

Passive smoking and breast cancer: is the evidence for cause now convincing?

It all depends on which studies you emphasise

Four years ago in the *Journal* we posed the question of whether active and passive exposure to cigarette smoke could cause breast cancer. We concluded, at the time, that biological plausibility had been established, but that the epidemiological evidence was inconclusive.¹ This was consistent with a 1997 report² of the California Environmental Protection Agency (Cal/EPA), which found that the link between environmental tobacco smoke (ETS) and breast cancer was inconclusive. However, in a recent draft review of the health effects of ETS,³ the Cal/EPA stated that the evidence for a causal association between ETS and breast cancer is now conclusive. Its latest report was based on a systematic review of 15 studies, 11 of which had been published since the 1997 report. Is this new conclusion justified?

Until the 1990s, most case-control and cohort studies examining the association between cigarette smoke exposure and breast cancer focused on active smoking. These studies did not adequately ascertain the whole-of-life ETS exposure of the participants.^{1,4,5} Notably, childhood exposure was usually ignored.⁶ This is of particular relevance, as chemical carcinogenesis studies of breast cancer in experimental animals, and other studies on the development of the mammalian breast, indicate that breast ductal cells would be most susceptible to chemical carcinogenesis during puberty and first pregnancy.⁵ Thus, it is possible that childhood, adolescent and adult exposure to cigarette smoke up until the delivery of a woman's first child is a crucial component of lifetime exposure. If an association with ETS did exist, case-control and cohort studies on active smoking and breast cancer could have underestimated the effects by inadequate assessment of ETS exposure.^{1,4,6}

The conclusion of the Cal/EPA report on ETS and breast cancer³ is based on a systematic review that gives prominence to the recent studies in which several sources of ETS exposure have been ascertained and to the clear dose-risk relationships seen in some studies. The meta-analysis used in the Cal/EPA's review yielded a relative risk of 1.40 (95% CI, 1.17–1.68) — a significantly increased risk.

However, a closer look at the studies reviewed in the latest Cal/EPA report raises some questions about its conclusion. Of the 15 studies in the review, five were cohort studies, of which none showed a statistically significant increase in breast cancer risk with ETS exposure. Several of these cohort studies had a very limited assessment of ETS — for example, defining exposure as simply being married to a smoker. However, one of the five cohort studies, which prospectively assessed childhood, adult and occupational ETS among US nurses,⁷ also showed no association. Moreover, another major cohort study⁸ published since the Cal/EPA review supports the conclusion of the US nurses' study in regard to ETS. In this report of a 5-year follow-up of a cohort of 116 564 Californian teachers, 1150 new cases of invasive breast cancer were diagnosed among the 76 189 never-smoking women who provided data on ETS.⁸ The study aimed to ascertain total lifetime

ETS exposure, although the published analysis is limited to household exposure throughout life. No significant association between ETS exposure and breast cancer was found for any age range of exposure or by menopausal status. However, a significant association was found between active smoking and breast cancer. The relative risks of acquiring breast cancer after ETS exposure in childhood, adulthood, or both childhood and adulthood, were 0.92, 0.93 and 0.93, respectively. Adding this new study to the Cal/EPA's meta-analysis, the overall relative risk, based on the six cohort studies, is 1.01 (95% CI, 0.92–1.12) — that is, there is no significant effect.

The strong association between ETS exposure and breast cancer emphasised in the Cal/EPA report³ is based on five case-control studies regarded as “unlikely to have missed important ETS exposures”. The summary odds ratio for these studies was 1.92 (95% CI, 1.54–2.39). The association was stronger in premenopausal women (summary odds ratio, 2.20; 95% CI, 1.70–2.85). However, if a true association exists, it is difficult to see why the two high-quality US cohort studies of nurses and teachers^{7,8} showed no association. In both studies, data

on ETS exposure were collected before the diagnosis of breast cancer, thus avoiding recall bias, and both groups are likely to have given reasonably complete and valid information, including data on childhood exposures.

Other research results add to the complexity of the issue. A 2002 systematic review, based largely on the same case-control studies as the Cal/EPA review,³ concluded that the strength of the association with breast cancer is similar for passive as for active smoking⁹ — a conclusion that others find implausible.⁷ One possible explanation for this seeming paradox could be that the association is linked mainly or exclusively to ETS exposure in childhood or early adolescence, as has also been suggested for active smoking, perhaps through hormonal mechanisms as well as the direct effects of carcinogens.¹⁰ The fact that p53-gene mutations in breast tumours are increased in smokers compared with non-smokers or ex-smokers suggests a genotoxic effect of smoking on breast tissue.¹¹ Further complexities related to genotype may emerge: one case-control study¹² showed that the association between passive smoking and breast cancer was stronger in rapid acetylators (ie, women who, owing to their specific NAT2 genotype, more rapidly metabolise carcinogenic compounds, such as aromatic amines, in tobacco smoke). However, with regard to active smoking, slow acetylators were more at risk.¹² Although many genotypes have been reported to affect the association between active or passive smoking and breast cancer,¹³ the results are inconsistent and do not explain the variable epidemiological results.

Is a causal association between ETS exposure and breast cancer now certain, as the Cal/EPA draft report proposes? The jury would be wise to stay out on this one. If the emphasis is put on cohort studies, there appears to be no association between ETS exposure and breast cancer. If the emphasis is put on case-control studies

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with more detailed information on ETS exposure — but the possibility of recall bias — there appears to be an increased risk, especially in premenopausal women. An analysis focusing on childhood and adolescent ETS exposure may be the key to solving the current confusion. Such an analysis could be based on a pooled analysis of available studies with access to the original data, or on further assessment and follow-up of the ongoing cohort studies. In the interim, it is prudent to accept the possibility of an association, while also accepting the limitations of the available evidence.

The International Agency for Research on Cancer has just released a major report on smoking, in which it states that the evidence does not support a causal link between either active or passive smoking and breast cancer.¹⁴ However, the report confirms a causal link between ETS and lung cancer, which, in itself, justifies efforts to restrict ETS.

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