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Review

The association between exposure to environmental tobacco smoke and breast cancer: A review by the California Environmental Protection Agency

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Abstract

Background. The California Environmental Protection Agency (Cal/EPA) recently completed a health effects assessment of exposure to environmental tobacco smoke (ETS) which resulted in California listing ETS as a Toxic Air Contaminant in January 2006. As part of the assessment, studies on the association between exposure to ETS and breast cancer were reviewed.

Methods. Twenty-six published reports (including 3 meta-analyses) evaluating the association between ETS exposure and breast cancer were reviewed. A weight-of-evidence approach was applied to evaluate the data and draw conclusions about the association between breast cancer and ETS exposure.

Results. The published data indicate an association between ETS and breast cancer in younger primarily premenopausal women. Thirteen of 14 studies (10 case–control and four cohort) that allowed analysis by menopausal status reported elevated risk estimates for breast cancer in premenopausal women, seven of which were statistically significant. Our meta-analyses indicated elevated summary relative risks ranging from OR 1.68 (95% C.I. 1.31, 2.15) for all 14 studies to 2.20 (95% C.I. 1.69, 2.87) for those with the best exposure assessment.

Conclusions. Cal/EPA concluded that regular ETS exposure is causally related to breast cancer diagnosed in younger, primarily premenopausal women and that the association is not likely explained by bias or confounding.

Keywords: Breast Cancer; Passive Smoking; Epidemiology; Toxic Air Contaminants

Contents

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Introduction

In 2005, as part of a regulatory program to identify environmental tobacco smoke (ETS) as a Toxic Air Contaminant in California, the California Environmental Protection Agency (Cal/EPA) Office of Environmental Health Hazard Assessment (OEHHA) completed an evaluation of the literature on the health effects of exposure to environmental tobacco smoke (Cal/EPA, 2005). We concluded that ETS exposure was causally associated with breast cancer in younger, primarily premenopausal women. This paper describes our weight-of-evidence evaluation and the rationale for our conclusion. We present more thorough evaluations of effects of confounding and exposure misclassification in studies of ETS and breast cancer than previously published reviews. Breast cancer is a serious health problem worldwide with over 1.1 million new cases diagnosed annually (Parkin et al., 2005). Since established lifestyle and genetic risk factors for breast cancer either require individual intervention or are impossible to modify (Wallack and Winkleby, 1987; King et al., 2003; Fitzgibbon et al., 2005; Benedet and Cabrero-Roura, 2002), identifying a risk factor readily modifiable by public health interventions, like ETS exposure, has important implications.

Methods

OEHHA applied a weight-of-evidence approach to determine whether there was sufficient evidence of a causal association between ETS exposure and breast cancer. We conducted exhaustive searches of the literature up to early 2005, including electronic searches and formal requests for information. Studies that allowed comparison of breast cancer risk related to ETS exposure in lifelong never smokers to that in never smokers without regular ETS exposure were emphasized. We conducted a meta-analysis of 19 studies of breast cancer in women across all ages, and a separate analysis of 14 of these studies where risk could be derived for younger, primarily premenopausal women (Johnson, 2005; Cal/EPA, 2005).

Weight-of-evidence approach

Under our "weight-of-evidence" approach using causal criteria guidelines (Institute of Medicine, 2004), the results of epidemiological studies, as well as other sources of data (e.g., toxicology studies), are considered in making a scientific judgment. Methodological issues considered in the review of the epidemiologic literature include the extent to which the analysis or design takes into account potential confounders, selection bias, the potential for exposure misclassification, prospective or retrospective assessment of exposure, and study power. The estimation of residential, occupational, and other non-residential ETS exposures during both childhood and adulthood is deemed to enhance study quality. Studies that utilized a referent population restricted to women without periods of regular ETS exposure, included examination of peripubertal adolescent and pre-pregnancy exposures, and reported menopausal status at the time of diagnosis (with adequate sample size) are preferable. Given that all of the criteria above are satisfied, a prospective study is emphasized over an otherwise equally strong retrospective study.

Meta-analysis

Detailed methods for the meta-analysis are provided elsewhere (Cal/EPA, 2005; Johnson, 2005). Briefly, we reviewed studies evaluating breast cancer risk associated with passive smoking among never-smoking women and classified them by the adequacy of their assessment of lifetime exposure to ETS. Minimum criteria for inclusion were that the study: (1) was published in the peer reviewed literature; (2) utilized established epidemiologic design; (3) reported quantitative measures of exposure; and, (4) allowed examination of effect on never smoking women. We summarized these relative risks (RRs) using both fixed and random effects models (DerSimonian and Laird, 1986; Greenland, 1998), and tested for heterogeneity using a χ^2 test. Data management was performed using Stata® software version 8.0 (StataCorp., 2003) and analysis performed using the meta command (Sharp and Stern, 1998), a user-written Stata® software program. Several studies were not included in the meta-analysis because they were published only as abstracts (Rookus et al., 2000; Woo et al., 2000), or did not present separate data for never smokers (Marcus et al., 2000). An additional paper (Liu et al., 2000) presented statistics based on a calculated passive smoking index not amenable to meta-analysis. Large differences between crude and adjusted estimates in this paper also decreased confidence in the results. Excluding this study had no impact on our conclusions since the direction of the relative risks reported agreed with the findings of our meta-analysis.

