

Environmental Tobacco/ Second Hand Smoke

Introduction

It is widely acknowledged that tobacco smoke is a known human carcinogen.¹ Approximately 60 percent of nonsmokers in the U.S. show biological evidence of exposure.² In California, where smoking rates are below the national average (14.8 percent currently smoke versus 20.9 percent nationwide)^{3,4} and strict antismoking legislation is in place, environmental tobacco smoke (ETS) exposures are likely to be less pervasive, yet remain significant.³ There is consistent evidence that ETS exposure, also referred to as second hand smoke (SHS), is an established risk factor for lung cancer.¹⁻³ Over the course of the last 30 years, nearly 100 studies of tobacco exposures and breast cancer have been published, with recent studies re-conceptualizing causal models in ways that promise to clarify the role of tobacco smoke exposures in the etiology of breast cancer.^{5,6}

In keeping with the CBCRP's emphasis on environmental, rather than lifestyle, factors for the purposes of this report, the focus of this chapter is the role of ETS exposure in breast cancer etiology. However, because much of the research and discussion of ETS exposure has been interwoven with that of the potential effects of active smoking, we include some discussion of the active smoking literature where we feel it helps clarify the role of ETS exposure.

Concept/Exposure Definition

Following the abundance of research documenting the adverse health effects of active smoking, researchers began to investigate the health consequences of exposure to ETS among

nonsmokers. ETS is comprised of a mixture of exhaled mainstream smoke and sidestream smoke released from the smoldering end of a cigarette or other smoking device. Other terms used to describe this exposure include passive smoking, second hand smoke, and involuntary smoking. As there currently is considerable debate over the most appropriate term, for the purpose of this report we will use the combined term environmental tobacco smoke/second hand smoke (ETS/SHS) throughout.

ETS/SHS is composed of both vapor and particles. Its composition changes during its dilution and distribution in the environment over time. The concentrations of ETS/SHS components in a physical space depend on the number of smokers, the rate at which they smoke, the type of smoking device used (e.g. filter versus non-filtered cigarettes, cigars, pipes, etc.), and the volume and ventilation characteristics of the space in which smoking is occurring.^{1,2} ETS/SHS is a complex mixture comprised of thousands of different compounds. The volatile phase contains 400–500 compounds, while more than 3,500 different compounds have been identified in the particulate phase. At least 50 known or suspected carcinogens have been identified in ETS/SHS, including the widely-studied known carcinogens polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines.^{2,3,7} Furthermore, at least twenty constituents of tobacco smoke (listed in Table 1 below) have been identified as mammary carcinogens.³ These carcinogens are not exclusive to tobacco smoke. Women can be exposed through many other sources, including occupational exposures, diet, and pesticides.⁷

Table 1. Mammary Carcinogens Identified in Tobacco Smoke

Benzene	N-nitrosodiethylamine	Acrylamide
Benzo[a]pyrene	N-nitrosodi-n-butyl-amine	Acrylonitrile
Dibenz[a,h]anthracene	4-Aminobiphenyl	1,3-Butadiene
Dibenzo[a,e]pyrene	Nitrobenzene	Isoprene
Dibenzo[a,h]pyrene	Ortho-Toluidine	Nitromethane
Dibenzo[a,l]pyrene	Propylene oxide	Vinyl chloride
Dibenzo[a,l]pyrene	Urethane	

Source: California Air Resources Board (ARB).³

Because the smoldering end of a cigarette burns at lower temperatures, leading to incomplete combustion of organic materials, the concentrations of many carcinogens can be considerably higher in sidestream, compared to mainstream, smoke.^{2, 7, 8} While the actual exposure to carcinogenic compounds is much higher in active smokers, ETS/SHS exposures can amount to the exposure equivalent of actively smoking several cigarettes a day.⁷

