusting for a number of confounders including age at menarche and first birth, alcohol consumption and BMI, relative to all non-smokers, breast cancer risk was significantly elevated among current [OR 2.1 (95% CI 1.2-3.4)], but not former smokers [OR 0.7 (95% CI 0.3-1.8)], initiating smoking prior to age 15 (ages 10-14) (see Table 7.ApA.6). Risk estimates were also higher among women smoking more than 20 years and initiating active smoking prior to age 15 [10-14 years old: OR 1.9 (95% CI 1.0-3.4); 15-19 years: OR 1.2 (95% CI 0.9-1.7); ≥ 20 years old: OR 1.5 (95% CI 1.0-2.2)]. A limitation of this study was the use of a referent population in which adult exposure to ETS was determined by a single question (have you lived with a housemate since the age of 18 years who smoked?).

Morabia et al. 2000, 1998. A population-based case-control study in Geneva, Switzerland investigated the association of breast cancer with passive and active smoking (Morabia *et al.*, 1996). An analysis of interactions between smoking and genotype evaluated the influence of slow and fast acetylation, based on genotypic variation in N-acetyltransferase 2 (NAT2) (Morabia *et al.*, 2000). Pooling premenopausal and postmenopausal women, the adjusted OR for breast cancer was 3.3 (95% CI 1.7-6.5) for active smokers (adjusted for age, education, and family history of breast cancer) (Table 7.ApA.5). After stratification by NAT2 status, breast cancer risk with active smoking increased for high acetylators (all women). In premenopausal women the NAT2 genotype did not influence the adjusted OR [2.9 (95% CI 1.1-7.5) for fast and slow acetylators]; however, among postmenopausal women, a statistically significant association with breast cancer was found in fast acetylators with active smoking [adjusted OR 8.2 (95% CI 1.4-46.0)], with a smaller and statistically nonsignificant effect observed in slow acetylators [adjusted OR 2.9 (95% CI 0.8-11.2)] (Table ApA.7). The number of unexposed cases (no active, no passive) was small in both fast and slow acetylators (<5 cases). However, when the authors repeated the analysis with a second, never-active smoker referent category, which included passive smokers (thereby mimicking the referent population in several previous studies), the OR for breast cancer in postmenopausal women among slow acetylators was 2.5 (95% CI 1.0-6.2),

and among fast acetylators the OR was reduced to 1.3 (95% CI 0.5-3.3). These differences indicate the importance of considering passive exposures in studies evaluating associations between breast cancer and tobacco smoke.

This group of breast cancer cases and controls was also used to determine the relationship between smoking and breast cancer by estrogen receptor status (Morabia *et al.*, 1998). Among the subjects for whom estrogen status was available, 74.4% of the tumors were ER+. Active tobacco smoking was a risk factor for both ER+ and ER- tumors among both pre- and postmenopausal women. Age-adjusted ORs were consistently higher for ER- tumors; however, risk estimates were not statistically different from ER+ breast tumor risk. For all women combined, ever-active smoking was associated with a significantly elevated risk for ER- tumors [age-adjusted OR 3.8 (95% CI 1.4-10.3) and OR 4.3 (95% CI 1.4-13.2) for < 20 and ≥ 20 cigarettes per day (cpd), respectively]. By comparison, ER+ breast cancer risks among ever-active smokers were lower [age-adjusted OR 2.2 (95% CI 1.3-3.6) and OR 2.4 (95% CI 1.4-4.5) at <20 and ≥ 20 cigarettes per day, respectively]. Breast cancer risk for ER- tumors was highest among postmenopausal women with ever-active smoking [age-adjusted < 20 cpd: OR 5.2 (95% CI 1.5-18.7); ≥ 20 cpd: OR 5.7 (95% CI 1.4-24.2). A limitation of this study was lack of adjustment for alcohol consumption, a potentially confounding factor.

Couch et al. (2001) examined the association of active smoking with the risk of breast cancer among women in families at high risk for breast cancer. This analysis focused on 132 families (of 534 breast cancer probands studied at University of Minnesota) thought to be at the greatest risk of breast cancer as indicated by having three or more members with either breast or ovarian cancer. Data on cancer incidence and breast cancer risk factors, including smoking habits, were collected by telephone interview.

The effects of smoking and relationship to the index case (proband) are shown in Table 7.ApA.2, analyzed both with data from all respondents (surrogates and self-reporters), and from self-respondents alone. Compared with never-smokers, ever smoking sisters and daughters of the proband had significantly elevated risks for breast cancer that were not seen among more distant relatives (granddaughters, nieces and marry-ins) after adjusting for age at menarche and first birth, BMI, alcohol, and oral contraceptive use.

Table 7.ApA.2. Breast cancer risk as a function of smoking status and relation to the case: all families.

		All respondents		Self-respondents	
Relationship	**Smoking**	**Cases**	**RR (95% CI)**	**Cases**	**RR (95% CI)**
Sister & daughter	**Never**	63	1.0	12	1.0
	Ever	32	1.8 (1.2; 2.7)	14	2.4 (1.2; 5.1)
Granddaughter & Niece	**Never**	108	1.0	47	1.0
	Ever	80	1.1 (0.8; 1.5)	40	1.2 (0.8; 1.8)
Marry-in	**Never**	112	1.0	47	1.0
	Ever	76	1.2 (0.9; 1.6)	39	1.2 (0.8; 1.9)

When the analysis was restricted to families with the highest risk, in this case, families with five or more cases of breast or ovarian cancer, ever-smoking among first-degree relatives of the

proband was associated with substantially elevated risk compared to never-smoking (RR 5.8, 95% CI 1.4-23.9) (Table 7.ApA.7).

This study suggests that smoking increases the risk of breast cancer among women at higher risk due to family history. Reporting bias is unlikely to have been great enough to explain the large risk increase among daughters and sisters given the similarity in risk estimates based on self-respondents alone and on self-respondents plus surrogates. The study did not take into account exposure to passive smoke among first-degree relatives. If a significant number of the proband women were themselves active smokers, their daughters may have received substantial ETS exposure at a susceptible stage in their own breast development.

Krajinovic et al., 2001. In a Canadian hospital-based case-control study with 149 breast cancer cases and 207 controls, the influence of multiple carcinogen-metabolizing enzymes (analysis of genetic variants) on breast cancer risk was investigated, including the potential modification of risk due to smoking. The risk from active cigarette smoking was elevated, although not statistically significant, among women carriers of the NAT2 rapid acetylator variant genotype [OR 2.6 (95% CI 0.8-8.2)] (Table 7.ApA.7), suggesting that gene-exposure interactions may influence breast cancer risk among active smokers. Interpretation is limited by the hospital-based study design.

Manjer et al. (2001) examined the association between smoking and the incidence of hormone receptor negative breast cancer among 10,902 women in Malmo, Sweden. The women in this prospective study had a mean age of 49.7 years at baseline, and were followed until 1997 for an average of 12.4 years. Analyses of estrogen and progesterone receptor status were performed for the 268 cases for which tumor tissue was available. At baseline, a self-administered questionnaire was used to assess smoking habits. Ever-smokers were defined as those who had ever smoked daily for at least six months. Current and ex-smokers were defined as ever-smokers who were or were not still smoking, respectively. Among ex-smokers, time since cessation was also recorded.

As shown in Table 7.ApA.3, ever smoking elevated the risk for all tumor types but not significantly so. However, for ER^- tumors the risks were more than doubled by ever smoking. There was no significant association between smoking and either ER+ or PgR+ tumors. A significant increase in risk for PgR^- tumors was only noted for ex-smokers.

Table 7.ApA.3. Smoking status and risk of cancer by tumor hormone receptor type

Tumor	Smoking	Cases	Adj RR (95% CI)	Tumor	Smoking	Cases	Adj RR (95% CI)
All	Never	127	1.00				
	Current	102	1.10 (0.84; 1.44)				
	≤ 19 cpd	72	1.05 (0.78; 1.42)				
	≥ 20 cpd	30	1.17 (0.78; 1.76)				
	Ex	68	1.34 (0.99; 1.81)				
ER+	Never	96	1.00	ER^-	Never	20	1.00
	Current	62	0.88 (0.63; 1.22)		Current	29	2.21 (1.23; 3.96)
	≤ 19 cpd	45	0.87 (0.60; 1.25)		≤ 19 cpd	20	2.04 (1.07; 3.88)
	≥ 20 cpd	17	0.82 (0.49; 1.39)		≥ 20 cpd	9	2.62 (1.17; 5.87)
	Ex	41	1.03 (0.71; 1.50)		Ex	19	2.67 (1.41; 5.06)
PgR+	Never	54	1.00	PgR^-	Never	62	1.00
	Current	45	1.10 (0.73; 1.66)		Current	46	1.08 (0.73; 1.60)
	≤ 19 cpd	33	1.11 (0.71; 1.74)		≤ 19 cpd	32	1.02 (0.65; 1.58)
	≥ 20 cpd	12	1.07 (0.57; 2.03)		≥ 20 cpd	14	1.13 (0.62; 2.03)
	Ex	20	0.94 (0.56; 1.58)		Ex	40	1.61 (1.07; 2.41)

The risk of cancer was significantly elevated for the ER^- /PgR^- combination (Table 7.ApA.4). The combination of ER^- /PgR+ also resulted in high risks but the confidence intervals were wide and included no effect. The results were similar when the analyses were restricted to peri- and postmenopausal women.

Table 7.ApA.4. Smoking status and risk of cancer: interaction of receptor types

	PgR Status			
ER status	**PgR+**		**PgR–**	
ER+	n = 105		n = 94	
	Never	1.00	Never	1.00
	Current	1.00 (0.65; 1.55)	Current	0.72 (0.43; 1.20)
	≤ 19 cpd	1.05 (0.65; 1.69)	≤ 19 cpd	0.67 (0.37; 1.20)
	≥ 20 cpd	0.95 (0.48; 1.90)	≥ 20 cpd	0.69 (0.31; 1.54)
	Ex	0.78 (0.44; 1.39)	Ex	1.26 (0.79; 2.12)
ER–	n = 14		n = 54	
	Never	1.00	Never	1.00
	Current	2.43 (0.66; 9.00)	Current	2.14 (1.11; 4.12)
	≤ 19 cpd	1.87 (0.43; 8.07)	≤ 19 cpd	2.06 (1.01; 4.23)
	≥ 20 cpd	2.70 (0.47; 15.6)	≥ 20 cpd	2.58 (1.04; 6.41)
	Ex	3.11 (0.76; 12.7)	Ex	2.55 (1.25; 5.20)

This study supports an association between ever-active smoking and an increased risk of breast cancer, most notably for tumors that are ER^-. In addition, the observation of non-significantly decreased risks for ER+ tumors among ever-smokers would be consistent with the anti-estrogenic effects often attributed to cigarette smoke exposure. Strengths of this study include its prospective nature, which limits bias associated with recall and case status. Investigator bias was

limited through the use of self-administered questionnaires. Smoking habits were ascertained only at baseline. This study suffered from no assessment of passive smoke exposure.

Collaborative Group study of breast cancer, alcohol, and smoking, 2002. In an effort to determine whether alcohol and smoking are independently associated with breast cancer risk, an international collaborative research group pooled data from 53 cohort and case-control studies of female breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer 2002). For the cohort studies case-control sampling was performed (all cases and 4 controls for each case), and thus, the investigators were able to treat the pooled data as one case control study of 58,515 cases of breast cancer. After controlling for alcohol, the investigators found no association of smoking with breast cancer risk (odds ratio = 0.99, 95% CI 0.92–1.05, for current smokers compared to never smokers). Alcohol, on the other hand, after controlling for smoking, was significantly associated with breast cancer risk (odds ratio = 1.46, 95% CI 1.33–1.61, at 45+ g/day alcohol), and smoking status did not modify the association. The investigators did not report data for ETS.

This study utilized limited exposure measures classifying smoker exposure only as ever vs. never and as ex- or current. They note under "Methods," "no attention was given to the reported associations of breast cancer with environmental tobacco smoke." Since this study includes nearly all of the published studies in the literature prior to 2002, it dilutes recent studies with more sensitive measurement of exposure effects resulting from utilizing non-ETS exposed referent categories, as well as those that consider potentially sensitive populations (e.g., exposure prior to first full term pregnancy, specific genotypes, and exposure greater than 30 years) (Terry *et al.*, 2002; Wells, 2003).