Results

Many case–control and cohort studies have evaluated exposure to ETS and breast cancer risk (Tables 1, 2), generally controlling for a number of covariates that affect breast cancer risk and diagnosis. The majority of studies presented RR estimates for ETS related to spousal or residential exposure. A few studies assessed risk from exposure at work. Only five contain quantitative long-term information on the three major sources of ETS exposure: childhood, adult residential, and occupational (Smith et al., 1994, Morabia et al., 1996, Zhao et al., 1999, Johnson et al., 2000, Kropp and Chang-Claude, 2002). Breast cancer relative risk estimates range from below null to 2.53 for all ages. Fourteen studies evaluated risk for breast cancer diagnosed in younger primarily premenopausal women, and relative risk estimates for this age group ranged from 0.93 to 7.1.

Meta-analyses

A meta-analysis including 19 studies of women of all ages yielded a summary relative risk estimate of 1.25 (95% CI: 1.08, 1.44) for breast cancer (Table 3). When meta-analysis was limited to the five studies (all case–control) which included all

Table 1
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], United States, 1979–1981	All ages	Spousal	19/76	1.94	0.9, 4.2	A, E, R
	Premenopausal	Spousal	6/27	7.1	1.6, 31.3	
	Postmenopausal	Spousal	13/49	0.9	0.4, 2.2	
	Non-smokers	Spousal	32/177	1.62	0.76, 3.44	
Smith et al. (1994), United Kingdom, 1982–1985	Diagnosis <36 years	No ETS	48/63	–	Ref	A, AF, AL, AM, BF, FH, HB, OC
	Adult only	Partner only	46/37	1.58	0.81, 3.10	
	Adult only	All sources	16/14	3.13	0.73, 13.31	
	Child or adult[b]	Total lifetime	204/199	2.53	1.12, 5.71	
Morabia et al. (1996), Switzerland, 1992–1993	Never active	No ETS	23/241	–	Ref	A, AF, AM, BMI, E, FH, OC
		All sources	98/379	2.3	1.5, 3.7	
	Premenopausal	All sources		3.6	1.6, 8.2	
Millikan et al. (1998), Carolina Breast Cancer Study, United States, 1993–1996	Never active	No ETS	89/88	–	Ref	A, AF, AL, AM, FH, HB, P, R
	Total study	ETS after age 18	158/165	1.3	0.9, 1.9	
	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	
	Postmenopausal	No ETS	37/39	1.0	Ref	A, AF, AL, AM, FH, HB, P, R
		ETS after age 18	87/104	1.2	0.7, 2.2	
Lash and Aschengrau (1999), United States, 1983–1986	Never active	Never passive	40/139	–	Ref	A, AL, BMI, EC, FH, HB, HR, P
		Passive only	80/267	2.0	1.1, 3.7	
	Relative to 1st pregnancy	Only before	6/15	2.8	0.8, 9.9	A, BMI, EC, FH, HB, HR, P
		Only after	35/102	2.4	1.2, 5.1	
		Both before/after	21/63	2.2	1.1, 4.7	
Zhao et al. (1999), China (time not specified)	Premenopausal	Passive only		2.56	1.63, 4.01	Unadjusted
		Overall risk	265/265	2.38	1.66, 3.40	
Delfino et al. (2000), United States (time not specified)	No active	No passive	33/96	–	Ref	A, FH, M
		Passive only	16/44	1.78	0.77, 4.11	[*]Estimates with low–risk controls
	Never smokers, Adult exposure[*]	Low	33/96	1.00	Ref	A, FH, M
		High	31/51	1.50	0.79, 2.87	
	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), Canada, 1994–1997	Premenopausal	No active/passive	14/35	–	Ref	A, AF, AH, AL, AM, BMI, E, P, PH, RE
		Passive only	208/194	2.3	1.2, 4.6	
	Exposure timing	Child only ETS	15/24	1.6	0.6, 4.4	
		Adult ETS only	50/43	2.6	1.1, 6.0	
		Child and 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, PH, RE
		Passive only	334/406	1.2	0.8, 1.8	
	Exposure timing	No active/passive	52/92	–	Ref	A, AF, AH, AL, AM, BMI, E, P, PH, RE
		Child only ETS	15/31	0.9	0.4, 2.0	
		Adult ETS only	83/109	1.1	0.6, 1.8	
		Child and adult ETS	234/266	1.3	0.8, 2.0	
		Overall risk		1.48	1.06, 2.07	
Marcus et al. (2000), United States, 1993–1996, Carolina Breast Cancer Study	ETS prior to age 18	No ETS exposure	257/248	–	Ref	A, R, includes ever active smokers in exposed groups
		Exposure	603/603	1.1	0.9, 1.3	
		No ETS/no active	99/119	–	Ref	
		Exposure	603/542	0.8	0.6, 1.1	
Liu et al. (2000)	Age 24–55 years	Childhood (home)		1.24	1.07, 1.43	M, AM, E, HB, FH, birth weight
		Adult (home)		4.07	2.21, 7.50	
		Adult (work)		1.27	1.04, 1.55	
Rookus et al. (2000), Netherlands, population based	Age 20–54 years	Daily at least 20 years or bedroom at least 1 year		1.2	0.8, 1.7	Lifetime physical activity and "other confounders"
Woo et al. (2000), United States, 1975–1987	Population registry	All ages		1.4	0.83, 1.33	
		Premenopause (<50)		2.78	1.37, 5.63	
		Postmenopause (>49)		0.91	0.71, 1.18	
Kropp and Chang-Claude (2002), Germany 1992–1995	Never active	No passive	44/144	–	Ref	AL, BF, BMI, E, FH, M
	Age <51 years	Any passive	153/310	1.59	1.06, 2.39	
		Former passive	92/191	1.55	1.00, 2.40	