Assessing exposure to ETS/SHS in epidemiologic investigations of breast cancer has been challenging. Problems include the lack of adequate long-term biomarkers or physical measurements, as well as difficulties in assessing ETS/SHS exposure via epidemiological instruments. Cotinine, the primary metabolite, or breakdown product, of nicotine, is presently the biomarker of choice for assessing ETS/SHS exposures. It is easily measured in a number of biologic media (e.g., blood, urine, saliva), is highly specific to tobacco smoke exposures, and has proved useful in distinguishing active from passive smokers.² Its usefulness in breast cancer research, however, is limited in that measurements can only capture recent exposures. Furthermore, it

only represents one component of a complex mixture and may not reflect exposures to other compounds of concern. Finally, cotinine levels are not simply a function of exposure but also reflect individual variations in metabolism and excretion rates. Thus, no good biomarker of chronic long-term exposure to ETS/SHS currently exists. Air monitoring and personal sampling are other approaches utilized to assess SHS exposures. Again, these are of limited usefulness in breast cancer research because they cannot be used to measure prior/long-term exposures.

Consequently, the majority of epidemiologic studies of tobacco exposure and breast cancer rely on questionnaires to estimate exposure. The quality of the data captured by epidemiological questionnaires is a function of reliability and validity. A questionnaire is considered reliable if the same person gives the same response when asked multiple times. Further, an instrument is valid if it actually measures what it is intended to measure. Reliability and validity studies of ETS/SHS questionnaires have shown that they are reasonably good at capturing current or recent exposures, demonstrating good agreement with cotinine levels.² However, evaluating the validity

of questionnaires to capture lifetime or early exposures is problematic, as there is no biological measure against which to compare. Evidence on the reliability of questionnaire answers is mixed. While people give consistent responses about the presence of spousal smoking, which is a key measure of adult exposure, the reliability of quantitative information about these exposures (i.e., how many cigarettes a spouse smokes in the woman's presence) may be less than optimal.²

Early studies of ETS/SHS exposure and breast cancer often relied on 'living with a smoking spouse' as the index of exposure. Thus, these studies were typically limited to evaluating adult household exposures. Prior to 1970, this may have been adequate at capturing the predominant source of ETS/SHS exposures for women during adulthood.⁹ However, as more women entered the workforce in the latter part of the last century, this measure missed the substantial contribution of workplace exposures. Prior to the enactment of restrictive legislation, California workplaces likely were the source of some fairly significant ETS/SHS exposures.¹⁰ More recent studies have attempted to assess ETS/SHS exposures across settings (household, workplace, social) and over time. This body of literature, however, is still relatively small (see Critical Review of the Literature subsection below). The vast differences in ETS/SHS exposure assessment are likely to have greatly contributed to the observed inconsistencies in findings of studies aimed at investigating ETS/SHS exposure in breast cancer etiology.

Biologic Plausibility

From a toxicological perspective, the relationship between tobacco smoke and breast cancer risk is likely to be complex, as there is evidence that

tobacco smoke may both be genotoxic and anti-estrogenic. As described above, tobacco smoke contains a multitude of known or suspected carcinogens, several of which are mammary carcinogens.^{2,3,7} Many of these carcinogens are lipophilic and accumulate in adipose tissue throughout the body, including the adipose-rich tissue of the breast.^{6,7} Metabolites of cigarette smoke have been found in the breast fluid of non-lactating smokers.^{11,12} The presence of smoking-specific DNA-adducts and p53 gene mutations in breast tissue are reportedly more prevalent in smokers compared to non-smokers.¹³⁻¹⁹ Thus, there is evidence that tobacco carcinogens not only reach the breast tissue, but also are able to induce biological effects that are common in breast carcinogenesis.

At the same time, breast cancer is an estrogen-mediated disease and there is considerable evidence that tobacco smoke has anti-estrogenic properties. Smoking has been linked to early menopausal age with fewer total years of menstruation, higher incidence of osteoporosis, and lower breast density,^{6,20-24} all of which would suggest a protective effect for breast cancer. Whether these effects appear in nonsmokers exposed to ETS/SHS has not generally been explored, although two recent studies have reported results to the contrary, with earlier age at menarche found among girls exposed to ETS/SHS.^{9,25}

Thus, tobacco exposures may work to both increase breast cancer risk through its genotoxic properties and decrease risk through its anti-estrogenic properties. How these mechanisms ultimately affect breast cancer risk may in part be determined by both the timing of exposure and the genetic susceptibility of an individual.