Egan et al., 2002. A U.S. cohort study (Nurse's Health Study) analyzed the influence of active and passive smoking on the incidence of invasive breast cancer. This analysis includes 78,206 women followed prospectively from 1982 until June 1996, reporting 3,140 cases of invasive breast cancer. The relative risk of breast cancer was 1.04 (95% CI 0.94-1.15) for current smoking and 1.09 (95% CI 1.00-1.18) for ex-smokers (previous active smoking, adjusted for age, age at menarche, age at first birth, history benign disease, family history of breast cancer, menopausal status, age at menopause, weight, height, alcohol, dietary factors, and hormone use). The relative risk was higher among ex-smokers that recently quit smoking [adjusted RR 1.17 (95% CI 1.01-1.40)] compared to never-smokers. If women exposed to passive smoke were excluded from the unexposed category, then the relative risks for current and past active smoking increased slightly [adjusted RR 1.15 (95% CI 0.98-1.34) and 1.17 (95% CI 1.01-1.34), respectively].

Analysis of breast cancer risk according to years of active smoking before and after childbirth was conducted to determine the influence of smoking on the immature breast. Smoking for any duration after childbirth was unrelated to breast cancer risk; however, risks were slightly elevated for smoking prior to childbirth [5 or more years of smoking adjusted RR 1.13 (95% CI 0.99 - 1.30), and 10 or more years adjusted RR 1.13 (95% CI 0.94 -1.37)]. The effect of smoking before pregnancy was stronger in women that began smoking younger. Compared to never-smokers, women initiating smoking before 16 years of age had significantly elevated breast cancer risk [adjusted RR 1.31 (95% CI 1.07-1.61)]. Among nulliparous women, no association was found between active smoking duration and breast cancer incidence. Additionally, smoking intensity before childbirth was marginally associated with increased breast cancer incidence [< 1

pack/day: adjusted RR 1.12 (95% CI 0.95-1.31); ≥ 1 pack/day: adjusted RR 1.21 (95% CI 0.98-1.51), p for trend 0.05].

This study suggests that overall active smoking was related to an increased risk of breast cancer in some groups. The risks appear higher when smoking was initiated at a young age or smoking occurred before first childbirth. The strengths of this study are its size, and the substantial data on reproductive risk factors, family history, and other potential confounders. Unfortunately, this study is subject to misclassification of ETS-exposed nonsmokers as a non-exposed population, thereby minimizing any potential observable risk.

Terry et al., 2002. A prospective Canadian cohort recently reported on the association between active smoking and breast cancer in 89,835 women enrolled within a multi-center, randomized trial of mammography screening. Women were recruited between 1980 and 1985 and followed through December 1993. Cancer cases (n = 1,306) were ascertained through linkages with population-based cancer database and national vital statistics. Active smoking, including average use and duration, were determined from baseline data.

The age-adjusted relative risk for breast cancer for current smoking was statistically significant [RR 1.15 (95% CI 1.05-1.27)], relative to all never-smokers. After adjustment for multiple factors (including age, study center, BMI, education, physical activity, multiple reproductive and menstrual factors, family history of breast disease, menopausal status, alcohol consumption and hormone replacement therapy), risk for current smokers remained similar [RR 1.14 (95% CI 1.03-1.27)]. Breast cancer risk increased with duration of smoking; women smoking over 40 years had a statistically elevated risk [RR 1.61 (95% CI 1.19-2.19)], with a significant p for trend 0.003. The risk for women smoking > 20 cigarettes per day for over 40 years was 1.83 (95% CI 1.29; 2.61).

Band et al., 2002. Cigarette smoking appears to have competing effects in the etiology of breast cancer, potentially reducing cancer risk via an antiestrogenic effect while increasing the risk of chemical carcinogenesis. Evidence from studies in active smokers demonstrates that cigarette smoke is anti-estrogenic (MacMahon *et al.*, 1982; Michnovicz *et al.*, 1986; Baron *et al.*, 1990; Jensen and Christiansen, 1988; Terry and Rohan, 2002)).

Breast cells undergo three periods of development, *in utero*, during puberty, and during pregnancy and lactation (Russo and Russo, 1994), which are characterized by rapid cell proliferation and differentiation. Band *et al.* (2002) examined the role of the timing of onset of cigarette smoking relative to menarche, pregnancy and menopause, in 1,018 diagnosed cases of breast cancer vs. 1,025 age-matched population controls. Information was collected by postal questionnaire on ethnic origin, marital status, education, smoking history and alcohol consumption, height, current weight and weight at age 18, age at menarche, parity, history of breast biopsy for benign breast disease, family history of breast cancer, and lifetime occupational history. Also collected were data on breastfeeding, birth control use and hormone replacement therapy. Of the 1,018 cases, 318 were premenopausal (44 yrs), and 700 were postmenopausal (64 yrs). Of the 1,025 controls, 340 were premenopausal (43 yrs), while 685 were postmenopausal (64 yr).

Among premenopausal women, smoking initiated within 5 years of menarche was associated with a significant risk of breast cancer in ever-pregnant women who smoked before their first pregnancy (adjusted OR 1.69, 95% CI 1.13; 2.51). A dose response was observed both in terms of cigarettes per day and in terms of pack years, particularly in nulliparous women where smoking <20 cpd was associated with an OR of 1.45 (95% CI 0.49; 4.29) which increased with higher cigarette consumption (≥ 20 cpd) to 7.08 (95% CI 1.63; 30.8). Among nulliparous women, smoking greater than 20 pack-years was also associated with significant risk OR 7.48 (95% CI 1.59; 35.2) (Table 7.ApA.6). In contrast, none of the smoking categories was significantly associated with breast cancer among postmenopausal women. Indeed, among postmenopausal women whose body-mass index increased from age 18 to present and who started to smoke after a full-term pregnancy, the risk of breast cancer was significantly reduced (0.49, 95% CI 0.27-0.89).

A strength of this study is the control for a large number of potentially confounding factors. The results demonstrated in this study support the authors' hypothesis that active cigarette smoking exerts two competing effects on breast cancer risk: 1) tumorigenic by action of the carcinogens in smoke and 2) protective by way of smoke's anti-estrogenic effects. In that hypothesis, the carcinogenic effect would be displayed most prominently in those whose exposures began close to menarche and before first pregnancy. This would characterize a time when estrogen levels were relatively high (thus less prone to significant disruption) and breast tissue sensitive due to rapid proliferation and incomplete differentiation. The antiestrogenic (protective) effects would be most pronounced in the postmenopausal women whose onset of smoking began after first pregnancy and who were relatively obese, leading to higher estrogen levels from aromatization of adrenal androgens in fat cells.

In this study, mailed questionnaires eliminated interviewer bias. The study was population-based with a high response rate, which minimizes selection bias. In addition, the proportion of never- and ever-smokers was similar among responders and non-responders for both cases and controls. However, the information for non-responders was obtained for only small subsets. The authors claim that recall and misclassification of age at commencement of smoking was not likely to systematically differ between cases and controls since smoking was not generally perceived as related to breast cancer. The absence of information on passive smoking could have led to misclassification of passive smokers as non-exposed but this would bias towards the null.

Kropp and Chang-Claude, 2002. This population-based case-control study examined the association between active and passive smoke exposure and breast cancer risk in women up to 50 years of age in southern Germany. Cases were defined as having incident in situ or invasive breast cancer diagnosed under the age of 51 (n = 468), and were matched by age and study region to 1,093 randomly selected controls. Multivariate analyses were adjusted for number of months of breastfeeding, BMI, education, family history, menopausal status and alcohol intake, number of pregnancies, use of oral contraceptives, and age at menarche and at first pregnancy. The referent category included only never smokers who had no residential or occupational ETS exposure. Active smoking was associated with breast cancer when analyzed by duration of active smoking (in years) (p for trend = 0.047) and age at initiation of smoking (p for trend = 0.015)(Table 7.ApA.6). Age at initiation of smoking was found to modify the effect of active smoking, with increased ORs in older age-at-initiation groups. Among high active smokers, high passive smoke exposure increased breast cancer risk about 50% over active smoking alone [OR

1.78 (95% CI 1.16-2.71) with additional passive smoking vs. 1.12 (95% CI 0.64-1.97) with no additional passive smoking].

Chang-Claude et al. (2002) examined the role of polymorphisms in the N-acetyltransferase 2 (NAT2) gene in the effects of active and passive smoke exposure on breast cancer risk. The current study was based on a population-based case-control study of 706 breast cancer patients diagnosed by age 50 and 1,381 controls. Data, including active smoking and childhood, adult and workplace smoke exposures, were collected by self-administered questionnaire The reference group contained neither ever-active smokers (>100 cigarettes in their lifetimes) nor ever-passive smokers (> 1 hr ETS per day for at least 1 year).

Smoke exposure was associated with increased risks of breast cancer that were similar in passive (OR 1.5, 95% CI 1.0; 2.2) and active (OR 1.4, 95% CI 0.9; 2.2) smokers. Among active smokers, there was a statistically significant trend for increased breast cancer risk with either increasing pack-years of smoking (>11 pk-yrs OR 1.79 (1.01;3.18) or duration (>20 yrs OR 1.84 (1.05;3.24) associated with slow acetylator status, and a decrease in risk with increased time since smoking cessation. This study was limited by its small size and possible recall bias.

Lash and Aschengrau, 2002. This case-control study of the association between active or passive smoking and breast cancer was conducted in a manner similar to their earlier study on this same topic (Lash and Aschengrau, 1999), but in a different population. The 666 cases were diagnosed with invasive breast cancer between 1987 and 1993 and, along with 615 controls, were drawn from residents of eight Massachusetts towns on Cape Cod. Smoking status was determined as ever active, ever passive only, and never active never passive. Odds ratios were adjusted for a history of radiation therapy, BMI, family history of breast cancer, histories of breast cancer and/or benign breast disease, alcohol consumption, age at first birth and parity.

In contrast to their previous study (Lash and Aschengrau, 1999), the risk of breast cancer among active smokers compared to never active never passive smokers was significantly decreased (OR 0.72, 95% CI 0.55-0.95). Neither duration of active smoking nor smoking before or after first pregnancy were associated with elevated breast cancer risk. (see Table 7.ApA.6).

The cases in this study were matched to controls by age and vital status, but no information was provided on either the age distribution or the menopausal status of the participants, both of which may be important in the interpretation of the reported null result. These results are in apparent conflict with the authors' earlier study. The present study was published as a brief communication and a more detailed report addressing these issues may be forthcoming.

Saintot et al. (2003). This study examined the interactions between polymorphisms of several xenobiotic enzymes and tobacco exposure in breast cancer risk among 282 breast cancer patients. This study employed a case-only design that does not permit calculation of ORs for exposure or genotype alone, but has higher statistical power for detecting gene-environment interactions than in a case-control study.

Breast cancer cases were recruited from the surgical wards of the Cancer Centre in Montpelier, France. between 1998 and 2001. Genetic polymorphisms were characterized for three enzymes: phenol-sulfotransferase (SULT1A1), cytochrome P450 1B1 (CYP1B1), and catechol-O-

methyltransferase (COMT). SULT1A1 activates the hydroxylated metabolites of some PAHs, and reduces the activity of estrogen. Individuals who are homozygous for His at codon 231 have lower transferase activity than either the heterozygote or the common homozygous Arg/Arg. CYP1B1 activates PAHs and heterocyclic aromatic amines, and catalyzes the hydroxylation of estrogens to the genotoxic catechol estrogen. Conversion of Val to Leu at codon 432 decreases the efficiency of catechol estrogen formation. COMT inactivates catechol estrogens by conjugation. The COMT (Met/Met) genotype has a significantly reduced methylation activity compared to the (Val/Val) genotype.

Unconditional logistic regression analysis was used to estimate the interaction between tobacco smoke exposure and the polymorphisms after adjustment for age at menarche, age at first full-term pregnancy, parity, oral contraceptive use, hormone replacement therapy, age at menopause and BMI. The analysis generates an OR of interaction (ORi), which is valid only if the gene polymorphisms and exposure in the population are mutually independent. The authors verified this assumption by estimating gene-exposure associations in controls from other published studies.