(continued on next page)

Table 1 (*continued*)

Case–control study	Study group	Smoking exposure	#Cases/#Controls	Adjusted OR (95% CI)	Factors adjusted
		Current passive	61/119	1.67 1.04, 2.69	
		Overall risk		1.59 1.06, 2.39	
Lash and Aschengrau (2002), United States, 1987–1995	Passive smokers	Never	80/53	– Ref	AF, AL, BMI, EC, FH, HB, P
		Ever passive	361/366	0.72 0.55, 0.95	
		Overall risk		0.85 0.63, 1.10	
Shrubsole et al. (2004), China 1996–1998, Shanghai Breast Cancer Study		No passive	176/184	– Ref	A, AF, AM, AME, BMI, E, I, M, PH
	All women	Spouse only	231/289	0.9 0.7, 1.2	
		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), United States 1996–1997		Spousal (months)			
	Ever passive	Never exposed	155/170	– Ref	A, BMI at age 20, FH, FP, HB, M, P, W
	Premenopausal	ETS only	163/166	1.21 0.78, 1.90	
	Postmenopausal	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; AL=Alcohol consumption; AM=Age menarche; AME=Age at menopause; BF=Breastfeeding; BMI=Body mass index; DNS=Data not presented; E=Education; EC=Earlier breast cancer diganosis; FH=Family history breast; FP=fertility problem; HB=History benign breast disease; HR=History radiation; M=Menopausal status; OC=Oral contraceptive; P=Parity; PH=Physical activity; R=Race; Re=Residence; W=Weight.

[a] From Wells (1998) 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.

major sources of lifetime passive smoke exposure (combined childhood residential, adult residential and occupational), the summary estimate was 1.91 (95% CI: 1.53, 2.39; p for homogeneity=0.235). The estimated summary relative risk was 1.06 (95% CI: 0.96, 1.17) for those studies with more limited exposure assessment. Among this group, the cohort and case–control studies yielded summary estimates of 1.02 and 1.14, respectively.

Analysis of the 14 studies reporting risk estimates or data for breast cancer in premenopausal women yielded a summary relative risk estimate of 1.68 (95% CI: 1.31, 2.15) using a random effects model (Table 4, Fig. 1). The summary estimate for premenopausal breast cancer for the five studies which adequately assessed major sources of lifetime passive smoke exposure was 2.20 (95% CI: 1.69, 2.87; p for homogeneity=0.35). Combining the studies with more limited exposure assessment yields a summary estimate of 1.33 (95% CI: 1.04, 1.70).

Three published meta-analyses describe pooled risk estimates not stratified by menopausal status. These include: Khuder and Simon (2000), a meta-analysis of eleven studies (OR 1.41; 95% CI: 1.14, 1.75); Morabia et al. (2001), a meta-analysis of six studies (OR 1.7; 95% CI: 1.3, 2.3); and Wells (1998), a meta-analysis of four studies (RR 1.71; 95% CI: 1.30, 2.25).

Discussion

Breast cancer in younger, primarily premenopausal women

The weight of evidence is consistent with a causal association between ETS exposure and breast cancer in younger, primarily premenopausal women. Thirteen of 14 studies that evaluated breast cancer risk in younger, primarily premenopausal women found relative risk estimates above one, seven of which were statistically significant. The summary risk estimates indicate significantly elevated risks; the highest estimates were obtained when summarizing the studies with better ETS exposure assessment. Cohort studies are generally considered a preferable design to case–control studies because they avoid the possibility of recall and response bias. However, the cohort studies that evaluated menopausal status or age under 50 as a surrogate did so at enrollment, not at diagnosis (or death). Thus, when these studies refer to "premenopausal" women, they mean women who were premenopausal or younger than age 50 at enrollment. The case–control studies generally considered age or actual menopausal status at diagnosis.

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 by categorizing some women diagnosed with breast cancer postmenopause as premenopausal. This misclassification of age or menopausal status may be another factor (in addition to limited exposure assessment) contributing to the null association observed in some of the cohort studies.