Genetic susceptibility to the genotoxic effects of tobacco smoke is reflected in an individual's inherited capacities in carcinogen metabolism and detoxification, DNA repair, and various cell-cycle-related and apoptotic pathways. Thus, smoking women with a genetically-determined high capacity (i.e., CYP1A1 variant genotype) to metabolize nongenotoxic pro-carcinogens to genotoxic ultimate carcinogens might be at greater risk of breast cancer than women who smoke, but are less effective in these metabolic processes. On the other hand, women exposed to tobacco who carry genotypes associated with higher detoxification of genotoxic carcinogens (i.e., NAT2 rapid acetylator genotype), might be at lower risk of breast cancer than are women with similar exposures and lower capacity to detoxify carcinogens. These same principles apply for genes relevant in DNA repair, cell cycle control, and apoptotic processes.

The idea that timing of exposure is critical in influencing risk is predicated on the fact that the rate of breast tissue proliferation and levels of cellular differentiation vary over the course of a woman's life and are tied to reproductive events.^{26,}²⁷ During times of rapid proliferation, breast tissue is likely to be more susceptible to the harmful effects of carcinogens. Highest rates of proliferation occur during childhood and decrease markedly after puberty, pregnancy, and lactation, as well as gradually with aging. Cellular differentiation of the breast tissue also occurs episodically with puberty, pregnancy, and lactation, reaching its fully differentiated state only after lactation occurs.²⁸ Less-differentiated tissue is likely to be more susceptible to carcinogenic insults. Thus, it has been suggested that the genotoxic effects of tobacco smoke may

be most evident when experienced early in life, especially before a woman's first pregnancy. Conversely, the anti-estrogenic effects of tobacco smoke may prevail when exposures are experienced later in life.^{26, 29}

Critical Review of the Literature

Over the past three decades, a large body of epidemiologic studies has evaluated the role of tobacco exposures (both active and passive smoking) and breast cancer risk. In the last five years, a number of U.S and international agencies have reviewed the research on tobacco exposures and breast cancer. While there is some dispute on this issue, as evidenced by the recent concurrent assessments by the U.S. Surgeon General and the California EPA, at least one report maintains that the weight of the more recent evidence supports an association in younger women, with remaining uncertainty about the effect on post-menopausal women. It is important to consider this current evidence in the context of the succession of expert reviews over the last few years, as summarized in Table 2.

One of the problems in evaluating the evidence for ETS/SHS exposure and breast cancer has been reconciling the findings for active and passive smoking. Early studies of tobacco exposures and breast cancer have yielded inconsistent findings, with some studies demonstrating risk reductions, but most studies showing null results or very small risk elevations.^{5, 33} The vast majority of these early studies on active smoking, however, did not account for ETS/SHS exposures in their analyses.^{6, 34-37} Given the pervasiveness of ETS/SHS exposures, it is likely that the 'unexposed' referent group used in these studies included substantial numbers of individuals exposed to ETS/SHS. If tobacco exposures are in fact causally related to

breast cancer risk, the inclusion of passive smokers in the referent category would serve to dilute the risk estimates for active smoking towards the null. This argument has been cited as a possible explanation for the apparent association of breast cancer with passive, but not active, smoking in the few of these early studies that measured ETS/SHS exposure.^{6, 37}

Consequently, many of the next generation of

studies on active smoking, especially those published within the last few years, carefully measured ETS/SHS exposures.^{9, 26, 38-47} The most recent large-scale reviews of active smoking and breast cancer conducted by IARC and the U.S. Surgeon General, both of which concluded there was no evidence of an association, were published before most of these results became available and therefore were not included in their assessments. Of the 11 recent geographically and

Table 2. Summary of conclusions from recent reviews by international, national, and state agencies on the relationship between smoking and breast cancer

