Published in final edited form as:
Prev Med. 2008 June ; 46(6): 492–496. doi:10.1016/j.ypmed.2007.11.016.

Evidence secondhand smoke causes breast cancer in 2005 stronger than for lung cancer in 1986

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Abstract

Objectives—To compare the strength of evidence from epidemiologic studies of secondhand smoke of the US Surgeon General's 1986 conclusion that secondhand smoke caused lung cancer with the California Environmental Protection Agency's (CalEPA) similar 2005 conclusion on breast cancer in younger, primarily premenopausal women.

Methods—We reviewed each report for criteria used to assess causality: numbers of studies, statistically significant increases in risk, and pooled summary risk estimates.

Results—Both the Surgeon General and CalEPA used updated Bradford Hill criteria for assessing causality and found that the evidence met those criteria. Six of 13 lung cancer studies (46%) had statistically significant increases (one of three cohort studies). Pooled risk estimates for lung cancer for spousal exposure were 1.53 for 10 combined case–control studies and 1.88 for seven studies with dose–response results. The CalEPA reported 10 of 14 studies (71%) had statistically significant increases in breast cancer risk (two of four cohort studies). Pooled relative risk estimates for younger, primarily premenopausal women were 1.68 (95% CI: 1.33, 2.12) for all exposed women and 2.19 (1.68, 2.84) for five studies with better exposure assessment.

Conclusions—The evidence from epidemiologic studies of secondhand smoke in 2005 for breast cancer in younger, primarily premenopausal women was stronger than for lung cancer in 1986.

Keywords

Breast neoplasms; Lung neoplasms; Meta-analysis; Review; Tobacco smoke pollution

Introduction

On January 26, 2006, the California Environmental Protection Agency's (CalEPA) Air Resources Board unanimously voted to add secondhand tobacco smoke (also referred to as passive smoking, involuntary smoking and environmental tobacco smoke (ETS)) to the state's list of "toxic air contaminants." Other toxic air contaminants include diesel particulate exhaust, benzene, formaldehyde, and polyaromatic hydrocarbons. The Board unanimously approved this regulation based on a report that assessed the exposures and health effects of secondhand smoke (California Environmental Protection Agency, 2005). This report, an update of a report on health effects of secondhand smoke the CalEPA prepared in 1996 (California Environmental Protection Agency, 1997; National Institutes of Health, 1999), was the result of a 5-year process that included public and scientific review. This state's Scientific Review Panel on Toxic Air

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Contaminants considered the report and CalEPA's responses to the public criticisms and required several revisions to the report before unanimously approving it. In addition to including the first outdoor measurements of secondhand smoke exposure, the CalEPA added four new entries to the list of diseases secondhand smoke causes: breast cancer in younger, primarily premenopausal women who have never smoked, asthma induction in adults, pre-term delivery, and altered vascular properties. (The CalEPA found the evidence for breast cancer in postmenopausal women "inconclusive.") The conclusion that secondhand smoke causes breast cancer in younger women who have never smoked is particularly important because the cancers tend to be particularly aggressive.

Despite the fact that the conclusion that secondhand smoke caused breast cancer in younger women was made by a leading government scientific agency using a modern version of the widely accepted Bradford Hill criteria and the importance of this conclusion, some, including the American Cancer Society (American Cancer Society, 2006a,b) and the U.S. Surgeon General (U.S. Department of Health and Human Services, 2006), have not accepted this conclusion. In order to provide a benchmark to assess the CalEPA's conclusion, we compared the evidence that formed the basis for the U.S. Surgeon General's conclusion that secondhand smoke caused lung cancer in 1986 (United States Office of the Surgeon General, 1986) with the evidence CalEPA used to reach a similar conclusion on breast cancer in 2005 (California Environmental Protection Agency, 2005).

Our analysis is not designed to re-articulate the details of the question of whether or not passive and active smoking causes breast cancer. The CalEPA report went into great depth (57 single-spaced pages on passive smoking and, in an appendix, 39 pages on active smoking) to evaluate the evidence and an article summarizing that evidence was recently published (Miller et al., 2007). The report can be accessed on the Web (California Environmental Protection Agency, 2005) as can the 1986 Surgeon General report. (United States Office of the Surgeon General, 1986) Rather, this analysis was designed to compare the amount and nature of the evidence reviewed by the CalEPA with that on passive smoking and lung cancer that existed in 1986 when the Surgeon General concluded that passive smoking caused lung cancer. The secondhand smoke evidence for breast cancer in younger, primarily premenopausal women is stronger and more consistent than the lung cancer evidence was in 1986.