Breast cancer in older postmenopausal women

There were nine studies from which we could extract breast cancer relative risk estimates for postmenopausal women. In contrast to the findings in younger women, relative risk estimates cluster around a null association. There are, however, elevated relative risk estimates in some studies

Table 2
Passive smoking and breast cancer risk: cohort studies

Cohort study	Passive smoking exposure	#Cases	Adjusted		Factors adjusted
			RR	95% CI	
Hirayama (1984)[a], Japan,	Never active	No ETS	–	Ref	A, AF, AM, BMI, E, FH, HB, OC
1966–1981, Study size=142,857	Spousal all	115	1.32	0.83, 2.09	
Jee et al. (1999),	Spousal smoking status				
Korea Medical Insurance	Non-smoker	DNS	–	Ref	A, RE, SES, SO, SV
Corp., 1992–1997,	Current	DNS	1.3	0.9, 1.8	
Study size=160,130,	Current +30 years	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	–	Ref	A, AF, AL, AM, AME, BMI, DF, DV, E,
Society CPS II,	Current smoker	166	1.0	0.8, 1.2	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	–	Ref	A, AM, AF, AH, AL, AME, CAR,
United States, 1982–1996,	Mother only	36	0.98	0.70, 1.38	FH, HB, HRT, M, P, WT18, WTA
Study size=78,206,	Father only	587	1.12	0.99, 1.27	
Total cases=3140	Both	127	0.92	0.76, 1.13	
	Current work or home				
	None	184	–	Ref	
	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	
Reynolds et al. (2004a),	Household				A, AF, AL, AM, BMI, FH, HRT, PH
California Teachers Study,	*Full study*				
United States 1995–2000,	Never	316	–	Ref	
Study size=116,544,	Childhood only	307	0.92	0.78, 1.07	
Total cases=1150	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	–	Ref	
	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	–	Ref	
	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 smoker+no ETS	40	–	Ref	
Japan, 1990–1999,	ETS	122	1.1	0.8, 1.6	
Study size=21,805,	*Premenopausal at baseline*				
Total cases=180	Never smoker+no ETS	9	–	Ref	
	ETS	68	2.6	1.3, 5.2	
	Postmenopausal at baseline				
	Never smoker+no ETS	31	–	Ref	
	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; DNS=Data not presented; DF=Dietary fat; DV=Dietary vegetable intake; E=Education; FH=Family history breast; HB=History benign breast disease; HRT=Hormone replacement therapy; Hu=Hormone use; 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.

[a] From Wells (1998) letter, Am J Epidemiol 147; 991-2.

for postmenopausal women either overall or in specific strata (i.e., long duration of exposure). The evidence to date for older/postmenopausal women is, therefore, considered inconclusive.

Biological plausibility

There are extensive data showing carcinogenesis in animals by individual chemical components of tobacco smoke,

Table 3
Summary estimates for passive smoking and overall breast cancer risk (at any age) 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		Statistical weight (random effects)
				Lower	Upper	
Hirayama, 1984	cohort	Likely	1.32	0.83	2.09	9.03
Sandler et al., 1985	cc	Likely	1.62	0.76	3.44	4.91
Smith et al., 1994	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 and 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 and Chang-Claude, 2002	cc	Unlikely	1.59	1.06	2.39	10.18
Lash and 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 summary RR[c]	Relative risk	95% confidence interval		Test for heterogeneity
		Lower	Upper	
All studies	1.25 (1.11)[d]	1.08 (1.04)	1.44 (1.19)	$p<0.001$
Important ETS sources collected	1.91 (1.89)	1.53 (1.57)	2.39 (2.27)	$p=0.235$
Important ETS sources missed	1.06 (1.03)	0.96 (0.96)	1.17 (1.11)	$p=0.106$
Cohort studies-important sources missed	1.02 (1.01)	0.92 (0.93)	1.14 (1.10)	$p=0.229$
Case–control studies-important 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 (1986). 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, 1992, 1998) after personal communication with the authors. Combined estimates: Hirayama, 1984, Wells letter (1998). 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.

including some carcinogens that are more abundant in sidestream or ETS than in mainstream smoke. Table 5 lists 20 IARC carcinogens, including some known human carcinogens, identified in tobacco smoke that induce rodent mammary tumors. Although identification of mammary carcinogens in animal models does not guarantee that these chemicals are mammary carcinogens in humans, it helps establish plausibility.

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). Mammary epithelium is capable of metabolic activation of carcinogens (Phillips et al., 2001). Firozi et al. (2002) and Li et al. (1996) found higher levels of DNA adducts in breast tissue of smokers than in non-smokers. Similarly, Faraglia et al. (2003) reported a significant linear trend between smoking status and DNA adducts in normal tissue of current smokers, former smokers and non-smokers ($p=0.04$), and between adducts and both active and passive smoking status (never either, ever passive, ever active only, ever both) ($p=0.03$).

The evidence supporting plausibility of a causal association between exposure to ETS and breast cancer thus includes the presence of carcinogens in ETS, capability of mammary epithelium to activate carcinogens, and demonstration of carcinogen–DNA adduct formation in breast tissue as a result of active smoking or ETS exposures.