Agency, Year Published	Type of Smoking Evaluated	Latest year of studies included	Conclusions
Surgeon General 2001 ³⁰	Active and Passive	2000	<p>“The totality of the evidence does not support an association between smoking and the risk for breast cancer”</p> <p>“...several issues were not entirely resolved, including whether starting to smoke at an early age increases risk, whether certain subgroups defined by genetic polymorphisms are differentially affected by smoking, and whether ETS exposure affects risk”</p>
IARC 2004 ¹	Active and Passive	2001	<p>“There is evidence suggesting a lack of carcinogenicity of tobacco smoking in humans for cancers of the female breast”</p>
Surgeon General 2004 ³¹	Active and Passive	2001	<p>“The evidence is suggestive of no causal relationship between active smoking and breast cancer.”</p> <p>“in light of the evidence showing no overall association between active smoking and breast cancer, passive smoking would also be expected not to be associated with breast cancer risks, assuming that the same mechanisms apply to both active and passive smoking”</p>
Surgeon General 2006 ²	Passive	2005	<p>“The evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer.”</p>
CAL EPA 2006 ^{3, 32}	Passive	2005	<p>“Overall, the weight of evidence...is consistent with a causal association between ETS exposure and breast cancer in younger, primarily pre-menopausal 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.”</p>

methodologically diverse studies that excluded women with ETS/SHS exposures from the referent group, all but two^{39, 45} reported an increased breast cancer risk associated with active smoking.^{9, 26, 38, 40-44, 48}

These more recent studies of active smoking and breast cancer have also begun to test some of the hypotheses suggested by the postulated competing anti-estrogenic and genotoxic effects of tobacco smoke. A number of these studies have suggested that an early age at smoking initiation imparts an increased risk, while a later age does not^{9, 38, 40, 41, 43, 46, 49, 50} which is consistent with the idea of adolescence being a particularly vulnerable period of the breast to the genotoxic effects of tobacco smoke. These results, however are not in agreement with many earlier studies⁵¹⁻⁵⁸ as well as some of the later studies.^{6, 59} The use of different cut-points for age at initiation, the increasing proportion of smokers initiating smoking during adolescence among more recent birth cohorts,⁶⁰ different referent groups (with most of the more recent positive studies removing ETS/SHS exposures), and the mix of pre- and post-menopausal populations across studies might explain such heterogeneity in results.

Overall, however, there is emerging evidence that the effects of smoking on breast cancer risk may be limited to women who began smoking at an early age. Because early smoking initiation is so highly correlated with duration of smoking (for which there also is substantial evidence of an effect), it is difficult to determine whether this is truly an age effect or simply a duration effect. Furthermore, some studies have suggested that the risks associated with early smoking may vary by menopausal status,^{29, 42, 44, 61} endogenous estrogen levels,⁴⁹ tumor hormone responsiveness,^{38, 39} and

certain genetic polymorphisms.^{47, 48}

There also is mounting evidence that active smoking prior to a first pregnancy may increase a woman's risk of breast cancer,^{9, 26, 38, 40, 43, 46, 62} which also supports the hypothesis that breast tissue may be especially vulnerable to carcinogens prior to terminal differentiation of the breast cells. It has been suggested that the best strategy for discriminating the competing effects that smoking may have on breast cancer risk would be in situations where the carcinogenic effect was maximized and the putative anti-estrogenic effect less evident and vice versa.²⁹ So, the chances of detecting the potential carcinogenic effects would be maximized by studying breast cancer in women who smoked only before and/or during a first pregnancy and then stopped. Conversely, smoking's anti-estrogenic effects would best be discerned in women who started smoking after a first pregnancy when the breast tissue is no longer as susceptible to carcinogenic insults. While only a few studies have been able to employ such a strategy,^{9, 43, 46, 63} the results tend to suggest elevated risk in women who smoked only before a first pregnancy, and a reduced (or no different risk) among women who solely smoked after their first pregnancy. This analytic strategy is difficult to implement, given the generally small proportion of women who take up smoking after having children.