Current smokers with the Any Val CYP1B1 allele had a higher risk of breast cancer (ORi 2.32, 95% CI 1.00; 5.38) compared to the control group of never smokers with the Leu/Leu genotype characterized by lower catalytic efficiency for the 4-hydroxylation of estrogens (Table 7.ApA.7). Current smokers with the His SULT1A1 variant had significantly elevated risk (ORi 2.55, 95% CI 1.21; 5.36) compared to never exposed Arg/Arg homozygotes. For these two enzymes, there was no significant effect in passive or former smokers. There were no statistically significant interactions between smoke exposure and the COMT polymorphisms.

The authors analyzed the interactions between different levels of smoke exposure among ever smokers and the CYP1B1 and SULT1A1 polymorphisms with stratification for menopausal status. Among carriers of the Val CYP1B1 variant, the “high-activity” form, breast cancer risk was significantly elevated for those who had smoked more than 5 cigarettes per day ($p<0.01$), or for more than 20 years ($p = 0.01$), or greater than 10 pack-years, or who started smoking before age 20. The results were similar for both pre- and postmenopausal women (see Table 7.ApA.7). Also as seen in the table, premenopausal women with the His SULT1A1 allele were at greater risk than unexposed women homozygous for Arg SULT1A1. This effect was statistically significant for women who had smoked more than 5 cigarettes per day ($p = 0.05$) or for more than 20 years ($p = 0.01$)

This study finds increased risk of breast cancer risk among both pre- and postmenopausal smokers carrying the Val CYP1B1 allele or among premenopausal smokers with the His SULT1A1 variant allele. However, the comparison groups are never-smokers with the Leu/Leu genotype for CYP1B1, and the Arg/Arg genotype for SULT1A1. A more telling comparison might have been between smokers and never-smokers with the same genotypes or among smokers with different genotypes. The results nevertheless suggest a significant gene-environment interaction for active smoking as well as plausible mechanisms for this interaction.

Zheng *et al.* (2002) conducted a case-control study to examine the role of polymorphisms of GSTM1 and GSTT1 in the association between exposure to cigarette smoke and breast cancer as modified by amount and duration of smoking, age at smoking initiation, and menopausal status.

A total of 338 incident cases of histologically confirmed breast cancer and 345 controls, frequency-matched by age, provided blood for genotype determination. Personal data were collected by standardized, structured questionnaires administered by trained interviewers. Unconditional logistic regression was used to analyze the association between GSTM1 and GSTT1 polymorphisms and breast cancer risk among smokers versus never-smokers after adjustment for BMI, alcohol use, months of lactation, age at first full-term pregnancy, family breast cancer history, menopausal status, age at menarche and age at menopause.

This study found no association between breast cancer risk and GSTM1 genotype irrespective of menopausal or smoking status. There was, however, significantly elevated risk associated with the GSTT1 null genotype itself, regardless of smoking status, in postmenopausal women (OR 1.9, 95% CI 1.2; 2.9). While none of the estimates reached statistical significance, there were suggestions that in postmenopausal women with the GSTT1 null genotype, smoking was associated with increased breast cancer risk (Table 7.ApA.7).

This study suggests that the GSTT1 null genotype may be associated with increased breast cancer risk among postmenopausal smokers if they started smoking before age 18. There is limited evidence of a dose-related increase in risk with duration of smoking, but not by pack-years or cigarettes consumed per day. However, stratification by genotype and menopausal status resulted in small numbers in the various smoking categories thus limiting the study's ability to detect significant associations.

Al-Delaimy et al. (2004) investigated the association between active smoking and invasive breast cancer as a function of estrogen receptor (ER) status in the Nurses' Health Study II, a large prospective cohort study. Data were collected biennially by mailed questionnaire during the ten-year follow-up. Breast cancer risk was modeled using multivariate Cox proportional hazard regression, stratified by age and adjusted for BMI, height, oral contraceptive use, parity, ages at menarche and at first birth, family history of breast cancer or benign breast disease, alcohol consumption and menopausal status.

Analysis of the entire cohort, irrespective of ER status, generally did not show a significant association between smoking and breast cancer except at the longest duration: 20+ years (RR 1.21, 95% CI 1.01; 1.45; p for trend 0.04). There was also a significant trend for duration of smoking prior to the first pregnancy ($p = 0.01$). However, when compared by ER status, ER+ women were at significantly greater risk of breast cancer if they smoked than were ER- women. For ER+ women there were significant trends associated with total duration of smoking ($p = 0.003$), with the highest risk at 20+ years (RR 1.37, 95% CI 1.07; 1.74), and with duration of smoking prior to first pregnancy ($p = 0.003$). Smoking initiation at earlier ages (before ages 15 or 19) also significantly elevated breast cancer risk among ER+ women (age 15: RR 1.49, 95% CI 1.03; 2.17) but not ER- women (RR 1.19, 95% CI 0.69; 2.08). This study suggests that smoking increases breast cancer in a fashion that is dependent on age at smoking initiation, duration of exposure, and perhaps most critically, estrogen receptor status. However, it likely underestimates the true association between tobacco smoke and breast cancer because no attempt was made to ensure that the non-smokers in the reference group were not exposed to ETS.

Reynolds et al. (2004a) conducted a prospective analysis of breast cancer risk associated with passive and active smoking in the California Teacher Study (CTS), a large cohort of professional

school employees. Of the 329,000 eligible women, 35% (116,544) were included in the study and followed from 1995 to 2000 with diagnosis of 2,005 breast cancer cases. A survey at baseline collected information on smoking history among active and former smokers, as well as on passive exposure among never-smokers. Other risk factors included in multivariate analyses were age, ethnicity, family history of breast cancer, alcohol consumption, age at menarche, pregnancy history, physical activity, BMI, menopausal status, and estrogen hormone therapy. Current smoking was associated with a significantly elevated risk (Hazard Ratio, HR) of breast cancer in the full cohort regardless of whether passive smokers were included (HR 1.32, 95% CI 1.10; 1.57), or excluded (HR 1.25, 95% CI 1.02; 1.53) from the reference group (Table 7.ApA.5). However, passive smoking in this analysis did not include workplace and other exposures. This effect was most pronounced in postmenopausal current smokers.

Among active smokers compared to never-smokers, there appeared to be an increase in risk with increased smoking intensity irrespective of menopausal status (Table 7.ApA.6). Similarly, the duration of smoke exposure was related to breast cancer risk in the total group (p trend = 0.009) and in postmenopausal women (p trend = 0.032), but not premenopausal women (p trend = 0.616). However, no statistical interaction with menopausal status was found. Initiation of smoking prior to, but not after, age 20 also elevated risk in the total sample and in postmenopausal women.

This study found significant associations between breast cancer and active but not passive smoking. When the analysis was limited to the 35,123 nondrinkers in this cohort, current smokers continued to have a significantly elevated risk of breast cancer (HR 1.66, 95% CI 1.15-2.40). This is in fact a higher HR than the study as a whole and refutes concerns that associations between smoke exposure and breast cancer are actually measuring a surrogate of alcohol exposure. A limitation of this study is utilizing a referent group that includes those passively exposed from sources outside the household.

Gammon et al. (2004) utilized data collected for the Long Island Breast Cancer Study Project, a case-control study, to evaluate the effects of both active and passive tobacco smoke exposure on breast cancer incidence. Information on active and passive smoke exposure (in the home only), alcohol use, menstrual history, hormone use, demographics, physical activity, pregnancy history, occupational history, residency history, pesticide use, and a number of other factors was obtained by interviewer-administered questionnaire. Breast cancer risk was evaluated in relation to active smoking, passive exposure only, active and passive exposure or neither, using unconditional logistic regression and accounting for a large number of covariates. Estimates were also made by various measures of active and passive smoke exposure including intensity and duration, timing of exposure in relation to first pregnancy, childhood exposures (both active and passive), and spousal exposure. Work exposure and other exposure to ETS were not evaluated in this study.

For all women, there was no statistically significant elevation in odds ratio compared to never exposed for active smoking, or both active and passive smoking (Tables 7.ApA.5 and 6). Risk appears to be elevated slightly for active plus passive smokers, although not significantly (OR 1.15; 95% CI 0.90-1.82).

This study's strengths include: accounting for a large number of confounders, an overall large sample of cases and controls, a lifetime assessment of residential passive smoke exposure and active smoking history, and a referent group that excluded active smokers. However, similar to many ETS studies, sources of exposure other than that in the home are lacking. Occupational exposures were much more common in the past and lack of accounting for this exposure is problematic. Thus there may be nonsmokers in the non ETS-exposed category that were exposed to ETS at work. This type of misclassification biases towards the null.

Zhang *et al*.(2004) published in the abstracts of the 37th annual meeting of the Society for Epidemiologic Research (June, 2004). In that study, 49,165 Canadian women aged 40 – 59 were followed for 14 years: Women had an elevated risk of breast cancer death if they had smoked 30 years or more (HR = 1.90;95% CI, 1.29, 2.80), compared to never smokers. When compared to nondrinkers who had never smoked, light to moderate drinkers (>0 and <20 g/day of alcohol) who smoked for more than 30 years were twice as likely to die of breast cancer (HR = 1.98; 95% CI, 1.13, 3.48). Heavy drinkers (20+ g/day of alcohol) who smoked this long had almost a three-fold risk of breast cancer death (HR = 2.72; 95% CI, 1.30, 5.67). Heavy drinkers who smoked 40+ cigarettes/day experienced an almost four-fold risk of breast cancer death (HR = 3.85; 95% CI, 1.34, 11.09). There was a positive dose response relationship between years smoked and breast cancer mortality ($p<0.05$) among both drinkers and non-drinkers, after adjusting for cigarettes per day smoked, alcohol consumption, and other potential confounders. Apparent in this study is an at least additive effect of alcohol and smoking and an effect of smoking independent from drinking .

Hanaoka *et al.* (2005) investigated the role of tobacco smoke exposure in the etiology of breast cancer in a prospective cohort study of middle-aged Japanese women. In 1990, a self-administered questionnaire collected baseline data on personal and family medical histories, smoking habits, alcohol use, dietary habits and other lifestyle factors. Passive smoking was defined as a history of exposure to residential ETS or routine exposure to ETS in any work and/or public setting. The age at inititation and frequency of exposure were also determined. Cancer incidence and mortality data were collected during follow-up through the end of 1999. Of the 21,805 women participating in the study, 180 developed breast cancer. Relative risks were estimated by the Cox proportional hazards model with adjustment for age, area, education, employment status, BMI, family history of breast cancer, benign breast disease, age at menarche, parity, menopausal status, and hormone and alcohol use.

There was a significantly elevated risk of breast cancer among premenopausal women who were ever smokers (RR 3.9, 95% CI 1.5; 9.9: Table 7.ApA.5). However, after menopause, no elevated risk was evident. Among all women (pre- and postmenopausal), active smoking was associated with an elevated risk of breast cancer that was of borderline statistical significance (RR 1.7, 95% CI 1.0; 3.1).

This population-based prospective study has the advantages of general applicability and limited recall or selection bias. Smoking habits and passive exposures were assessed in more than one environment, and thus better capture the subjects' actual exposures than studies based on marriage to a smoking spouse. The referent group consisted of those without exposure to ETS either as adults (home or occupation/out of home exposures) or childhood (home only). Smoking and occupational/out of home exposure was only assessed at baseline. Cessation of smoke

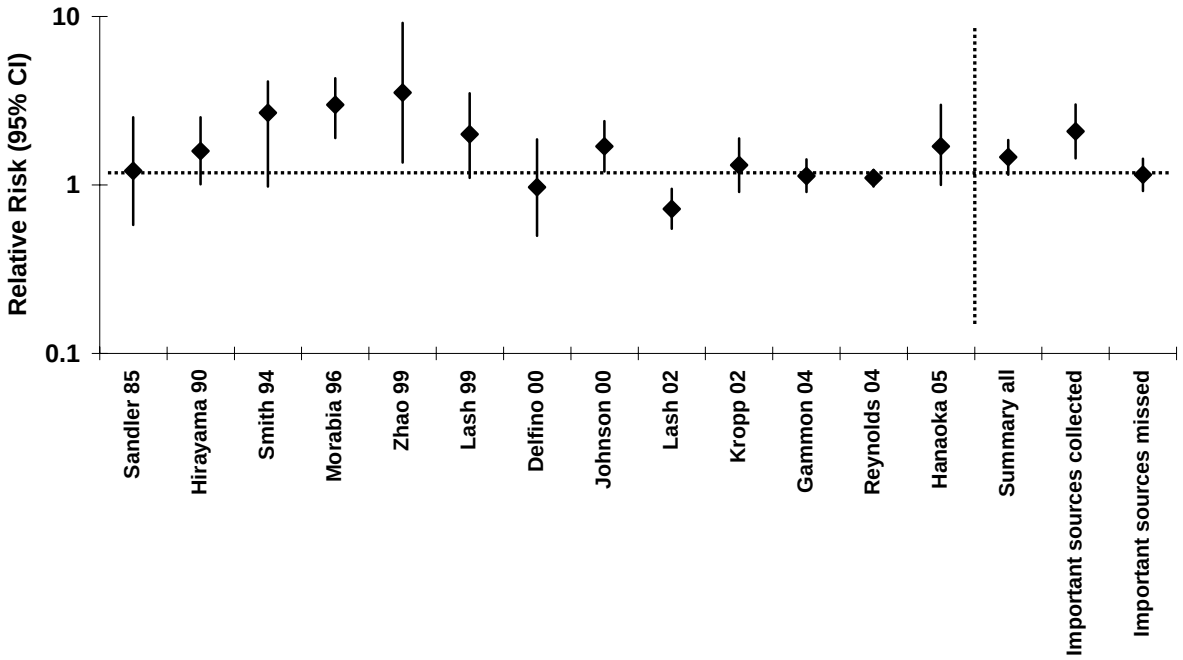
exposure during the 10-year follow-up could result in some misclassification that might bias the results towards the null. Due to the small size of the study, some strata in the analysis are only sparsely populated thus limiting the study's power to detect an effect. Data presented are inadequate to determine if a dose response for active smoking was present. Nevertheless, this study provides clear evidence that active smoking significantly increases the risks of breast cancer among premenopausal women. This is the first prospective cohort study to utilize a referent population that excluded both ETS exposure in childhood and from adult residential and occupational sources.