The difference in observed relative risk estimates for breast cancer in younger (<50 years) compared to older women may seem at first glance inconsistent with an effect of ETS exposure. Due to the multi-factorial nature of breast cancer, it is difficult to provide a simple explanation for this observation. However,

Table 4
Summary 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		Statistical weight (random effects)
				Lower	Upper	
Hirayama, 1984[b]	Cohort	Likely	1.50	0.50	4.20	2.39
Sandler et al., 1985[c]	cc	Likely	7.10	1.60	31.3	1.43
Smith et al., 1994[d]	cc	Unlikely	2.53	1.12	5.71	3.38
Morabia et al., 1996	cc	Unlikely	3.60	1.60	8.20	3.37
Millikan et al., 1998	cc	Likely	1.50	0.80	2.80	4.44
Delfino et al., 2000	cc	Likely	2.69	0.91	8.00	2.32
Zhao et al., 1999[e]	cc	Unlikely	2.56	1.63	4.01	5.69
Johnson et al., 2000	cc	Unlikely	2.30	1.20	4.60	4.16
Wartenberg et al., 2000[f]	cohort	Likely	1.15	0.82	1.60	6.58
Kropp and Chang-Claude, 2002	cc	Unlikely	1.59	1.06	2.39	6.03
Shrubsole et al., 2004[g]	cc	Likely	1.10	0.83	1.46	6.96
Gammon et al., 2004	cc	Likely	1.21	0.78	1.90	5.73
Hanaoka et al., 2005	cohort	Likely	2.60	1.30	5.20	4.03
Reynolds et al., 2004a	cohort	Likely	0.93	0.71	1.22	7.04

Meta-analysis results summary RR[h]	Relative risk	95% confidence interval		Test for heterogeneity
		Lower	Upper	
All studies	1.68 (1.38)[i]	1.31 (1.21)	2.15 (1.56)	$p<0.001$
Important ETS sources collected	2.20 (2.18)	1.69 (1.70)	2.87 (2.79)	$p=0.354$
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 (1991,1992,1998) 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 (1991,1992, 1998).
[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] Parentheses in summary RRs denote fixed effects model.

there is a relatively higher percentage of poorly differentiated medullary and inflammatory breast carcinomas with relatively more estrogen receptor negativity in younger women (Anderson et al., 2004). Well-differentiated papillary and mucinous tumors with high estrogen receptor positivity are more common in older women (Anderson et al., 2004). Such differences in tumor biology lend credence to the biological plausibility of a difference in risk associated with ETS exposure by age at diagnosis.

Additional support for biological plausibility is provided by positive dose–response observed either overall or in premenopausal women in a number of studies (Morabia et al., 1996; Jee et al., 1999; Johnson et al., 2000; Kropp and Chang-Claude, 2002; Shrubsole et al., 2004; Hanaoka et al., 2005) (Table 6).

Consistency

Study findings are consistent across study design, geographical regions, and menopausal status. All but one of the studies which evaluated younger, primarily premenopausal women separately found elevated risk estimates. In contrast, risk estimates for older women ever regularly exposed to ETS cluster around a null association.

Strength of association

Meta-analyses indicated elevated summary relative risks ranging from OR 1.68 (95% C.I. 1.31, 2.15) for all 14 studies to 2.20 (95% C.I. 1.69, 2.87) for those with complete lifetime exposure assessment. Relative risk estimates from studies with more thorough exposure assessment ranged up to 3.6. These estimates are relatively large compared to other relative risks of common diseases associated with environmental exposures, and are greater than relative risk estimates for lung cancer from ETS exposure (Cal/EPA, 2005).

Confounding

An unknown confounder could bias the results of any observational study, but given the breadth of research that has been done on breast cancer risk, the possibility seems remote. Quantitative evaluation of known potential confounders suggests that they do not account for the positive association between ETS exposure and breast cancer. Studies included in the meta-analysis for younger women considered and adjusted for as necessary most of the known major risk factors for breast cancer (Table 7). In order for bias from confounding to have a major impact on study results, the confounding variable

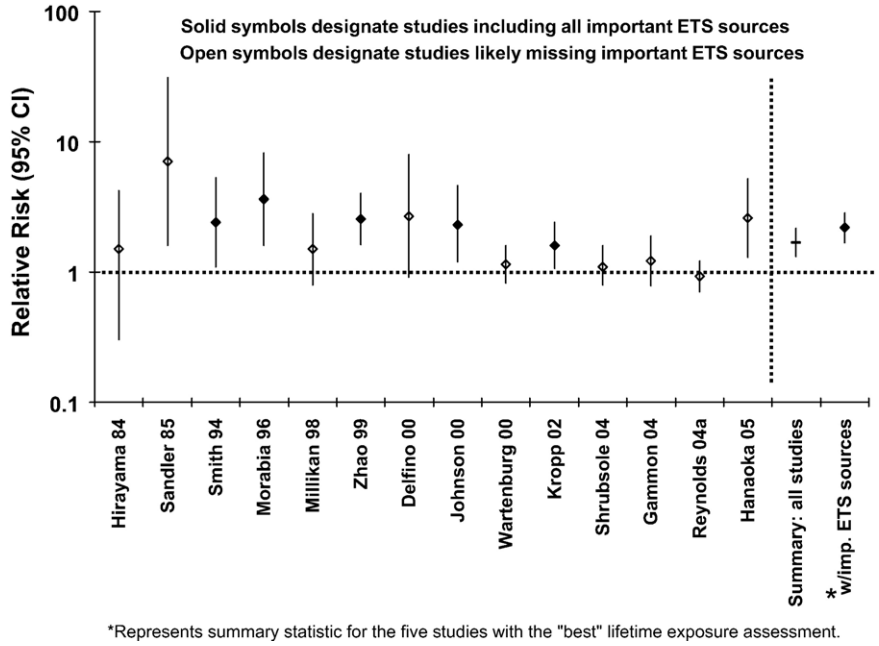

Fig. 1. Summary of relative risk estimates for ETS and breast cancer in premenopausal women.

