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Epidemiological evidence on environmental tobacco smoke and cancers other than lung or breast

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ABSTRACT

We reviewed 87 epidemiological studies relating environmental tobacco smoke (ETS) exposure to risk of cancer other than lung or breast in never smoking adults. This updates a 2002 review which also considered breast cancer. Meta-analysis showed no significant relationship with ETS for nasopharynx cancer, head and neck cancer, various digestive cancers (stomach, rectum, colorectal, liver, pancreas), or cancers of endometrium, ovary, bladder and brain. For some cancers (including oesophagus, colon, gall bladder and lymphoma) more limited data did not suggest a relationship. An increased cervix cancer risk (RR 1.58, 95%CI 1.29–1.93, n = 17 independent estimates), reducing to 1.29 (95%CI 1.01–1.65) after restriction to five estimates adjusting for HPV infection or sexual activity suggests a causal relationship, as do associations with nasosinus cancer observed in 2002 (no new studies since), and less so kidney cancer (RR 1.33, 95%CI 1.04–1.70, n = 6). A weaker association with total cancer (RR 1.13, 95%CI 1.03–1.35, n = 19) based on heterogeneous data is inconclusive. Inadequate confounder control, recall bias, publication bias, and occasional reports of implausibly large RRs in individual studies contribute to our conclusion that the epidemiological evidence does not convincingly demonstrate that ETS exposure causes any of the cancers studied.

1. Introduction[1]

In 2002, one of us (PNL) reviewed the evidence relating environmental tobacco smoke (ETS) exposure to risk of cancer of sites other than the lung in never smoking adults (Lee, 2002). That review, based on 38 studies, concluded that the epidemiological evidence then available provided little support for the view that ETS causes cancer at any of the sites considered. However, it did note that three small, relatively weak, studies all reported a statistically significant association of ETS with nasosinus cancer. Since that review, the literature has expanded considerably, and it seems appropriate to carry out an updated review. As the literature on breast cancer is now so substantial, we consider this separately (Lee and Hamling, 2016, submitted for publication), restricting ourselves here to the other cancers considered previously. As before, attention is restricted to never smokers because many of the cancers are associated with active smoking, and reliable detection of any effect of ETS exposure on a smoking-associated disease in the presence of a history of smoking is extremely difficult (Lee, 1992).

Our review also compares and contrasts our conclusions with those of what we will term "authoritative reviews" of health effects of ETS published since our earlier review (California Environmental Protection Agency, 2005; International Agency for Research on Cancer, 2004, 2012; US Surgeon General, 2006) as well as with those of other published reviews relating to specific cancers.

Before discussing the evidence from the individual studies in detail, it is important to be aware of a number of issues that are generally relevant. These were discussed in more detail earlier (Lee, 2002) and are only outlined below.

1.1. Confounding

Since ETS exposure is associated with dietary and other lifestyle factors associated with adverse health (Dallongeville et al., 1998; Forastiere et al., 2000; Iribarren et al., 2001; Thornton et al., 1994) it is important that studies adequately adjust for these

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[1] BMI, body mass index; CI, confidence interval; ETS, environmental tobacco smoke; HPV, human papillomavirus; HRT, hormone replacement therapy; OC, oral contraceptive; NSAID, non-steroidal anti-inflammatory drug; RR, Relative risk.

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factors, especially where a weak relationship between ETS and incidence of a cancer is seen.

1.2. Misclassification bias

The tendency for some current or former smokers to deny having smoked, coupled with the tendency of spouses to have similar smoking habits, is known to bias upward the relationship of spousal smoking to lung cancer (Fry and Lee, 2001; Hackshaw et al., 1997; Lee et al., 2016). The same bias may be relevant for other cancers strongly associated with active smoking.

1.3. Publication bias

Researchers may be less likely to publish, and editors less likely to accept for publication, studies showing no statistically significant association between exposure and disease (Sutton et al., 2000; Thornton and Lee, 2000). This may lead to the published evidence overestimating any true associations. Large cohort studies from which results for only some cancer types have been published strongly suggest the possibility of publication bias.

1.4. Diagnostic inaccuracy

Clinical diagnosis of cancers is subject to substantial errors (Burton et al., 1998; Szende et al., 1996) and such misdiagnosis may bias estimated RRs in either direction.