Gram et al. (2005) examined breast cancer risk in women related to age of smoking initiation in a large prospective cohort in Norway and Sweden from 1991 through 2000. Comparing smokers to never- smokers, they found significantly increased risks for smoking >10 cigarettes/day for 20+ years (RR 1.34; 95%CI 1.06-1.70), and initiating smoking prior to first birth (1.27; 95%CI 1.00-1.62), before menarche (RR 1.39; 95%CI 1.03-1.87), or before age 15 years (RR 1.48; 95%CI 1.03-2.13) (Table 7.ApA.5 and 6). Their findings support a link between active smoking during peri-adolescence and before childbirth and increased breast cancer risk.

7.ApA.2 Active Smoking: Discussion and Conclusion

While there continues to be some heterogeneity in study results, overall, the studies presented in Appendix 7A in this update (along with in vitro and animal data on carcinogenesis) provide evidence of a role for active smoking in causation of breast cancer, and include evidence of a dose-response. In 11 of 13 studies examining breast cancer risk from active smoking (Figure Figure 7.ApA.1 below) compared to a referent population of never-smoking women not exposed to ETS, point estimates were greater than 1 (many of them significantly so). Of the six studies considered by OEHHA as "most informative" based on best exposure assessment and design (see Section 7.4.1.6) (Smith *et al*., 1994; Morabia *et al*., 1996; Zhao *et al*., 1999; Johnson *et al*., 2000; Kropp and Chang-Claude, 2002; Hanaoka *et al*., 2005), all have point estimates above one (Figure 7.ApA.1). There are now studies providing some evidence for gene-environment interactions, as well as studies demonstrating susceptible subpopulations with highly significant increased breast cancer risk associated with active smoking (e.g., those with familial high risks in Couch *et al*., 2001). Furthermore, some studies demonstrate significant risks related to the hormonal receptor status of the tumor (Manjer *et al*., 2001; Morabia *et al*., 1998). Finally, six recent prospective cohort studies (supported by similar findings in case control studies) found statistically significantly elevated breast cancer risk associated with active smoking for at least some of the metrics of exposure (Egan *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*. 2004a, Hanaoka, 2005; Zhang *et al*., 2004; Gram *et al*., 2005). A number of studies (Table 7.ApA.5) found statistically significant elevated breast cancer risk for current or ever active smokers (Lash and Aschengrau, 1999; Johnson *et al*., 2000; Terry *et al*., 2002; Morabia, 2002, Reynolds *et al*., 2004; Zhang *et al*., 2004; Hanaoka *et al*., 2005). Long duration of exposure or higher pack-years (Table 7.ApA.6) was associated with significantly elevated breast cancer risks in a number of studies (Millikan *et al*., 1998; Lash and Aschengrau, 1999; Johnson *et al*., 2000; Band *et al*., 2002; Terry *et al*., 2002; Reynolds *et al*., 2004; Gram *et al*., 2005). A meta-analysis conducted by Johnson (2005) examined 13 studies of active smokers (controlling for passive smoking) and found a significantly elevated risk, OR 1.48 (95% CI 1.17-1.86). In those studies with a more complete passive exposure assessment, and thus cleaner referent groups, the breast cancer risk from active smoking was estimated at 2.08 (95% CI 1.44-3.01).

Figure 7.ApA.1 Summary Breast Cancer Risk Estimates for Active Smoking Compared to Never Smoking Women who were Never Regularly Exposed to ETS (Based on Johnson 2005, table 5)



Morabia *et al*. (1996), Kropp and Chang-Claude (2002), and Johnson *et al*. (2000) all reported that the risk estimate for breast cancer in active smokers increased when ETS-exposed women were excluded from the non-exposed referent group. In a case-control study, Johnson *et al*. (2000) demonstrated statistically significant elevated risks when comparing smokers to never-active never-passive nonsmokers (OR 2.3; 95% CI 1.2-4.5) after accounting for a number of confounders including reproductive health, SES, and alcohol consumption. When childhood exposures were included, risks increased. Significant dose-response trends were observed for both years of smoking and pack-years. Johnson *et al*. (2003) found increased risks in parous women related to number of years of smoking before a first full-term pregnancy.

Considering the epidemiological studies, the biology of the breast and the toxicology of tobacco smoke constituents together, the data provide support for a causal association between active smoking and elevated breast cancer risk.

7.ApA.3. Breast Cancer After Exposure *In Utero*

Sanderson et al. 1996. Data from two population-based case-control studies were combined and examined for associations between perinatal factors and risk of developing invasive breast cancer, including maternal smoking. Age, menopausal status, and maternal smoking were

considered as confounders in the relationship between perinatal factors and breast cancer risk. Among women age 30 years or younger, maternal smoking was associated with an increased risk of breast cancer [OR 1.9 (95% CI 1.0-3.4)] (see Table 7.ApA.8); after adjusting for birth weight (as maternal smoking is associated with low birthweight), a statistically nonsignificant increased risk remained [OR 1.9 (95% CI 0.9-3.8)]. This adjustment for birth weight may represent some degree of over adjustment. In women ages 50-64, a statistically nonsignificant increase in breast cancer was associated with maternal smoking [OR 1.3 (95% CI 0.9-2.1), adjusted for age and menopausal status]. However, data on birthweight were missing for 11% of women ages 21-30 and 25% of women age 50-64. Additionally, no other smoking exposure, whether active or passive, was included in the analysis.

Weiss et al., 1997. A multi-center U.S. case-control study analyzed various prenatal and perinatal risk factors for breast cancer among young women (under age 55), particularly factors with the potential for estrogenic effects, including maternal tobacco smoking during pregnancy. In women diagnosed under age 45 with complete maternal data, no significant association was observed between maternal smoking during pregnancy and breast cancer risk in the daughter [OR 1.06 (95% CI 0.8-1.4)] after adjustment for age, family history, reproductive history, body mass index, alcohol consumption, and mammogram utilization (Table 7.ApA.8). Additionally, although smoking status of the actual cases/controls (daughters) was reportedly included in the questionnaire, no data on the prevalence of smoking exposure (active or passive) was included or adjusted for in this published report.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
		Studies included in Cal/EPA, 1997				
Morabia *et al.* (1996)	Total Study	No current or passive	28/241	-	Referent	A, AF, AL, AM, BMI, E, FH,
Switzerland, 1992-1993		Ever active	31/131	2.2	1.0-4.4	HB, OC, SF
		Studies included in this update				
Millikan *et al.* (1998)	Total Study	Never	248/253	-	Referent	A, AF, AL, AM, FH, HB, P, R
Carolina Breast Cancer Study		Current	93/93	1.0	0.7-1.4	
United States, 1993-1996		Former	157/127	1.3	0.9-1.8	
Case Source = population registry						
Controls = population	Premenopausal cancer	Never	123/110	-	Referent	A, AF, AL, AM, FH, HB, P, R
		Current	46/45	0.9	0.5-1.5	
		Former	72/62	1.0	0.6-1.6	
	Postmenopausal cancer	Never	125/143	-	Referent	A, AF, AL, AM, FH, HB, P, R
		Current	47/48	1.2	0.7-2.0	
		Former	85/65	1.5	1.0-2.4	
Lash and Aschengrau (1999)	Total Study	Never active/passive	40/139	-	Referent	A, AL, BMI, EC, FH, HB, HR,
United States, 1983-1986		Ever active	137/338	2.0	1.1-3.6	P
Case Source = general population						
Controls = population		Active only before 1st pregnancy	7/6	5.6	1.5-21.0	A, BMI, EC, FH, HB, HR, P
		Active only after 1st pregnancy	63/110	2.1	1.1-4.0	
		Active before & after 1st pregnancy	57/175	1.1	0.6-2.0	
Delfino *et al.* (2000)	Total Study	No active/passive	33/96	-	Referent	A, FH, M
United States		Former	40/99	0.94	0.53-1.68	*Risk estimates w/ all controls
Years Diagnosis = DNS		Current	5/24	0.55	0.18-1.67	
Case Source = Clinic/Breast Centers						
Controls = Clinic/Breast Centers						

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Johnson *et al.* (2000)	Premenopausal cancer	No active/passive	14/35	-	Referent	A, AF, AH, AL, AM,
Canada, 1994-1997		Former	182/150	2.6	1.3-5.3	BMI, E, P, PH, RE
Case Source = population registry		Current	116/133	1.9	0.9-3.8	
Controls = population		Ex- or Current	298/282	2.3	1.2-4.5	
		Former - adult only	21/23	1.6	0.6-4.2	BMI, E, P, PH, RE
		Former - child & adult	160/124	2.6	1.3-5.3	
		Current - adult only	10/21	1.0	0.3-2.8	BMI, E, P, PH, RE
		Current - child & adult	106/112	2.1	1.0-4.4	
	Postmenopausal cancer	No active/passive	52/92	-	Referent	A, AF, AH, AL, AM,
		Former	307/324	1.4	0.9-2.1	BMI, E, P, PH, RE
		Current	202/190	1.6	1.0-2.5	
		Ex- or Current	509/514	1.5	1.0-2.3	
		Former - adult only	49/36	1.8	1.0-3.4	BMI, E, P, PH, RE
		Former - child & adult	257/288	1.3	0.8-2.0	
		Current - adult only	28/27	1.6	0.8-3.2	BMI, E, P, PH, RE
		Current - child & adult	174/162	1.8	1.1-2.9	
Morabia *et al.* (2000)	Pre- and postmenopausal combined	Never active/never passive	160/162	-	referent	A, E, FH
Switzerland						
Case source: population		Active		3.3	1.7-6.5	
Controls: general population						
Kropp and Chang-Claude (2002)	Premenopausal cancer	No active/passive	44/144	-	Referent	Al, BF, BMI, ED FH, MS
Germany, 1992-1995		Former	113/299	1.15	0.76-1.74	
Case source = population registry		Current	158/334	1.47	0.99-2.20	
Controls = population						

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Marcus *et al.* (2000)		**Age at start (years)**				
United States, 1993-1996	Current smokers	Never	445/423	1.0	Referent	A
Case source = cancer registry		10-14	34/15	2.1	1.2-3.4	
Controls = population (vehicle reg)		15-19	103/90	1.0	0.7-1.4	
		≥ 20	82/71	1.2	0.8-1.6	
Rookus *et al*. (2000)	Premenopausal	Never active/ passive		1.0	Referent	PH
Netherlands		Current active		1.2	0.8-1.6	
		Former active		1.4	1.0-2.0	
Band *et al.* (2002)	Premenopausal	Smoking initiation (y)				AF, AL, AM, AMP, BF, BMI,
Canada, 1988-1989	Ever Pregnant	< 5 before menarche	104/83	1.69	1.13-2.51	E, FH, HB, HU, MS, M, OC, R
Case source = cancer registry		≥ 5 before menarche	58/70	1.05	0.67-1.65	
Controls = population (voter list)		Before 1st pregnancy	148/131	1.47	1.02-2.10	
		After 1st pregnancy	11/18	0.83	0.37-1.85	
		Before full term preg	113/105	1.37	0.93-2.01	
		After full term preg	7/15	0.67	0.26-1.73	
	Postmenopausal	Ever pregnant	334/343	0.93	0.74-1.17	
		Nulliparous	46/37	1.26	0.66-2.41	
Egan *et al.* (2002)	Full study	Never	1359	1.0	Referent	A, AF, AL, AM, AMP, FH,
United States, 1982-1996		Current active	573	1.04	0.94-1.15	HB, HU, MS, WT
Case & control source: Nurses		Former active	1208	1.09	1.00-1.18	
Health Study						
Terry *et al.* (2002)	Full study	Never		1.00	Referent	A, AL, AM, BMI, E, FH,
Canada, 1980, 1985		Current active		1.14	1.03-1.27	HB, HU, M, P
		Former active		0.99	0.90-1.09	
Lash and Aschengrau (2002)	Full study	Never active/ passive	80/53	1.0	Referent	AF, AL, BMI, FH, HB, HR, P
United States, 1987-1993		Ever active	361/366	0.72	0.55-0.95	
Reynolds *et al*. (2004)	Full study	Never active/ passive	316	1.00	Referent	A, AF, AL, AM, BMI, E, FH,
United States, 1995-2000		Current active	141	1.25	1.02-1.53	HB, HU, M, P, PH, R
California Teachers Study		Former active	690	1.03	0.89-1.18	
		Ever active*	831	1.06	0.92-1.21	

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.5. Active smoking and breast cancer risk: studies of current and former smokers.

Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted*
Gammon *et al*. (2004)	Full study	Never active/ passive	155/170	1.0	Referent	A, BMI, FH, HB, M, P#, WT
United States, 1996-1997		Ever active	127/131	1.06	0.76-1.48	
Case source: population		Ever active + passive	631/625	1.15	0.90-1.48	
Controls: general population		Before+after 1st preg	551/563	1.08	0.82-1.43	
Hanaoka *et al.* (2005)		Never	162	1.0	Referent	A, AL, AM, E, ES, FH, HB,
Japan, 1990-1999	Full study	Current active	14	1.9	1.0-3.6	HU, MS, P
Case source: population	Premenopausal	Ever	11	3.9	1.5-9.9	
Controls: general population	Postmenopausal	Ever	7	1.1	0.5-2.5	
Gram *et al.* (2005)	Full study	Never		1.0	Referent	A, AL, FB, HU, MS, P
Norway/Sweden, 1991-2000		Current active	130	1.17	0.95-1.45	
Case source: population		Ever active	245	1.0	0.98-1.50	
Controls: general population	Premenopausal	Active 20+ years	276	1.21	0.91-1.61	
	Postmenopausal	Active 20+ years	198	1.31	0.92-1.88	

*Reynolds pers. Comm. To M. Miller. Former and current smokers combined with passive smokers excluded from reference group

Factors adjusted for: A=Age, AF=Age first childbirth, AH=Adult height, AL=Alcohol consumption, AM=Age menarche, AMP=age at menopause, BF=breast feeding BMI=Body mass index, E=Education, EC=Earlier breast cancer diagnosis, ES=emplotment status, FH=Family history breast, HB=History benign breast disease, HR=History radiation, M=Menopausal status, MS=marital status, OC=oral contraceptive use P=Parity, PH=Physical Activity, P# = number pregnancies, R=Race, RE=Residence, WT = adult weight.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
		Studies included in Cal/EPA, 1997				
Morabia *et al.* (1996)	Total Study	No current or passive	28/241	-	Referent	A, AF, AL, AM, BMI, E, FH,
Switzerland, 1992-1993		Ever active 1-9 cpd	31/131	2.2	1.0-4.4	HB, OC, SF
		Current 1-9 cpd	10/78	1.5	0.6-3.9	
		Current <20 pack yrs	23/129	2.1	1.0-4.5	
		Studies included in this update				
Millikan *et al.* (1998)	Total Study	**Packs/day**				
Carolina Breast Cancer Study		Never	248/253	--	Referent	A, AF, AL, AM, FH, HB, P, R
United States, 1993-1996		< ½	85/82	1.1	0.8-1.6	
		½ -1	91/71	1.3	0.9-1.9	
Case Source = population registry		> 1	72/66	1.1	0.7-1.7	
Controls = population	Premenopausal	Never	123/110	--	Referent	A, AF, AL, AM, FH, HB, P, R
		< ½	41/42	1.0	0.6-1.7	
		½ -1	46/34	1.2	0.7-2.1	
		> 1	30/30	0.9	0.5-1.7	
	Postmenopausal	Never	125/143	--	Referent	A, AF, AL, AM, FH, HB, P, R
		< ½	44/40	1.3	0.8-2.2	
		½ -1	45/37	1.4	0.8-2.4	
		> 1	42/36	1.4	0.8-2.5	
	Total Study	**Duration (yrs)**				
		Never	248/253	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 10	63/62	1.0	0.7-1.5	
		11-20	57/68	0.8	0.5-1.2	
		> 20	129/89	1.6	1.1-2.3	
	Premenopausal	Never	123/110	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤10	48/45	1.0	0.6-1.7	
		11-20	35/37	0.8	0.6-1.4	
		>20	35/24	1.4	0.8-2.6	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity; PAS = previous active smoking; PH = Physical Activity; R = Race; RE = Residence, RH = reproductive history; WT = adult weight

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Millikan *et al.* (1998) (continued)	Postmenopausal	Never	125/143	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 10	15/17	1.1	0.5-2.4	
		11-20	22/31	0.8	0.4-1.5	
		> 20	94/65	1.7	1.1-2.6	
		Time since cessation (yrs)				
	Former Smokers	Never	248/253	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 3	49/19	2.2	1.2-4.0	
		4-9	41/24	1.7	1.0-3.0	
		10-19	31/44	0.8	0.5-1.4	
		≥ 20	36/40	1.1	0.7-1.9	
	Premenopausal	Never	123/110	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 3	23/11	1.3	0.6-2.9	
		4-9	15/14	0.9	0.4-2.1	
		10-19	20/24	0.9	0.4-1.8	
		≥ 20	14/13	1.3	0.5-3.1	
	Postmenopausal	Never	125/143	--	Referent	A, AF, AL, AM, FH, HB, P, R
		≤ 3	26/8	3.4	1.4-8.1	
		4-9	26/10	3.0	1.3-6.7	
		10-19	11/20	0.6	0.3-1.4	
		≥ 20	22/27	1.1	0.6-2.2	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Lash and Aschengrau (1999)		**Cigarettes/day**				
		Never	40/139	--	Referent	A, BMI, EC, FH, HB, HR, P*
United States, 1983-1986		<20	84/160	2.1	1.0-4.6	*Plus duration smoking
		>20	16/42	1.6	0.6-4.3	
		Duration Years				
Case Source = general population		0-19	34/54	2.6	1.2-5.5	A, BMI, EC, FH, HB, HR, P*
Controls = population		20-39	46/117	1.5	0.7-3.2	*Plus cigarettes per day
		>40	54/147	2.4	1.1-5.5	
		Years since cessation before index year				
		<5 or current	22/75	2.3	0.8-6.8	A, BMI, EC, FH, HB, HR, P*
		5-15	33/54	3.9	1.4-10.0	*Plus cigarettes per day
		>15	82/209	2.2	1.0-4.9	and duration active smoking
		Age Initiated Smoking				
		<17	28/75	2.4	0.8-7.2	A, BMI, EC, FH, HB, HR, P*
		17-20	60/138	2.3	1.0-5.5	*Plus cigarettes per day
		>21	47/106	2.4	1.0-5.7	and duration active smoking
Delfino *et al.* (2000)		**Duration Smoking**				A, FH, M
		Never/No Passive	33/96	1.00	Referent	*Risk estimates w/ all controls
United States		<13 years	14/42	0.94	0.43-2.03	
(time period not specified)		13-26 years	10/42	0.70	0.30-1.62	
Case Source = clinic/breast centers		>26 years	20/38	0.74	0.34-1.61	
Controls = clinic/breast centers		**Cigarettes per Day**				
		None	33/96	1.00	Referent	A, FH, M
		< 8 per day	19/45	1.04	0.50-2.13	*Risk estimates w/ all controls
		8-25 per day	18/46	0.75	0.35-1.58	
		>25 per day	7/31	0.51	0.19-1.35	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Johnson *et al.* (2000)	Premenopausal	**Age initiated smoking**				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
Canada, 1994-1997		> 20 years	38/33	2.1	0.9-4.8	P, PH, RE
Case Source = population registry		16-19 years	138/123	2.4	1.2-4.9	
Controls = population		< 15 years	121/126	2.1	1.0-4.3	
				P trend=0.63		
		Cigarettes per day				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
		< 10 cpd	91/75	2.5	1.2-5.2	P, PH, RE
		10-19 cpd	101/100	2.3	1.1-4.6	
		> 20 cpd	102/104	2	1.0-4.0	
				P trend=0.99		
		Duration Active Smoking				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
		1-11 years	109/91	2.7	1.2-6.1	
		11-20 years	72/90	1.9	0.8-4.5	
		> 21 years	114/98	2.1	0.9-4.7	
				P trend=0.91		
		1-10 pack-years	161/151	2.4	1.2-4.7	
		11-20 pack-years	81/74	2.3	1.1-4.7	
		12-30 pack-years	38/40	1.7	0.8-3.9	
		> 30 pack-years	10/11	1.5	0.4-5.9	
				P trend=0.92		
		Years since Cessation				
		No active/passive	14/35	--	Referent	A, AF, AH, AL, AM, BMI, E,
		> 20 years	42/34	2	0.9-4.6	P ,PH, RE
		11-20 years	76/58	2.9	1.3-6.1	
		< 10 years	64/58	2.5	1.2-5.5	
				P trend=0.08		

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Johnson *et al.* (2000) (continued)	Postmenopausal	**Age initiated smoking**				
		No active/passive	52/92	1.0	Referent	A, AF, AH, AL, AM, BMI, E, P, PH, RE
		> 20 years	167/173	1.4	0.9-2.3	
		16-19 years	230/209	1.5	1.0-2.4	
		< 15 years	110/129	1.2	0.7-1.9	
				P trend = 0.19		
		Cigarettes per day				
		No active/passive	52/92	1.0	Referent	A, AF, AH, AL, AM, BMI, E, P, PH, RE
		< 10 cpd	120/132	1.4	0.8-2.2	
		10-19 cpd	182/183	1.5	0.9-2.3	
		> 20 cpd	203/194	1.4	0.9-2.1	
				P trend = 0.08		
		Duration				
		No active/passive	52/92	--	Referent	A, AF, AH, AL, AM, BMI, E, P, PH, RE
		1-20 years	160/179	1.2	0.8-1.9	
		21-35 years	154/159	1.3	0.8-2.1	
		> 35 years	194/165	1.7	1.1-2.7	
				P trend = 0.003		
		1-10 pack-years	166/176	1.4	0.9-2.1	
		11-20 pack-years	110/139	1.2	0.7-1.9	
		12-30 pack-years	109/84	1.9	1.1-3.1	
		> 30 pack-years	118/99	1.6	1.0-2.6	
				P trend = 0.01		
		Years since Cessation				
		No active/passive	52/92	--	Referent	A, AF, AH, AL, AM, BMI, E, P, PH, RE
		> 20 years	110/138	1.1	0.7-1.8	
		11-20 years	93/105	1.3	0.8-2.1	
		< 10 years	104/81	1.8	1.1-3.0	
				P trend = 0.03		