must be strongly related to both the exposure and the disease (Axelson, 1978). For most known breast cancer risk factors, relative risks are low. In addition, few if any of these factors are strongly correlated with ETS. Thus, they would be expected to have little impact as confounding variables and even less in terms of residual confounding. For example, while increasing alcohol consumption has been correlated with higher likelihood of ETS exposure (Reynolds et al., 2004c) and increasing hours per week of exposure (Friedman et al., 1983), the association between alcohol consumption and breast cancer is relatively weak. The Collaborative Group on Hormonal Factors in Breast Cancer identified an elevated relative risk only in those consuming >15 g/day (RRs approximately 1.2). Only those consuming>45 g/day had significantly higher risk (RR 1.49) but these women represented only 2.4% of cases and 1.3% of controls (Collaborative Group, 2002). A relatively infrequent behavior associated with only a small increase in relative risk could not substantially alter the breast cancer risk estimates. In most studies, controlling for known risk factors has little impact on the breast cancer risk estimates. Since 11 of the 14 studies in the meta-analysis considered alcohol, only residual confounding is a concern and could not account for the observed elevations in breast cancer risk.

We compared adjusted and unadjusted relative risks from 11 studies in our meta-analysis for which this information was provided or could be derived. We found very little difference between crude and adjusted relative risks and adjustment was just as likely to increase as decrease any association (Table 7). A sensitivity analysis involving the removal of studies from our meta-analysis that did not adjust for each particular risk factor (Table 8) resulted in summary estimates that were only slightly different from our overall result.

If the small group of women never regularly exposed to tobacco smoke differs systematically from those exposed to tobacco smoke in ways related to breast cancer risk, it would be possible that those differences might bias the ETS results. In a separate analysis, we used data from the Johnson et al. (2000) study to compare breast cancer risk factors in never-smoking passive smokers ($n=402$) with risk factors in never-smoking subjects who had no regular lifetime ETS exposure ($n=49$). Risk factors evaluated included number of live births, months of breastfeeding, age at menarche, overall level of physical activity, level of alcohol consumption 2 years before diagnosis or interview, BMI two years prior to diagnosis, family income, and years of education. The only substantive difference found was that unexposed women tended to be more physically active than those exposed to secondhand smoke ($p=0.03$). However, this association is relatively weak, and the highest quartile of physical activity only reduces breast cancer risk in most studies by 20–40% (Bernstein et al., 2005). As such, confounding due to physical activity is an unlikely explanation for the relative risks of 1.68 to 2.20 that we obtained for premenopausal women.

Moreover, it is unlikely that bias or confounding would produce an association in younger (mostly premenopausal) but not older (postmenopausal) women within the same studies. Finally, the similarity of the summary relative risks for cohort studies (missing important sources of exposure) and the subset of case–control studies likely missing important sources of exposure, argues against recall bias or confounding as the explanation for the more elevated relative risks observed in those case–control studies with more complete exposure assessment.

Publication bias

A funnel plot analysis did indicate the possibility of publication bias; however, this result was driven by several

Table 5
Mammary carcinogens present in ETS

Compound	Cigarette mainstream smoke (amount per cigarette)[a]	Cigarette sidestream smoke (amount per cigarette)[b]	Cigarette smoke-polluted environments[c]	IARC classification[d]	Mammary gland tumors: affected species[e]
Aromatic hydrocarbons					
Benzene	28–106 μg	71–134 μg	5–22 μg/m^3	1	Mouse
Benzo[a]pyrene	5.6–41.5 ng	52–95 ng	0–3.6 ng/m^3	2A	Rat
Dibenz[a,h]anthracene	4 ng			2A	Mouse[f]
Dibenzo[a,e]pyrene	Present			2B	Rat[g]
Dibenzo[a,h]pyrene	Present			2B	Rat[h]
Dibenzo[a,i]pyrene	1.7–3.2 ng			2B	Rat[h]
Dibenzo[a,l]pyrene	Present			2B	Rat[h]
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	2B	Rat
Nitromethane	0.5–0.6 μg			2B	Rat[h]
Propylene oxide	0–100 ng			2B	Rat[i]
Urethane	20–38 ng			2B	Mouse, hamster
Vinyl chloride	11–15 ng			1	Rat, mouse, hamster
Arylamines and nitroarenes					
4-Aminobiphenyl	2–8 ng	21–32 ng		1	Rats
Nitrobenzene	25 μg			2B	Mice[j]
ortho-Toluidine	30–200 ng			2A	Rats

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

large cohort studies with poor exposure assessment which failed to find an association. The results of the meta-analysis show that several large, unpublished studies with complete lifetime exposure assessment would have to exist in order to significantly alter our findings. The existence of such unpublished studies is very unlikely.

Case–control vs. cohort studies: exposure misclassification and limitations

Overall the case–control studies provide consistent evidence of an association between ETS and breast cancer primarily in younger (<50 years) women, while the cohort studies are inconsistent. There are a number of possible reasons for these seemingly discrepant results.