In summary, at least some of the rationale for initially rejecting a causal relationship between ETS/SHS exposures and breast cancer has been based on the apparent lack of an association of active smoking with breast cancer.^{1, 31} The flurry of studies recently published tend to show a positive association between breast cancer and active smoking, at least within certain

subpopulations or those exposed early in life or over the course of many years.^{3,64} It should also be noted that some of these recent studies with positive findings were specifically designed to investigate the association between smoking and breast cancer. On the other hand, almost all of the earlier studies were so-called secondary data analyses, meaning that these studies were designed to examine different exposures (i.e., diet or physical activity), and smoking was collected as a potential confounder. Thus, the quality of smoking data, especially ETS/SHS exposure, differs significantly between these groups of studies.

There is a significant body of research that has focused on the effect of genetic polymorphisms relevant to tobacco carcinogens on the association between active smoking and breast cancer risk. These studies have focused on a variety of genes involved largely in carcinogen activation and detoxification. Results from these studies have largely been inconsistent, with the exception of the NAT2 slow acetylator and the GSTM1 null genotypes. The inconsistency is likely due to

differences in methodologies, smoking cut-off points, and small samples sizes.⁶⁵ A more detailed discussion of this body of work goes beyond the scope of this review, which is aimed at ETS/SHS exposure.

As pointed out above, a number of studies have directly investigated the role of ETS/SHS exposure in breast cancer etiology. To date there have been eight prospective cohort studies^{9, 40, 42, 43, 66-69} and 15 case-control studies.^{26, 37, 39, 41, 44, 45, 55, 61, 70-76} Results have been fairly mixed, with four of the eight cohort studies yielding positive results and ten of the 16 case-control studies reporting positive findings. The most recent large-scale reviews published in the last year^{2, 3} have considered nearly all of these studies in their assessments. In addition to a qualitative assessment of the literature, both the California EPA and the U.S. Surgeon General performed quantitative meta-analyses to generate summary risk estimates (see Table 3 below).

While each agency employed slightly different methods and included slightly different subsets of studies, the summary point estimates are generally

Table 3. Summary of results from recent ETS/SHS exposure meta-analyses

Agency	Exposure	Subset of Studies	Number of studies	Summary RR (95% CI)
CAL EPA	Lifetime	All	19	1.25 (1.08–1.44)
CAL EPA	Lifetime	Those with full exposure assessment	5	1.91 (1.53–2.39)
CAL EPA	Lifetime	Pre-menopausal women	14	1.68 (1.31–2.15)
Surgeon General	Lifetime	All	10	1.40 (1.12–1.76)
Surgeon General	Any	Cohort	7	1.02 (0.92–1.13)
Surgeon General	Any	Case-control	14	1.40 (1.17–1.67)
Surgeon General	Best	Pre-menopausal women	11	1.64 (1.25–2.14)

similar, yet the conclusions from each agency are different. California EPA felt the evidence was strong enough to declare a causal relationship between ETS/SHS and breast cancer among premenopausal women. This conclusion was bolstered by their analysis, in which they only included those studies with full lifetime exposure assessment (including childhood residential and adult residential and occupational sources) and found even stronger risk elevations. The U.S. Surgeon General's office, however, while noting the strength of the association among premenopausal women, cited the lack of association among cohort studies, the strong potential for recall and selection bias among many of the case-control studies—where many of the positive findings tended to come from hospital-based, rather than population-based, studies—and evidence of publication bias as arguments limiting their ability to declare causality. These differing conclusions highlight the state of the evidence to date and point towards needed future directions.

Conclusion and Future Directions

While overall the evidence to date suggests there may be a causal association between ETS/SHS exposure and breast cancer, there remains substantial variability in results. Clearly more research is needed to discern whether such discrepancies are a function of methodological flaws related to study design or are a reflection of varying risks associated with differing times of exposure and/or subpopulations of susceptible individuals. Most of the positive findings are derived from case-control studies. These case-control studies tend to have more fully characterized exposure assessments (taking into account timing, duration, and intensity in various settings) than the cohort studies, and thus may be

less likely to have misclassified exposure. Only one cohort study has been published to date that has been able to characterize ETS/SHS exposures in settings other than the home and for a variety of time periods.⁴² In keeping with the conclusions of the California EPA report, this study reported an effect for both active smoking (RR = 3.9, 95% CI = 1.5–9.9) and ETS/SHS exposure (RR = 2.6, 95% CI = 1.3–5.2) for premenopausal women, but not postmenopausal women (RR = 1.1, 95% CI = 0.8–1.6 for active smoking; RR = 0.7, 95% CI = 0.4–1.0 for ETS/SHS).⁴²