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Marcus *et al.* (2000)		**Age initiated smoking**				
Carolina Breast Cancer Study	Former smokers	Never	445/423	--	Referent	A, R
United States, 1993-1996		10-14 years	10/12	0.7	0.3-1.8	
		15-19 years	114/106	1.0	0.8-1.4	
Case Source = population registry		≥ 20 years	74/69	1.1	0.8-1.6	
Controls = population	Current smokers	Never	445/423	1.0	Referent	A, R
		10-14 years	34/15	2.1	1.2-3.4	
		15-19 years	103/90	1.0	0.7-1.4	
		≥ 20 years	82/71	1.2	0.8-1.6	
	Smoked < 20 yrs	Never	445/423	--	Referent	A, R
		10-14 years	34/15	2.1	1.2-3.4	
		15-19 years	103/90	1.0	0.7-1.4	
		≥ 20 years	82/71	1.2	0.8-1.6	
	Smoker >20 years	Never	445/423	1.0	Referent	A, R
		10-14 years	11/5	2.0	0.7-6.7	
		15-19 years	67/68	0.9	0.6-1.3	
		≥ 20 years	63/57	1.2	0.8-1.7	
	Smoked < 1 pk/day	Never	445/423	1.0	Referent	A, R
		10-14 years	11/5	2.0	0.7-6.7	
		15-19 years	67/68	0.9	0.6-1.3	
		≥ 20 years	63/57	1.2	0.8-1.7	
	Smoked ≥ 1 pk/day	Never	445/423	1.0	Referent	A, R
		10-14 years	32/22	1.4	0.8-2.4	
		15-19 years	149/128	1.1	0.9-1.5	
		≥ 20 years	92/82	1.2	0.8-1.6	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Egan *et al.*, (2002)		Never active	1,359	1.0	Referent	A, AF, AH, AL, AM, AMP, FH,
United States, 1982-1996		Current	573	1.04	0.94-1.15	HB, HU, M, PAS, WT
		Ex-smokers	1,208	1.09	1.00-1.18	
		Ex- <5 yrs	189	1.17	1.01-1.40	
		No active/passive		1.0	Referent	
		Current	573	1.15	0.98-1.34	
		Ex-smokers	1,208	1.17	1.01-1.34	
	Parous smokers	Started age <16	218	1.31	1.07-1.61	
		Started age >16	1,288	1.12	0.96-1.31	
	Preparous smoking	0 yrs	1,340	1.0	Referent	
		< 5 yrs	563	1.10	0.96-1.26	
		≥ 5 yrs	943	1.13	0.99-1.30	
		< 1 pk/day		1.12	0.95-1.31	
		≥ 1 pk/day		1.21	0.98-1.51	
				P for trend = 0.05		
Band *et al.* (2002)	**Premenopausal**	Never	114/138	--	Referent	AM, AL, E, R, FH, HB, BMI,
	Ever pregnant	Ever	164/153	1.42	1.00-2.00	MS, AMP, RH, MB, OC
Canada, 1988-1989		**Cigarettes per day**			P=0.05	
		< 20	87/86	1.36	0.91-2.05	P= 0.14
Cases : cancer registry		≥ 20	72/66	1.39	0.91-2.14	P= 0.13
Controls: general population		**Years of smoking**				
		< 20	75/84	1.24	0.81-1.89	P= 0.32
		≥ 20	84/69	1.50	0.98-2.28	P= 0.06
		Pack-years				
		< 20	93/101	1.25	0.84-1.86	P= 0.27
		≥ 20	61/51	1.46	0.92-2.32	P= 0.11

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Band *et al.* (2002)		**Smoking initiation from onset of menarche**				
(continued)		< 5 years	104/83	1.69	1.13-2.51	P= 0.01
		≥ 5 years	58/70	1.05	0.67-1.65	P= 0.83
		Smoking initiation in relation to 1st pregnancy				
		before	146/131	1.47	1.02-2.10	P= 0.04
		after	11/18	0.83	0.37-1.85	P= 0.64
	Nulliparous	never	14/28	--	Referent	--
		ever	25/21	2.09	0.78-5.59	P= 0.14
		Cigarettes per day				
		< 20	14/17	1.45	0.49-4.29	P= 0.50
		≥ 20	11/4	7.08	1.63-30.8	P= 0.009
		Years of smoking				
		< 20	13/10	3.55	0.97-13.0	P= 0.06
		≥ 20	12/10	2.27	0.72-7.13	P= 0.16
		Cigarette pack-years				
		< 20	14/16	1.67	0.55-5.04	P= 0.37
		≥ 20	11/4	7.48	1.59-35.2	P= 0.01
Kropp and Chang-Claude (2002)		**Never**	44/144	--	Referent	
Germany, 1992-1995		**Duration (yrs)**				
		1-9	47/153	0.99	0.61-1.60	AL, E, FH, M, BMI, MB
		10-19	91/202	1.40	0.90-2.16	
		≥ 20 years	133/278	1.45	0.96-2.19	P=0.047
		Age (yrs) at initiation of active smoking				
		9-15	46/128	1.02	0.62-1.68	AL, E, FH, M, BMI, MB
		16-18	134/321	1.29	0.86-1.94	
		≥ 19	91/184	1.54	0.99-2.37	P= 0.015

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Lash and Aschengrau (2002)		Never	80/53	--	Referent	
United States, 1987-1995		Ever	361/366	0.72	0.55-0.95	AF, AL, BMI, EC, FH, HB, P
		Duration (yrs)				
		0-20	71/77	0.69	0.48-1.0	AF, AL, BMI, EC, FH, HB, P
		20-< 40	145/139	0.87	0.74-1.0	
		≥ 40	117/117	0.90	0.80-1.0	
	Pregnancy demarcated					
	All before first		21/20	.73	0.42-1.3	AF, AL, BMI, EC, FH, HB, P
	Before and after first		196/205	.69	0.49-0.96	
	All after first		59/70	.66	0.42-1.0	
	Never gave birth		78/65	.82	0.48-1.4	
Terry *et al*., 2002		**Cigarettes/day**				
Unites States.		Never	1,306/498,516	1.0	Referent	A,AL,AM,E,
		1-9	265/102,182	0.97	0.85; 1.11	FH,HB,HU,M,OC,P,
		10-19	317/120,688	0.98	0.86; 1.11	
		20-29	483/166,846	1.10	0.99; 1.23	
		30-39	72/29,414	0.90	0.71; 1.16	
		40+	79/23,194	1.34	1.06; 1.69	
			P for trend	0.05		
		Years smoked				
		Never	1,306/498,516	1.0	Referent	
		1-9	204/84,398	0.93	0.80; 1.09	
		10-19	279/113,276	0.97	0.85; 1.11	
		20-29	426/156,621	1.06	0.94; 1.19	
		30-39	268/79,907	1.14	0.99; 1.31	
		40+	46/8,966	1.61	1.19; 2.19	
			P for trend	0.009		

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Terry *et al.*, 2002 *(continued)*.		**Pack-years**				
		Never	1,306/498,516	1.0	Referent	
		1-9	396/156,089	0.98	0.87; 1.10	
		10-19	251/98,989	0.97	0.85; 1.12	
		20-29	204/76,188	1.08	0.93; 1.25	
		30-39	191/58,288	1.21	1.04; 1.42	
		40+	151/42,986	1.37	1.15; 1.62	
			P for trend	0.003		
Gammon *et al.* (2004)		**Cigarettes/day**				
United States, 1997-1997		Never	155/170	1.0	Referent	A, BMI, HB,MS,P#
		Ever 1-9	210/216	1.10	0.82-1.47	
		10-19	172/160	1.24	0.91-1.70	
		20+	369/373	1.13	0.86-1.48	
		Current 1-9 cpd	49/44	1.38	0.86-2.23	
		10-19	63/59	1.30	0.84-2.00	
		20+	150/141	1.31	0.94-1.82	
		Current Pack-yrs				
		<20	91/88	1.41	0.95-2.08	
		20+	168/151	1.33	0.97-1.83	
Gram *et al.* (2005)	Current smokers	Cigarettes per day				A, AF, AL, BMI, OC
Norway/Sweden, 1991-2000		Never	137	1.0	Referent	
		Current 1-9	135	0.96	0.74-1.25	
		10+	225	1.28	1.01-1.63	
				P trend = 0.03		
		Years smoked				
		1-19	68	0.93	0.68-1.28	
		20-24	96	1.09	0.81-1.45	
		25+	196	1.26	0.98-1.63	
				P trend = 0.05		

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)	Factors Adjusted
Gram *et al.* (2005)		**Pack-years**			
(continued)		0-14	162	0.95 0.74-1.20	
		15-19	90	1.28 0.96-1.72	
		20+	108	1.48 1.14-1.96	
				P trend = 0.001	
		Latency			
		1-19	48	0.75 0.52-1.08	
		20-24	116	1.20 0.91-1.58	
		25+	196	1.27 0.98-1.64	
				P trend = 0.02	
Reynolds *et al.* (2004)	Full study	**Cigarettes per day**			
United States, 1995-2000		Never	1174	1.00 Referent	A,AF, AL, AM, BMI, FH, HU, MS,
		< 10	343	1.04 0.92-1.18	P, PH, menstrual status,
		10-19	260	1.14 0.99-1.30	
		≥ 20	209	1.22 1.05-1.42	
				P trend =0.004	
		Smoking years			
		≤ 10	176	0.99 0.85-1.17	
t		11-20	193	1.17 1.00-1.37	
		21-30	163	1.17 0.99-1.38	
		≥ 30	251	1.15 1.00-1.33	
				P trend =0.009	
		Pack-years			
		≤ 10	338	1.02 0.91-1.16	
		11-20	165	1.24 1.05-1.46	
		21-30	94	1.12 0.91-1.39	
		≥ 30	173	1.25 1.06-1.47	
				P trend =0.002	
		Age smoking start			

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.6. Active smoking and breast cancer risk: studies which included a dose response analysis.

Study	Study Group	Smoking exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted
Reynolds *et al.* (2004)		≥ 20	285	1.03	0.90-1.17	
(continued)		< 20	507	1.17	1.05-1.30	
		Smoking and 1st preg				
		Pre-partum < 5 yr	110	0.99	0.80-1.21	
		Pre-partum ≥ 5 yr	406	1.13	1.00-1.28	
		Post-partum only	42	0.89	0.65-1.21	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure		Genotype				Factors Adjusted
Millikan *et al.* (1998)			NAT1*10		NAT1-non*10		
	PREMENOPAUSAL Former Smokers:						
	Years since cessation:	Never smoker	1.0	Referent	1.0	Referent	A,R
		≤ 3	1.6	0.6-4.5	2.1	0.6-7.2	
		4-9	0.8	0.2-3.0	0.8	0.3-2.2	
		10-19	0.9	0.4-2.3	1.0	0.4-2.7	
		≥ 20	0.6	0.2-1.9	1.7	0.5-6.2	
	POSTMENOPAUSAL Former Smokers:						
	Years since cessation:	Never smoker	1.0	Referent	1.0	Referent	A, R
		≤ 3	9.0	1.9-41.8	2.5	0.9-7.2	
		4-9	7.0	2.0-25.2	1.5	0.5-4.5	
		10-19	0.6	0.2-1.9	0.6	0.2-1.8	
		≥ 20	0.6	0.2-1.5	1.7	0.7-4.3	
			NAT2 fast		NAT2 slow		
	PREMENOPAUSAL	Quit ≤ 3 years	1.5	0.6-4.0	1.9	0.5-7.9	
		Current Smokers	1.1	0.5-2.3	0.8	0.4-1.6	
	POSTMENOPAUSAL	Quit ≤ 3 years	7.4	1.6-32.6	2.8	0.4-8.0	
		Current Smokers	1.4	0.7-2.8	1.1	0.6-2.2	
Morabia *et al.* (2000)			NAT2 slow		NAT2 fast		
	PREMENOPAUSAL	no active/passive	1.0	Referent	1.0	Referent	
		ever passive	3.2	0.9-11.5	3.3	0.7-15.7	A, E, FH
		ever active	2.9	0.8-10.3	3.0	0.7-11.8	
	POSTMENOPAUSAL:	no active/passive	1.0	Referent	1.0	Referent	
		ever passive	1.1	0.3-4.3	11.6	2.2-62.2	A, E, FH
		ever active	2.9	0.8-11.2	8.2	1.4-46.0	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure		Genotype				Factors Adjusted
Delfino *et al.* (2000)			NAT2 slow				
	PREMENOPAUSAL		1.15	0.49-2.77			A, FH, HB, MS
	POSTMENOPAUSAL		1.29	0.74-2.27			
Krajinovic *et al.* (2001)			NAT2	rapid vs slow			
	PRE-, POSTMENOPAUSAL	Never	1.0	Referent			
		Ever	2.6	1.1-6.3			
Chang-Claude *et al.* (2002)			NAT2 fast		NAT2 slow		A, AF, AL, E, FH,
	PRE-, POSTMENOPAUSAL		1.22	0.59-2.54	1.67	0.67-2.89	M, MB,
Zheng *et al*. (2002)	Smoking started <18 years of age		GSTT1 null		GSTT1 positive		A, AF, FH, M, MB
	PRE-, POSTMENOPAUSAL		1.7	0.8-3.7	1.0	0.7-1.6	
	POSTMENOPAUSAL		2.9	1.0-8.8	1.1	0.6-1.9	
	Current smokers						
	PRE-, POSTMENOPAUSAL		1.1	0.4-2.7	1.1	0.6-1.9	
	POSTMENOPAUSAL		2.3	0.6-8.9	1.1	0.6-2.1	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure		Genotype				Factors Adjusted
Saintot *et al*. (2003)			CYP1B1 high/low		SULT1A1 low/high		AF, AM, AMP, BP, FH,
	All		1.72	0.67-4.42	0.54	0.22-1.33	
	PREMENOPAUSAL	≤ 5 cig/day	3.09	0.61-15.60	0.67	0.19-2.31	HB, HU
	POSTMENOPAUSAL		1.37	0.39-4.82	0.40	0.10-1.67	
	All		2.32	1.28-4.21	1.65	0.97-2.80	
	PREMENOPAUSAL	> 5 cig/day	2.00	0.87-4.57	2.11	1.00-4.46	
	POSTMENOPAUSAL		3.56	1.40-9.02	1.50	0.67-3.39	
	All		2.37	1.24-4.51	1.71	0.97-3.03	
	PREMENOPAUSAL	>20YRS DURATION	2.79	1.06-7.33	2.83	1.23-6.54	
	POSTMENOPAUSAL		2.23	0.90-5.52	1.17	0.49-2.76	
	All		2.01	0.97-4.15	1.00	0.53-1.92	
	PREMENOPAUSAL	≤ 10 pack-years	2.03	0.70-5.87	1.44	0.58-3.54	
	POSTMENOPAUSAL		2.05	0.74-5.73	0.70	0.25-1.93	
	All		2.38	1.23-4.63	1.68	0.93-3.04	
	PREMENOPAUSAL	> 10 pack-years	2.22	0.86-5.70	1.89	0.83-4.30	
	POSTMENOPAUSAL		2.81	1.07-7.43	1.59	0.65-3.85	
	All		2.81	1.46-5.41	1.49	0.85-2.60	
	PREMENOPAUSAL	start ≤ 20 years old	3.25	1.28-8.25	1.91	0.91-4.04	
	POSTMENOPAUSAL		2.67	1.00-7.18	1.31	0.50-3.39	
	All		1.45	0.67-3.15	1.07	0.52-2.22	
	PREMENOPAUSAL	start >20 years old	0.89	0.26-3.03	1.14	0.35-3.66	
	POSTMENOPAUSAL		2.25	0.79-6.43	0.98	0.38-2.57	
			COMT high/low				
	PRE-, POSTMENOPAUSAL		1.42	0.65-3.13			