Methods

We compared the evidence from epidemiologic studies cited by the Surgeon (United States Office of the Surgeon General, 1986) with that cited by CalEPA on breast cancer in younger, primarily premenopausal women in 2005 (California Environmental Protection Agency, 2005). The Surgeon General gave particular weight to high exposure categories where dose–response results were reported and used all exposed subjects where dose–response results were not reported. We compared the total number of studies, the types of studies (cohort or case–control), the number of studies with risks greater than 1.0, the number of studies with statistically significant increases in risk for all exposed or among those with the highest exposure to secondhand smoke or with a statistically significant test for trend for secondhand smoke dose–response analyses, and the magnitude of the pooled risk estimates. We also enumerated what criteria and other evidence each report examined to come to the conclusion of causality.

Results

Table 1 summarizes the criteria for evaluating the evidence and the amount and nature of evidence presented in each report.

Both the Surgeon General and the CalEPA evaluated the evidence using very similar, updated versions of the Bradford Hill criteria for causality (strength of association, consistency of association, temporality, coherence and biological plausibility, dose–response, experimental evidence). The Surgeon General report gave special attention to disease misclassification, misclassification of the subject's personal smoking status or exposure to ETS, and the expected ETS lung cancer risk based on the active smoking risk. Specific subsections of the CalEPA report addressed the following issues in detail: limitations of the studies, concerns about bias in case–control studies, the potential for confounding, controversies regarding relative potency of active and passive smoking, anti-estrogenicity of active and passive smoking, exposure misclassification, windows of susceptibility, publication bias, and the similar risks observed for active and passive smoking.

In 1986, the Surgeon General reported that 11 of 13 lung cancer studies had point estimates of the risk ratio above 1.0, with 6 of the 13 (46%) reporting statistically significant increases in risk for all exposed women or for at least one high exposure category (United States Office of the Surgeon General, 1986). This summary included one study with a statistically significant increase in one histological subgroup only (Pershagen, 1989). One (Hirayama, 1984) of 3 (Hirayama, 1984; Garfinkel, 1980; Gillis et al., 1984) cohort studies reported a statistically significant elevated risk. The pooled risk estimates for spousal exposure were 1.53 for 10 combined case–control studies and 1.88 for the high exposure categories for 7 studies with dose–response results; no confidence intervals were reported (United States Office of the Surgeon General, 1986) (Table 2, p. 100).

In 2005, the CalEPA reported that 13 of the 14 studies had point estimates for breast cancer in younger or premenopausal women above 1.0, with 7 (Sandler et al., 1986; 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) of the 14 studies (50%) reporting statistically significant elevations in risk for all exposed women. Three more studies, while not reaching statistical significance for all exposures, reported significant elevation in risk for a high exposure group (Hirayama, 1992; Gammon et al., 2004) or a statistically significant dose–response relationship with increasing secondhand smoke exposure (Shrubsole et al., 2004). Using a similar approach as the 1986 Surgeon General report, 10 of 14 studies (71%) reported a statistically significant increase in risk overall (Sandler et al., 1986; 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) or for higher exposure (Hirayama, 1992; Smith et al., 1994; Morabia et al., 1996; Johnson et al., 2000; Kropp and Chang-Claude, 2002; Gammon et al., 2004; Hanaoka et al., 2005). Two (Hirayama, 1992; Hanaoka et al., 2005) of four (Hirayama, 1992; Wartenberg et al., 2000; Reynolds et al., 2004; Hanaoka et al., 2005) cohort studies reported a statistically significant elevated risk. The pooled relative risk estimates for younger, primarily premenopausal women were 1.68 (1.33–2.12) for all exposed women and 2.19 (1.68–2.84) for the five studies with the most complete exposure assessment (all 5 of which had statistically significant results for all exposed women) (Smith et al., 1994; Morabia et al., 1996; Zhao et al., 1999; Johnson et al., 2000; Kropp and Chang-Claude, 2002).

Discussion

The evidence from epidemiologic studies of secondhand smoke used by the CalEPA to draw a causal conclusion for secondhand smoke and breast cancer in younger, primarily premenopausal women in 2005 was stronger than that used by the Surgeon General in 1986 to conclude a causal relationship between secondhand smoke and lung cancer. (While the volume of studies on passive smoking and lung cancer has increased since the 1986 Surgeon General report, the general pattern of mostly case–control studies showing significantly elevated risks has continued; the analysis of secondhand smoke and lung cancer in the 2004 IARC report that

examined studies published up to 2001 found 16 of 40 case–control studies and 3 of 8 cohort studies had a statistically significant elevation in risk for some measure of secondhand smoke (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2004).) In the 2006 Surgeon Generals' review of 13 studies of secondhand smoke and lung cancer published between 1996 and 2002, 8 of 12 case–control and 1 of 3 cohort studies found statistically significant increases in risk (U.S. Department of Health and Human Services, 2006). For breast cancer, the 2005 CalEPA report had a higher percentage of studies that were individually statistically significant and more cohort evidence in support of increased risk than the 1986 Surgeon General report had when it drew a causal conclusion for lung cancer. Both reports relied primarily on case–control studies to reach their conclusions, supported by some results from cohort studies.