It is generally agreed that cohort studies are less prone to bias. However, none of the cohort studies included full information on all three aspects of lifetime exposure. Studies with more complete lifetime exposure ascertainment, which limits ETS-exposed women in the "non-exposed" referent group, consistently demonstrate higher breast cancer risks in both active and passive smoking studies (Johnson, 2005; Cal/EPA, 2005). Utilizing a limited evaluation of exposure, such as only considering spousal smoking, leads to exposure misclassification. Since follow-up exposure ascertainment is seldom conducted in cohort studies, changes in passive and active smoking status cannot be incorporated into the assessment. Such studies underestimate risk of lung cancer (Johnson et al., 2001b) and cardiovascular disease (Whincup et al., 2004). In their prospective study, Whincup et al. (2004) showed that cotinine levels at baseline were more strongly associated with the risk of coronary heart disease in the earlier than later years of follow-up, as the exposure measure was further removed in time and exposure misclassification increased. Thus for many of the prospective studies, limited exposure assessment contaminates the referent group with individuals exposed to ETS and biases the relative risk estimates downwards.

Table 6
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 days per month (d/mo)	Almost none 1.0 1–3 d/mo 0.6 (0.4, 2.4) >1 day/week 2.2 (1.4, 3.7) *p* trend 0.002
Shrubsole et al., 2004	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 and 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 years smoking 1.7 (1.0, 2.8)
Morabia et al., 1996	Ever passive exposure	1–50 h/day-years 2.2 (1.3, 3.7) >50 h/day-years 2.5 (1.5, 4.2)

In general, the large American cohort studies provide little evidence of an association between ETS and breast cancer. There are important limitations to these three cohort studies, however. Wartenberg et al. (2000) evaluates death from breast cancer rather than breast cancer incidence. Breast cancer mortality is a less direct measure of outcome (i.e., a poor proxy for incidence), and introduces the possibility that factors that impact a woman's probability of dying from breast cancer, once diagnosed, could bias the observed risks for developing breast cancer. The limited exposure ascertainment would have reduced this study's ability to identify an association between breast cancer and passive smoking (Johnson, 2001a; Wells, 2001). The large, prospective study by Egan et al. (2002) did not exclude all women with regular passive smoking exposure (childhood or adult) from the referent exposure category, and only asked about current workplace exposure at one timepoint (1982); this may have significantly inhibited the ability to observe an association (Johnson and Wells, 2002). While Reynolds et al. (2004a,b) has the advantages of being large, prospective, and designed specifically to examine breast cancer, the published analysis only examined residential ETS exposure; the authors note that occupational sources were the primary source of exposure within this cohort since the early 1980s.

Three non-U.S. cohorts present elevated relative risk estimates for breast cancer in association with spousal smoking (Hirayama, 1984; Jee et al., 1999; Hanaoka et al., 2005). Hanaoka et al. (2005) identified a significant association for premenopausal women combining residential and occupational ETS exposure. It is noteworthy that the exposure assessment in this study was more complete than any of the other cohort

Table 7
Confounders considered in studies included in meta-analysis of premenopausal breast cancer

Study	BMI	Family history	Hormone use	Alcohol	SES (any measures)	Physical activity	History benign breast disease	Age at menarche	Reproductive measures[a]	Breast-feeding
Hanaoka, 2005	X	X	X	X	X	X	X	X	X	
Kropp, 2002	X	X	X	X	X			X	X	X
Johnson, 2000	X	X	X	X	X	X	X	X	X	X
Zhou, 1999		X	X	X	X		X	X	X	X
Morabia, 1996	X	X	X	X	X		X	X	X	
Smith, 1994		X	X	X			X	X	X	X
Shrubsole, 2004	X	X	X	X	X	X	X	X	X	
Reynolds, 2004a	X	X	X	X	X	X	X	X	X	
Gammon, 2004	X	X	X	X	X	X	X	X	X	X
Wartenberg, 2000	X	X	X	X	X		X	X	X	
Delfino, 2000	X	X			X		X	X	X	X
Millikan, 1998	X	X		X			X	X	X	X
Sandler, 1985					X					
Hirayama, 1984										

[a] Either age at first birth or parity.

Table 8
Comparison of unadjusted (crude) and adjusted relative risks in studies of breast cancer and ETS

Study	Crude RR (95% CI)	Adjusted RR	Difference	*p*-value (for the difference in RRs)[a]
Morabia	2.23 (1.43–3.46)	3.2 (1.7–5.9)	−0.97	0.35
Kropp	1.62 (1.10–2.38)	1.59 (1.06–2.39)	0.03	0.95
Johnson (child only)	1.56 (0.64–3.81)	1.6 (0.6–4.4)	−0.04	0.97
Johnson (adult only)	2.91 (1.40–6.03)	2.6 (1.2–5.5)	0.31	0.83
Hanaoka[b]	2.9 (1.4–5.8)	2.6 (1.3–5.2)	0.3	0.83
Smith (1–200 cig-years)[b]	2.74 (1.14–6.61)	2.82 (1.0–6.68)	−0.08	0.97
Smith (>200 cig-years)[b]	2.09 (0.86–5.12)	2.24 (0.75–6.68)	−0.15	0.92
Wartenberg (current)[b]	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.00	N/A
Wartenberg (former)[b]	1.0 (0.8–1.2)	1.0 (0.8–1.2)	0.00	N/A
Gammon	1.33 (0.86–2.05)	1.21 (0.78–1.90)	0.12	0.77
Millikan	1.10 (0.65–1.84)	1.5 (0.8–2.8)	−0.40	0.46
Shrubsole	1.02 (0.75–1.39)	1.0 (0.6–1.8)	0.02	0.95
Zhou	2.56 (1.64–4.00)	2.56 (1.63–4.01)	0.00	N/A