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.7. Active smoking and breast cancer risk: case-control studies with gene modifications

Case-control Study	Smoking Exposure	Genotype				Factors Adjusted
Cohort						
Couch *et al.* (2001)	Ever smoking in relatives of BC patient	High BC risk		Highest BC risk*		AF, AL, AM, BC, BMI
	1st degree relatives (sisters, daughters)	1.8	1.2-2.7	5.8	1.4-23.9	
	2nd degree relatives	1.1	0.8-1.5	1.6	0.8-3.2	
	Marry-ins	1.2	0.9-1.6	1.2	0.8-1.9	

Factors adjusted for: A = Age; AF = Age first childbirth; AH = Adult height; AL = Alcohol consumption; AM = Age menarche; AMP = age at menopause; BMI = Body mass index; E= Education; EC = Earlier breast cancer diagnosis; FH = Family history breast; HB = History benign breast disease; HR = History radiation; HU = hormone use; M = Menopausal status; MB = # months breast feeding; MS = marital status; OC = oral contraceptives; P = parity PAS = previous active smoking; PH = Physical Activity; P# = number pregnancies, R = Race; RE = Residence, RH = reproductive history; WT = adult weight. *Highest risk families as those with ≥5 cases of ovarian or breast cancer or those with ≥2 observed cancers more than expected.

Table 7.ApA.8. In Utero exposure to tobacco smoke and breast cancer.

Case-control Study	Study Group	Smoking Exposure	#Cases/ #Controls	Adjusted OR (95% CI)		Factors Adjusted[a]
Sanderson *et al.* (1996)		Perinatal				
	Women ages 21-45	No	447/580	--	Ref	A, M
United States, 1983-1990		Yes	257/325	1.1	0.9-1.3	
Case Source = population registry		Missing	42/55			
Controls = population	Women ages 50-64	No	336/376	--	Ref	A, M
		Yes	46/40	1.3	0.9-2.1	
		Missing	19/23			
	Women < age 30	No	DNS[2]	--	Ref	DNS[2b]
		Yes	DNS[2]	1.9	1.0-3.4	
		Missing	DNS[2]			
Weiss *et al.* (1997)		Perinatal				
	Women ages 20-44	No	352/331	--	Ref	A, AF, AL, AM, BMI, FH,
United States, 1990-1992		Yes	170/153	1.06	0.8-1.4	MAM, PA, PB
Case Source = population registry		Cigarettes/trimester				
Controls = population		<10	109/84	1.19	0.9-1.7	A, AF, AL, AM, BMI, FH,
		>10	55/58	0.98	0.6-1.5	MAM, PA, PB
		Other[3c]	5/11	0.41	0.1-1.3	

[a] Factors adjusted for: A=Age, AF=Age first childbirth, AL=Alcohol consumption, AM=Age menarche, BMI=Body mass index, FH=Family history breast, M=Menopausal status, MAM=Number mammograms previous, PA=Combination parity & full term births, PB=Previous breast biopsy;
[b] DNS = Data not presented in original publication.
[c] These women did not smoke the same number of cigarettes/trimester.

Appendix 7B:
Lung Cancer Deaths Attributable to Environmental Tobacco Smoke

In order to assess the impact of ETS on population mortality, we estimate the number of lung-cancer deaths attributable to ETS in a single year. The calculation, based on the equations of U.S. EPA (1992c), apportions the overall number of lung-cancer deaths into four categories: (1) deaths in mainstream smokers and former smokers, (2) ETS-attributable deaths in nonsmokers exposed to spousal smoking, (3) ETS-attributable deaths in non-smokers not exposed to spousal smoking, (4) deaths not related to tobacco smoke.

7.ApB.1 Methods

The equations, which require algebraic manipulation to derive, use the assumption that risk is linear in dose, as specified in the NRC model for relative risk in epidemiology studies: $R(d_E) = (1 + Z * ßd_N)/(1 + ßd_N)$ where $R(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS). Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N. ß is the amount of increased risk per unit dose.

Algebraic manipulations then derive risks relative to deaths not related to tobacco smoke from two kinds of relative risks obtained from epidemiological studies:

R1, risks for smokers relative to non-smokers, and
R2, risks for non-smoking spouses of smokers relative to non-smoking spouses who were not so exposed.

Also needed for the calculations are
P1, the proportion of smokers in the population,
P2, the proportion of non-smokers exposed to spousal ETS, and
Z, as defined above.

The equations giving risks relative to other baselines are

$R01 = R1(P2*R02 + (1 – P2)R02/R2)$ where R01 is the risk of ever-smokers relative to never-smokers with no background.

$R02 = (Z – 1)/(Z/R2 – 1)$ where R02 is the passive risk relative to no background.

$R03 = R02/R2$ where R03 is the risk for never-smokers with background ETS only relative to no background ETS.

$R11 = R1(P2\ R2 + 1 – P2)$ where R11 is the risk of ever-smokers with spousal ETS relative to never-smokers with only background ETS.

Z: exposure ratio between spousal exposure plus background and background alone determined by cotinine measurements in nonsmoking with and without spousal ETS exposure (Wells, pers. comm.).

Using the three risks relative to the zero-ETS baseline permits calculation of the proportions of lung cancer deaths into the four smoking categories, each with its indicated numerator:

Table 7.ApB.1 Numerators for Attributable Risk Equations

Category	Numerator
Ever smokers	P1(R01-1)
Never smokers exposed to spousal ETS	(1-P1)P2(R02-1)
Never smoker not exposed to spousal ETS	(1-P1)(1-P2)(R03-1)
Not related to tobacco smoke	1

The denominator for each proportion is the sum of the four numerators. Multiplication of each resulting proportion by the overall lung cancer deaths in the population provides the estimate of lung cancer deaths attributable to that category.

7.ApB.2 Results

Separate estimates are made for males and females reflecting the gender differences in exposure prevalence to active and passive smoking and hence, lung cancer risk. Two adjusted ORs are used from Fontham *et al*. (1994) to provide a range of probable attributable deaths. These include 1.29 (95% CI 1.04; 1.60) for the risk of all lung carcinomas among nonsmoking women with spousal exposure, and 1.74 (95% CI 1.14; 2.65) for lung cancer among nonsmoking women with ≥ 48 adult smoke-years of exposure to spousal ETS.

Table 7.ApB.2 Input Parameters for Lung Cancer Attributable Risk Estimates

Input	Females	Males	Source
R2 low	1.29	1.29	Fontham, 1994
R2 high	1.74	1.74	Fontham, 1994
R1	8.27	13.54	Thun, 2000
P1 former	0.228	0.231	Wells pers com
P1 current	0.187	0.343	Wells pers com
P1 ever	0.42	0.57	Wells pers com
P2	0.56	0.22	Wells pers com
Z	3.14	2.02	Wells pers com
U.S. Pop 2004	78,857,000	70,235,000	Census Bureau
U.S. LC deaths 2003	68,800	88,400	NCI - SEER

The methodology used here is based on that used by the U.S. EPA (1992c), and is applied to the population 35 years old and older to reflect the low incidence of lung cancer before age 35. It applies to males the R2 values determined for females since the data from which to calculate R2 for males are lacking. Values for P1 and P2 were derived by Wells from data provided by Dr. Schoenborn of the National Center for Health Statistics (pers. comm.). The value of Z was estimated by Wells based on several studies. It is lower for males than for females reflecting the smaller proportion of males, versus females, who are never-smokers exposed to spousal smoking. The method also takes into account smokers who have quit smoking for five or more

years, the proportion of which is estimated to be 80%, based on studies by Lash *et al*. (1999) and Johnson *et al*. (2000). This value is used for both genders.

Table 7.ApB.3 National ETS-Attributable Lung Cancer Deaths

	Eversmokers	Spouse ETS	Background ETS	Non-tobacco smoke	Total from ETS
R2=1.29					
Female	53523	2048	512	12717	2560
Male	78780	408	455	8758	863
Both				**Total**	3423
R2 = 1.74					
Female	55522	4294	1074	7909	5368
Male	82330	1271	2227	2572	3498
Both				**Total**	8866

We estimate that for the nation in 2003, the number of ETS-attributable lung cancer deaths associated with spousal smoking and background ETS exposure for both genders combined is in the range of 3423 to 8866. The deaths among males are lower than among females reflecting the lower proportion of non-smoking males with spousal exposure. On the other hand, this analysis does not address ETS exposure at work or in other venues that may be generally higher for males than for females.

The number of ETS-attributable lung cancer deaths in Californian may be crudely estimated by taking California's population as 12% of the national population, and assuming the same rates of exposure to active and spousal smoking. This would result in estimates for females and males, respectively, of 307 and 104 deaths when R2 = 1.29, and 644 and 420 for R2=1.74. The total ETS attributable lung cancer deaths in California would thus be expected to be in the range of 411-1064.

Table ETS-Attributable Lung Cancer Deaths in California in 1999

	R=1.29	R=1.74
Female	307	644
Male	104	420
Both	411	1064

California deaths may be somewhat lower than these estimates because it is expected that the rates of smoking cessation and the number of homes with smoking restrictions may be higher in California than in the rest of the country. However, California-specific estimates of the rate of smoking cessation for five or more years among individuals 35 and older were not available. By presenting a range of estimates based on high and low risk values, it is likely that the true number of deaths is included. In addition, OEHHA calculated a slightly higher summary OR of 7.8 based on more recent studies that included occupational exposure. However, this higher estimate included studies that were not specific to the U.S., while the estimate used here was thought to be more representative of the U.S. population.