There is evidence that exposure between puberty and first full term pregnancy is particularly dangerous (Russo and Russo, 2004), and this is a time when many young women work as waitresses. Waitresses have the highest prevalence of exposure to secondhand smoke of any occupational group (Shopland et al., 2004) and the levels of secondhand smoke pollution are highest of any venue that has been studied (Hammond, 1999). (Waitresses have the highest nonsmokers' lung cancer rate among all occupational groups (Siegel, 1993).) Applying the prevalence of exposure and the 1.7 relative risk for breast cancer among younger, primarily premenopausal women (Table 1) to waitresses, yields a 30% attributable risk for breast cancer among this occupational group.

Those who doubt the causality of the association have argued that confounding may explain the results. In fact almost all of the studies on breast cancer, especially those producing the higher risk estimates, controlled for most or all of known or suspected confounders for breast cancer (BMI, family history, hormone use, alcohol, socio-economic status, physical activity, benign breast disease, age at menarche, reproductive measures, and breast-feeding; see the CalEPA report (California Environmental Protection Agency, 2005; Miller et al., 2007). (See CalEPA Tables 7.4.1I and 7.4.1L for a detailed presentation of confounders by study and Section 7.4.1.4.2.3.3 for a short discussion of confounding.) Furthermore, it is unlikely that these factors are true confounders because the risks associated with tobacco smoke exposure were similar with and without control for confounders. The discussion of confounding is more extensive than for lung cancer in the 1986 Surgeon General report (United States Office of the Surgeon General, 1986).

The "biological plausibility" argument in the 1986 Surgeon General report was limited to noting that active smoking caused lung cancer, so it was reasonable to assume that passive smoking would, too (United States Office of the Surgeon General, 1986). The CalEPA report presented direct toxicological evidence that there are 20 identified mammary carcinogens in rodents for tobacco smoke (see Table 2) (California Environmental Protection Agency, 2005). CalEPA also presented molecular epidemiology consistent with the hypothesis that tobacco-induced breast cancers may be concentrated in women with a genetic susceptibility to the carcinogens in tobacco smoke (California Environmental Protection Agency, 2005).

The 2006 Surgeon General report on secondhand smoke (U.S. Department of Health and Human Services, 2006) and the 2005 CalEPA report (California Environmental Protection Agency, 2005) both present meta-analyses of the risk of breast cancer associated with secondhand smoke that found virtually the same elevations in risk (compare Table 7.10 in the Surgeon General report with Table 7.4.1B of the CalEPA report) but arrived at different conclusions regarding causality. While the Surgeon General report concludes that "the evidence is suggestive but not sufficient to infer a causal relationship between secondhand smoke and breast cancer," the conclusion in the CalEPA Report is that "regular ETS exposure is causally related to breast cancer diagnosed in younger, primarily pre-menopausal women

and that the association is not likely explained by bias or confounding." The primary reason for this different conclusion is the converse of the biological plausibility argument that the Surgeon General made for secondhand smoke causing lung cancer in 1986: since active smoking did not cause breast cancer, how could passive smoking (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2004; American Cancer Society, 2006a,b; U.S. Department of Health and Human Services, 2006), p. 446)? The statement that active smoking was not associated with an increase in risk for breast cancer was based on a pooled analysis of 53 studies that compared breast cancer in current smokers to never smokers and found no increase in risk (Hamajima et al., 2002), as well as two major consensus documents, the 2004 Surgeon General report on active smoking (U.S. Department of Health and Human Services, 2004) and the 2004 International Agency for Research monograph on tobacco smoke (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2004), that also reached negative conclusions regarding the link between active smoking and breast cancer.

While both these consensus reports on active smoking were published in 2004 (IARC Working Group on the Evaluation of Carcinogenic Risk to Humans, 2004; U.S. Department of Health and Human Services, 2004), the literature base for their conclusions ended in 2002. Studies of active smoking and breast cancer, that took care to minimize inclusion of passive smokers in the reference group, however, have demonstrated an increased risk of breast cancer in active smokers. Meta-analysis of these studies demonstrates a significantly increased risk of breast cancer associated with active smoking (Johnson, 2005) that is similar to the increased risk associated with secondhand smoke. Because of the fact that the link between active smoking and breast cancer was not widely understood, CalEPA (California Environmental Protection Agency, 2005) included a discussion of this issue in its report (Section 7.4.1.1. and Appendix A to Chapter 7). The CalEPA reported six recent prospective cohort studies that each found statistically significant increased breast cancer risks associated with at least some measure of active smoking (California Environmental Protection Agency, 2005).