[a] Method used to compare relative risks from Altman, DG, Bland, MJ. Interaction revised: the difference between two estimates, BMJ, Vol. 326, p. 219.
[b] Crude RRs are adjusted only for age (Smith and Wartenberg), and age and region (Hanaoka).

studies, and the referent group contained no smokers or passively exposed women. Overall, while seven cohort studies (six incidence and one mortality) provided inconsistent evidence of an association between ETS exposure and breast cancer risk (Hirayama, 1984; 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 in many, thus decreasing the ability to find evidence of an effect.

Controversies regarding relative potency of active and passive smoking

The inconsistent results of studies examining active smoking and breast cancer argue against any determination of an association between passive smoking and breast cancer. The Surgeon-General's report (U.S. DHHS, 2004) on active smoking and the 2004 IARC report on tobacco smoke concluded that there is little or no evidence of an effect of active smoking on breast cancer risk and, therefore, did not consider the effects of ETS in any detail.

Despite inconsistency in study results, there is evidence of a role for active smoking in causation of breast cancer at least for some metrics of exposure (Couch et al., 2001; Manjer et al., 2001; Morabia et al., 1998; Egan et al., 2002; Terry et al., 2002; Reynolds et al., 2004a, Hanaoka et al., 2005; Zhang et al., 2004; Gram et al., 2005) and particularly for longer duration and higher exposure in premenopausal women (Terry et al., 2002). Nearly all studies that utilize a non-active/non-passive smoking referent population and which quantified the estimate of ETS exposure from the key sources find significant associations with breast cancer in at least some age or susceptibility groupings for both active and passive smoking (Johnson, 2005).

The similar magnitude of the observed active and passive smoking risks makes it more difficult to establish a passive smoking risk. It is generally thought that the risk from active smoking should be higher than from passive smoking because it appears to involve much higher exposure to tobacco smoke. Several hypotheses suggested as explanations for the apparently flat dose–response for breast cancer between active and passive smoking have been examined in various papers (Lash and Aschengrau, 1999, 2002; Morabia, 2002; Russo and Russo, 1994; Terry and Rohan, 2002; Band et al., 2002), but to date these remain speculative.

Anti-estrogenicity of active smoking

The anti-estrogenic activity of current active smoking may obscure any overall association between active smoking and breast cancer. The Surgeon General's report (U.S. DHHS, 2004) on active smoking and others (Baron et al., 1990; Jensen and Christiansen, 1988; Terry and Rohan, 2002) note the potential competing effects between carcinogenicity and anti-estrogenicity of active smoking on breast tissue. Band et al. (2002) demonstrated elevated relative risk among women initiating smoking at young ages and before first childbirth, and a substantial reduction in relative risk in heavier postmenopausal women who smoked. This is consistent with protection from anti-estrogenic activity of active smoking in those women with higher postmenopausal estrogen secondary to aromatization of adrenal androgens by adipose tissue.

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 (before full maturation of breast tissue). In a rodent model of mammary carcinogenesis, Russo and Russo (1994) demonstrated that early stage mammary epithelial cells present primarily prior to puberty are more readily transformed *in vivo* by chemical carcinogens than those present after puberty, which in turn are more sensitive to transformation than those present following pregnancy and lactation. Studies of girls treated for Hodgkins lymphoma (Bhatia et al., 1996; Aisenberg et al., 1997), girls evaluated for scoliosis (Doody et al., 2000), and studies of Japanese bomb survivors (NRC, 1990; Tokunaga et al., 1994) clearly indicate that peripubertal radiation exposure greatly increases the

relative risk of early-onset breast cancer. In addition, epidemiological studies show that early age at first pregnancy as well as multiple pregnancies protects against breast cancer. Thus, epidemiological data also support the concept of windows of susceptibility for the response of breast tissue to carcinogens. Studies that do not evaluate exposure during these windows may misclassify the biologically relevant exposure and thus fail to detect a real association. A consistent pattern of windows of susceptibility regarding tobacco smoke has not been demonstrated to date.

Public health implications

In this review, we have identified exposure to ETS as a modifiable risk factor for breast cancer in younger/premenopausal women. Toxicology and epidemiology studies have identified the period from peripuberty to first term pregnancy as a time of potential increased sensitivity to mammary carcinogens. Public education efforts should be directed at reducing the exposure to tobacco smoke among adolescent girls and young adult women (a period of potential high exposure from parents, peers, and occupationally e.g., in non-smoke-free restaurants and bars).

Since ETS exposure is a risk factor for breast cancer, future studies of breast cancer should include full lifetime historical data on ETS exposure. Additional prospective studies of both active and passive smoking that clearly quantify full lifetime exposures and examine high-risk subpopulations and windows of susceptibility will contribute to a better understanding of the magnitude of risk for breast cancer. Studies that examine biologic mechanisms that would explain the similarity of risks seen in active and passive smoking are warranted.

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