On the other hand, the case-control studies tend to be smaller and more susceptible to the possibility of selection and recall biases. A few of the key positive findings from the case-control studies were from studies in which participants were recontacted specifically and solely to ask about ETS/SHS exposures, raising the likelihood of differential recall between cases and controls.^{41, 55} However, those studies that employed the most detailed ETS/SHS exposure assessment^{37, 41, 44, 73, 77} consistently reported statistically significant risk elevation for women with the highest levels of ETS/SHS exposure. The need for more cohort studies with full characterization of ETS/SHS exposures across time periods and settings (home, workplace, social) is glaringly apparent. It also is critical to create a 'clean' referent group in all these studies that includes lifetime never smokers with no ETS/SHS exposures for any time period or from any setting. To date, investigators from only one cohort study characterized their referent group according to these criteria.⁴²

Given the likely complexity of mechanisms underlying the relationship between smoking and breast cancer, it is very important not only to construct a full lifetime exposure profile for ETS/

SHS exposure, but also to examine the risks in the context of the hormonal milieu in which the exposure occurs. The provocative finding recently reported by Manjer and colleagues⁴⁹—of an increased risk of breast cancer associated with active smoking only among women with high levels of endogenous estrogens—deserves more attention. Furthermore, consideration of genotypes both that affect the activation, detoxification, DNA repair, and cell cycle control/apoptotic processes in tobacco-related carcinogens, as well as estrogen metabolism, may help to reveal the mechanistic pathway by which smoking exposures may differentially influence risk during different time periods of life.

Finally, while most of the studies to date have taken into account confounding by other known breast cancer risk factors, more attention to some covariates may be warranted. The large collaborative pooled analysis of active smoking and breast cancer published in 2002 suggested that the smoking-related risk of breast cancer reported in the literature was entirely an artifact of alcohol consumption.⁷⁸ In this pooled analysis of over 50,000 cases of breast cancer, it was reported that when the analysis was limited to nondrinkers, there was no longer a smoking-related risk. In the recent analysis by Reynolds, et al., stratifying the data by alcohol consumption did not eliminate the smoking-related risks.⁹ Nevertheless, given that both active and passive smoking are strongly correlated with alcohol consumption, this issue deserves further attention and highlights the importance of going beyond simple covariate adjustment to examining the potential for effect modification for this and other covariates.

California has one of the lowest rates of active smoking and some of the strictest anti-tobacco

legislation in the country. Consequently, most Californians are fortunate not to have to endure substantial exposures to ETS/SHS. From an attributable risk perspective, ETS/SHS exposure (if it is in fact related to breast cancer), is unlikely to be a large contributor to breast cancer incidence in California. There are, however, certain subpopulations that remain at risk for substantial exposures. Children, especially those riding in motor vehicles with smoking adults, are at risk for fairly high exposures.⁷⁹ Women working in the hospitality industry (bars and restaurants) are also at particular risk for high exposures. In fact, waitresses (an occupational group often dominated by young women), experience the highest occupational exposures to ETS/SHS (72.3 percent nationwide).⁸⁰ While California legislation prohibits smoking in such workplaces, compliance, although improving, is still far from complete.⁸¹ Legislation is currently pending in California that would ban smoking in cars with young children present.⁷⁹ Thus, elucidating the breast cancer risk associated with both active and passive smoking during early life may be particularly important in helping to provide the impetus to eliminate these exposures.

From a public health perspective, if tobacco smoke is found to be causally related to breast cancer, it could point to one of the few modifiable avenues for preventing this disease. Furthermore, research has suggested that women fear breast cancer more than other smoking-related diseases that carry a higher mortality threat.^{82, 83} If tobacco smoke exposure is found to be linked to breast cancer risk, it may serve as an especially strong motivating factor in reducing tobacco use and its accompanying host of related adverse health outcomes.

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