The fact that the risks associated with active smoking are not much larger than the risks associated with passive smoking despite the much larger dose of smoke that smokers receive also concerns some researchers. The available evidence indicates that, like heart disease (Barnoya and Glantz, 2005), the dose–response curve is not linear. There are several possible explanations for the fact that the risks of active and passive smoking are not more different (Morabia et al., 2001; California Environmental Protection Agency, 2005; Johnson, 2005), none of which is considered definitively established. One explanation is that active smoking damages ovaries and depresses estrogen levels, which is associated with lower breast cancer risk. This effect would tend to counter the effects of the carcinogens in the smoke in active smokers more than passive smokers who do not receive a large enough dose of smoke to depress estrogen levels. Another explanation is related to the idea that the women who are genetically susceptible to tobacco-induced cancers develop them at a younger age.

The biological mechanisms that give rise to the lack of a linear dose–response curve between active and passive smoking is clearly an important area for further basic research. The fact that the biology is not completely worked out, however, has never been required before as a prerequisite for the identification of a risk. For example, it took over a decade between when the increased risk for heart disease from passive smoking was first identified (see, for example, Glantz and Parmley, 1991) and when there was a reasonably complete understanding of the biology to explain why the effects of active and passive smoking were so similar (see, for example, Barnoya and Glantz, 2005). Indeed, even though the tobacco industry has routinely demanded detailed biological explanations before determining causality ever since the original Surgeon General report (U.S. Public Health Service, 1964) concluded that active smoking caused lung cancer in men in 1964, neither the Surgeon General nor the CalEPA has required that every detail of the biology be defined before accepting a clearly observed risk, such as

exists for lung cancer and secondhand smoke and breast cancer in younger, primarily premenopausal women.

Acknowledgments

We would like to thank Andrew Hyland, Howard Morrison and A. Judson Wells for their feedback on an earlier draft of the manuscript. Dr. Glantz' work was supported by National Cancer Institute Grant CA-61021. The granting agency played no role in the conduct of the research or the preparation or revision of the manuscript.

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Table 1

Summary of evidence on secondhand smoke and lung cancer from the 1986 Surgeon General's report (United States Office of the Surgeon General, 1986) compared to evidence on breast cancer in younger, primarily premenopausal women from the California EPA 2005 report (California Environmental Protection Agency, 2005)

Factor	**Lung cancer (Surgeon General Report 1986)**			**Breast cancer in younger women (California EPA 2005)**		
Used updated Bradford Hill criteria for causality			Yes			Yes
Consideration/Adjustment for potential confounders			Yes			Yes
Considered biological plausibility			Yes			Yes
Examined dose–response			Yes			Yes
Considered effect of active smoking			Yes			Yes
Examined toxicology			No			Yes
Studies	Cohort	Case–Control	Total	Cohort	Case–Control	Total
Total number of studies	3	10	13	4[a]	10	14
Positive (relative risk>1.0)	3	8	11 (85%)	3	10	13 (93%)
Statistically significant results[b]	1	5	6 (46%)	2	8	10 (71%)
Pooled risk estimates			Relative risk[c]			Relative risk (95% CI)
All studies	All case–control studies (spousal risk)		1.53	All studies (all exposed)		1.68 (1.33–2.12)
Specific subsets	7 case–control studies with dose–response information (high exposure category)		1.88	5 studies with better exposure assessment (all exposed)		2.19 (1.68–2.84)

[a] Excludes Egan et al. (2002) who reported no premenopausal risk estimates but said pre- and post-menopausal results were similar and reported a 1.07 overall risk estimate for all breast cancer.

[b] Studies with statistically significant increases in risk (at the 95% confidence level) for all exposed or among those with the highest exposure to secondhand smoke or with a statistically significant test for trend for secondhand smoke dose–response analyses.

[c] No confidence intervals reported for pooled estimates.

Table 2

Mammary carcinogens in tobacco smoke

Aromatic hydrocarbons	**Aliphatic compounds**
Benzene	Acrylamide
Benzo[*a*]pyrene	Acrylonitrile
Dibenz[*a*,*h*]anthracene	1,3-Butadiene
Dibenzo[*a*,*e*]pyrene	Isoprene
Dibenzo[*a*,*h*]pyrene	Nitromethane
Dibenzo[*a*,*I*]pyrene	Propylene oxide
Dibenzo[*a*,*l*]pyrene	Urethane
	Vinyl chloride
Nitrosamines	*Arylamines and nitrarenes*
N-nitrosodiethylamine	4-Aminobiphenyl
N-nitrosodi-*n*-*butyl*-amine	Nitrobenzene
	Ortho-toluidine

Source: CalEPA report Table 7.4.1E, p. 107 (California Environmental Protection Agency, 2005).