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7.6.1. *IARC Monographs on the Evaluation of carcinogenic risks to humans* cited in this chapter

Pages	Compound or topic
IARC (1972). Volume 1. *Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, N-Nitroso Compounds, and Natural Products*. 1972; 184 pages	
40-50	lead, arsenic
74-79	4-aminobiphenyl
95-124	N'-nitrosodimethylamine, N-nitrosodiethylamine
IARC (1973a). Volume 2. *Some Inorganic and Organometallic Compounds* . 1973; 181 pages.	
48-149	arsenic, lead, cadmium, chromium VI, nickel
IARC (1973b). Volume 3. *Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds* . 1973; 271 pages.	
45-48	benz[a]anthracene
69-196	benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, benzo[e]pyrene, chrysene, dibenz[a,h]anthracene
201-237	dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, dibenzo[a,l]pyrene, indeno[1,2,3-cd]pyrene
241-268	benz[c]acridine, dibenz[a,h]acridine, dibenz[a,j]acridine, 7H dibenzo[c,g]carbazole
IARC (1974a). Volume 4. *Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents*. 1974; 286 pages.	
27-39	aniline
87-111	1-naphthylamine, 2-naphthylamine
127-143	hydrazine, 1,1-dimethylhydrazine
173-179	maleic hydrazide
197-210	N-nitrosodi-n-butylamine
IARC (1974b). Volume 5. *Some Organochlorine Pesticides*. 1974; 241 pages.	
83-124	DDT
157-166	endrin
IARC (1974c). Volume 7. *Some Anti-Thyroid and Related Substances, Nitrofurans and Industrial Chemicals*. 1974; 326 pages.	
111-140	urethane
197-221	acetamide, benzene
291-318	vinyl chloride
IARC (1975). Volume 9. *Some Aziridines, N-, S- and O-Mustards and Selenium*. 1975; 268 pages.	
245-260	selenium
IARC (1976a). Volume 10. *Some Naturally Occurring Substances*. 1976; 353 pages.	
99-119	coumarin, cholesterol
IARC (1976b). Volume 11. *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics.* 1976; 306 pages.	
39-112	cadmium, nickel
157-167	ethylene oxide
191-199	propylene oxide
231-240	γ-butyrolactone
IARC (1977). Volume 15. *Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals.* 1977; 354 pages.	
155-175	catechol, hydroquinone, resorcinol
265-271	succinic anhydride

Pages	Compound or topic
IARC (1978a). Volume 16. *Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals.* 1978; 400 pages.	
325-341	N-phenyl-2-naphthylamine
349-366	*ortho*-toluidine
IARC (1978b). Volume 17. *Some N-Nitroso Compounds.* 1978; 365 pages.	
51-189	N-nitrosodi-n-butylamine, N-nitrosodiethanolamine, N-nitrosodiethylamine, N'-nitrosodimethylamine, N-nitrosodi-n-propylamine
221-226	N-Nitroso-N-methylethylamine
281-301	N'-nitrosonornicotine, N-nitrosopiperidine
313-326	N-nitrosopyrrolidine
IARC (1979). Volume 19. *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein.* 1979; 513 pages.	
52	methyl acrylate
73-113	acrylonitrile
157-186	ethylene
213-274	propylene, styrene
377-438	vinyl chloride
479-494	acrolein
IARC (1980). Volume 23. *Some Metals and Metallic Compounds*. 1980; 438 pages.	
39-141	arsenic, lead
205-415	chromium VI, lead
IARC (1982a). Volume 27. *Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking Water and Dental Preparations.* 1982; 341 pages.	
39-80	aniline, *ortho*-anisidine
155-175	*ortho*-toluidine
IARC (1982b). Volume 29. *Some Industrial Chemicals and Dyestuffs.* 1982; 416 pages.	
93-148	benzene
331-397	2-nitropropane, formaldehyde, benzene
IARC (1983a). Volume 30. *Miscellaneous Pesticides.* 1983; 424 pages.	
103-129	malathion
295-318	captan
IARC (1983b). Volume 31. *Some Food Additives, Feed Additives and Naturally Occurring Substances*. 1983; 314 pages.	
95-132	cholesterol
247-263	3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)
IARC (1983c). Volume 32. *Polynuclear Aromatic Compounds, Part 1: Chemical, Environmental and Experimental Data*. 1983; 477 pages.	
95-268	anthracene, benz[a]acridine, benz[c]acridine, benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[ghi]fluoranthene, benzo[a]fluorene, benzo[b]fluorene, benzo[c]fluorene, benzo[ghi]perylene, benzo[c]phenanthrene, benzo[a]pyrene, benzo[e]pyrene, carbazole, chrysene, coronene
277-451	dibenz[a,h]acridine, dibenz[a,j]acridine, dibenz[a,c]anthracene, dibenz[a,h]anthracene, dibenz[a,j]anthracene, 7H dibenzo[c,g]carbazole, dibenzo[a,e]fluoranthene, dibenzo[a,e]pyrene, dibenzo[a,h]pyrene, dibenzo[a,i]pyrene, dibenzo[a,l]pyrene, 1,4-dimethylphenanthrene, fluoranthene, fluorene, indeno[1,2,3-cd]pyrene, 1-methylchrysene, 2-methylchrysene, 3-methylchrysene, 4-methylchrysene, 5-methylchrysene, 6-methylchrysene, 2-methylfluoranthene, 3-methylfluoranthene, 1-methylphenanthrene, perylene, phenanthrene, pyrene , triphenylene

Pages	Compound or topic
IARC (1985a). Volume 36. *Allyl Compounds, Aldehydes, Epoxides and Peroxides.* 1985; 369 pages.	
75-161	eugenol, acetaldehyde, acrolein
189-243	ethylene oxide, propylene oxide
IARC (1985b). Volume 37. *Tobacco Habits Other than Smoking; Betel-Quid and Areca-Nut Chewing; and Some Related Nitrosamines.* 1985; 291 pages.	
209-261	4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosoanabasine, N'-nitrosoanatabine, N'-nitrosonornicotine
IARC (1986a). Volume 38. *Tobacco Smoking.* 1986; 421 pages.	
83-126	Tobacco smoke; chemistry and analysis
194-198	Tobacco smoke; Summary, biological data
309-314	Tobacco smoke carcinogenicity: conclusions and evaluations
387-394	Appendix 2 (compounds in tobaco smoke previously evaluated in the IARC Monograph series).
IARC (1986b). Volume 39. *Some Chemicals Used in Plastics and Elastomers.* 1986; 403 pages.	
99-112	methyl acrylate
155-179	butadiene
IARC (1986c). Volume 40. *Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation.* 1986; 444 pages.	
223-273	2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) , 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2), 2-amino-9H-pyrido[2,3-b] indole (A-α-C), 2-amino-3-methyl-9H-pyrido [2,3-b]indole (MeA-α-C), 2-amino-3-methyl-3H-imidazo(4,5-f)quinoline (IQ)
IARC (1990). Volume 49. *Chromium, Nickel and Welding.* 1990; 677 pages.	
49-445	chromium VI, nickel
IARC (1991a). Volume 51. *Coffee, Tea, Mate, Methylxanthines and Methylglyoxal.* 1991; 513 pages.	
483	chromium VI (correction)
IARC (1991b). Volume 53. *Occupational Exposures in Insecticide Application, and Some Pesticides.* 1991; 612 pages.	
179-249	DDT
IARC (1992). Volume 54. *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals.* 1992; 336 pages.	
237-285	butadiene
IARC (1993a). Volume 56. *Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins.* 1993; 599 pages.	
115-129	caffeic acid
165-195	2-amino-3-methyl-3H-imidazo(4,5-f)quinoline (IQ)
229-242	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)
IARC (1993b). Volume 57. *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines.* 1993; 427 pages.	
323-335	2,6-dimethylaniline
IARC (1994a). Volume 58. *Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry.* 1994; 444 pages.	
119-237	cadmium

Pages	Compound or topic
IARC (1994b). Volume 60. *Some Industrial Chemicals.* 1994; 560 pages.	
45-213	ethylene, ethylene oxide, propylene, propylene oxide
233-319	styrene
389-433	acrylamide
IARC (1995a). Volume 62. *Wood dust and Formaldehyde.* 1995; 405 pages.	
217-362	formaldehyde
IARC (1995b). Volume 63. *Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals.* 1995; 558 pages.	
337-407	acrolein, crotonaldehyde, furan
431-441	benzofuran
IARC (1996a). Volume 65. *Printing Processes and Printing Inks, Carbon Black and Some Nitrocompounds.* 1996; 578 pages.	
381-408	nitrobenzene
549	acrolein (correction), formaldehyde (correction)
IARC (1996b). Volume 66. *Some Pharmaceutical Drugs.* 1996; 514 pages.	
485	formaldehyde (correction)
IARC (1996c). Volume 67. *Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses.* 1996; 424 pages.	
395	nickel (correction)
IARC (1999a). Volume 71. *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide.* 1999; 1589 pages.	
43-225	acrylonitrile, butadiene
319-335	acetaldehyde
367-382	γ-butyrolactone
433-451	catechol
691-719	hydroquinone
991-1013	hydrazine
1079-1094	2-nitropropane
1119-1131	resorcinol
1211-1221	acetamide
1319-1323	carbazole
1425-1436	1,1-dimethylhydrazine
1489-1496	methyl acrylate
IARC (1999b). Volume 73. *Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents, and Some Other Substances.* 1999; 674 pages.	
49-58	*ortho*-anisidine
IARC (2000). Volume 77. *Some Industrial Chemicals.* 2000; 564 pages.	
193-225	coumarin
267-322	*ortho*-toluidine
403-438	N-nitrosodiethanolamine
487-501	nitromethane
IARC (2001). Volume 78. *Some Internally Deposited Radionuclides.* 2001; 596 pages.	
465-477	α-emitting radionuclides
IARC (2002). Volume 82. *Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene.* 2002; 590 pages.	
367-550	naphthalene, styrene

Pages	Compound or topic
IARC (2004a). Volume 83. *Tobacco Smoke and Involuntary Smoking.* 2004; 1452 pages.	
59-94	Tobacco smoke - composition
1180-1188	Active smoking – summary of overall effects
1189-1203	Environmental tobacco smoke - composition
1409-1413	Lung cancer
1271- 1283	Breast cancer
IARC (2004b). Volume 84. *Some Drinking-water Disinfectants and Contaminants, including Arsenic.* 2004; 512 pages.	
39-267	arsenic
IARC (2005). Volume 87. *Inorganic and organic lead compounds (In preparation): see http://www-cie.iarc.fr/htdocs/announcements/vol87.htm for summary*	
	lead
IARC (1982c). Supplement No. 4. *Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs, Volumes 1 to 29).* 1982; 292 pages.	
25-27	acrylonitrile
37-38	4-aminobiphenyl
50-51	arsenic
56	benzene
71-73	cadmium
91-93	chromium VI
105-108	DDT
131-132	formaldehyde
136-138	hydrazine
149-150	lead
164-170	1-naphthylamine, 2-naphthylamine, nickel
213-215	N-phenyl-2-naphthylamine
227-233	benzo[a]pyrene, styrene
245-246	*ortho*-toluidine
260-262	vinyl chloride
IARC (1987a). Supplement No. 6. *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42.* 1987; 729 pages.	
21-23	acrolein
27-31	acrylonitrile
60-63	4-aminobiphenyl
68-76	aniline, arsenic
91-95	benzene
132-135	cadmium
168-175	chromium VI
212-215	DDT
321-324	formaldehyde
341-343	hydrazine
351-354	lead
406-414	1-naphthylamine, 2-naphthylamine
417-420	nickel
461-462	N-phenyl-2-naphthylamine
523-527	*ortho*-toluidine
566-569	vinyl chloride

Pages	Compound or topic
IARC (1987b). Supplement No. 7. *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42.* 1987; 440 pages.	
56-74	(Table of all listings for Volumes 1 - 42)
77-80	acetaldehyde, acrolein, acrylonitrile
91-92	4-aminobiphenyl
99-106	aniline arsenic
120-122	benzene
136	butadiene
139-142	cadmium
161-168	cholesterol, chromium VI
186-189	DDT
205-207	ethylene oxide
211-216	formaldehyde
223-224	hydrazine
230-232	Lead
260-269	1-naphthylamine, 2-naphthylamine, ortho-toluidine, nickel
318-319	N-phenyl-2-naphthylamine
328-329	propylene oxide
345-347	styrene
373-376	vinyl chloride
389-390	acetamide