1.5. Errors in determining ETS exposure

While random errors in determining ETS exposure will underestimate a true relationship, recall bias, a perennial problem in case-control studies, may lead to overestimation. Objective measures of exposure based on biomarkers such as cotinine avoid the issue of recall bias, but are rarely used.

1.6. Reference group

Some case-control studies ask detailed questions about multiple sources of ETS exposure during the subject's lifetime, and use those with no reported exposure at all as the reference group. Since everyone is likely to have had some ETS exposure in their life, RR estimates are highly dependent on which subjects get included in the reference group, and may be unusually subject to recall bias. Estimates based on whether or not the subject is married to, or work with, a smoker may be more reliable.

1.7. Plausibility

Since exposure to tobacco smoke constituents from ETS is much less than that from active smoking, with studies based on cotinine indicating relative exposure factors of less than 0.5% (Benowitz et al., 2009; Office of Population Censuses and Surveys (1996); Pirkle et al., 1996) and studies on particulate matter a lower factor still (e.g. Phillips et al., 1998a; b; Phillips et al., 1994), it seems implausible that ETS might increase risk of cancers not associated with active smoking, or produce increases in risk similar to those seen for smoking.

2. Materials and methods

Attention is restricted to epidemiological prospective, case-control or cross-sectional studies published up to and including November 2015, which involve five or more cancers of any of the specific types considered, and which provide relative risk (RR) estimates for never (or virtually never) smokers for one or more defined ETS exposure types or dose-related ETS indices. RRs generally compare subjects exposed and unexposed to ETS from various different sources including spouse, household, workplace, childhood, travel, social and total, the final category including biochemical assessments of exposure. Note that the term "relative risk" is taken to include estimates of it, such as the odds ratio or hazard ratio. Studies using near equivalent definitions of "never smokers" are accepted when similar definitions are unavailable, so never smokers could include occasional smokers, those with a minimal duration of smoking or number smoked, or long-term ex-smokers.

Up until November 2015, potentially relevant papers were regularly sought from MedLine searches restricted to humans and using the search terms "(passive smoking OR environmental tobacco smoke OR involuntary smoking) AND cancer", from files on smoking and health which were collected for many years within our company, and from references cited in the papers obtained and in other reviews.

For each cancer and exposure index, RRs and 95% confidence intervals (CIs) were extracted/which were adjusted for the most potential confounding factors. Where necessary, these estimates were derived by combining independent RRs by fixed effect meta-analysis (Fleiss and Gross, 1991), or by combining non-independent RRs, e.g. for different exposure levels with the same reference group (Hamling et al., 2008).

Where four or more studies provided independent estimates of risk, random effects meta-analysis (Fleiss and Gross, 1991) was used to derive an overall RR estimate with CI, and a test of publication bias (Egger et al., 1997) was conducted. Where a study provides multiple estimates for a given sex, only one estimate was used in the main meta-analysis, preference being given to estimates for adult rather than for childhood exposure, and to estimates for spousal exposure or exposure to a cohabitant rather than for workplace, social or total exposure. For each cancer type, further meta-analyses for prospective and non-prospective studies separately were carried out whenever four or more of the analysed studies were of prospective design and four or more were of non-prospective design. For some cancers, for reasons discussed in the results section, some meta-analyses were rerun omitting estimates from specific studies.

Where data permitted, additional meta-analyses were conducted based on more specific exposure definitions; at home, at work, in childhood or total. Where multiple estimates were available for a study, preference was given to the estimate for the widest definition of exposure (e.g. any cohabitant rather than spouse for at home exposure) and to the estimate likely to be the most relevant (e.g. mother rather than father for childhood exposure, where an estimate relating to overall childhood exposure was not available). A definition of total exposure had to include exposure both inside and outside the home.

3. Results

3.1. Appendix tables

Details of each study and the meta-analyses are given in Appendix Tables. Following a summary of relevant characteristics for each study in Appendix Table 1, results are presented in Appendix Tables 2–12 for the following 11 cancer groupings: head and neck; digestive system; cervix; endometrium; ovary; kidney; bladder; brain; lymphoma; other sites and total cancer incidence. For each study providing data, results are presented (by sex if possible) relating to various ETS exposure indices. For each study/sex/index, the tables show the source and timing of the exposure, the number