DRAFT

Diet as a potential major confounder of the relationship between ETS exposure and lung cancer risk in non-smokers

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Introduction

This note summarizes the main arguments to support the idea that diet may be a potential major confounder of the relationship between ETS exposure and lung cancer risk in non-smokers. It could form the basis for re-writing into a paper or leading article at a later date.

1. There is strong evidence that various aspects of diet are associated with an increased risk of cancer of a wide range of sites, including of the lung

A recent review by Block et al (1992) summarizes succinctly the overwhelming epidemiological evidence that fruit and vegetable intake is associated with a reduced cancer incidence. About 200 published studies were considered and the consistency of the findings is really very impressive indeed. For lung cancer, an association was observed in all but two of 32 studies and the authors estimated that infrequent consumers of fruits and vegetables have on average 2.2 times the risk of those who are frequent consumers. A similar magnitude of association, and consistency of findings, is seen for a wide range of other types of cancer. Only for breast and prostate cancer is the association markedly less, though even then the tendency is for infrequent consumers to have higher risks. The association cannot be explained as a result of

confounding by smoking, fat consumption, education or socioeconomic status or by publication bias. The association is dose-related, and is likely to be underestimated by epidemiological studies, due to the well known difficulties of accurately quantifying consumption in dietary questionnaires. There is a plausible mechanism to explain the association, based on the central role of oxidative events and free radical damage in cancer causation, and the fact that dietary antioxidants, present in fruit and vegetables, can block or repair such damage.

Associated with the evidence that fruit and vegetable consumption is protective for cancer is the considerable attention given to the possibilities that specific dietary components can confer protection from cancer. Particular interest has centred on beta-carotene and vitamin C in this respect.

In 1975 Bjelke reported results from a prospective study in Norway showing a marked increased risk of lung cancer in those with a low dietary vitamin A intake. Given the recognized role of vitamin A (retinol) in cell differentiation, and given the fact that high doses of retinoids (vitamin A analogues) had been shown in animals to protect against cancers caused by various known carcinogens, there was, at the time, considerable interest in the possibility that vitamin A might be protective against cancer in humans. Subsequently, Peto et al (1981) put forward the hypothesis that beta-carotene, a major vitamin A precursor present in vegetables and fruits, might be much more important in protecting against human cancer. They noted that serum levels of beta-carotene are responsive to dietary intake, unlike serum levels of vitamin A,

which are maintained within a narrow range in well-nourished populations by vitamin A in the liver. They also noted evidence that beta-carotene had antioxidant activity and that it had anticarcinogenic activity in animal studies.

Wald (1987) reviewed the considerable evidence that had accumulated by that time relating risk of cancer to both retinol and beta-carotene. Evidence from epidemiological dietary studies did not, as a whole, show an association between retinol intake and the risk of cancer in developed countries, but there was a quite consistent inverse association between beta-carotene intake and the risk of cancer. Evidence from prospective biochemical epidemiological studies demonstrates that low serum retinol is associated with a high risk of cancer but only within the first three years, indicating that it is probably a metabolic consequence of cancer. A low serum beta-carotene level is also associated with a high risk of cancer, but here the association persists for many years before the diagnosis of cancer, indicating that it probably also precedes its development. Wald pointed out that the inverse association between beta-carotene and the risk of cancer may be due to beta-carotene affecting risk directly, or it may reflect an indirect association with some other component of vegetables or with a non-vegetable component of diet that is itself related indirectly to vegetable consumption.

Ziegler et al (1992) considered that the negative relationship between beta-carotene and cancer in epidemiological studies was most consistently observed for cancer of the lung. They pointed out, however, that the possible role of other carotenoids, other

constituents of fruits and vegetables, had not been adequately explored. They also described ongoing work to try to evaluate these alternative hypothesis, including determination of those food groups and nutrients that are highly correlated with vegetable and fruit intake, development of methods for optimal determination of the common carotenoids in blood (lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene and beta-carotene), and lung cancer case-control studies.

Van Poppel (1993) also summarized epidemiological evidence relating carotenoids to cancer. He noted that the prospective studies are remarkably consistent for an inverse relation of carotenoids with lung cancer, although the evidence is less consistent for other types of cancer. He noted that there were quite a large number of human intervention studies which are ongoing using beta-carotene (sometimes in conjunction with other agents such as retinol, vitamin C and E) as inhibitory agents. Studies performed so far suggest that beta-carotene can affect carcinogenesis, though not at all stages and not at all cancer sites. Follow-up is still ongoing however in the large studies in Finland and USA of the effects of beta-carotene on lung cancer.

Block (1991) reviewed evidence from 46 studies of non-hormone dependent cancers in which a dietary vitamin C index has been calculated. 33 found statistically significant protection, with high intake conferring approximately a two-fold protective effect compared with low intake. Of 11 lung cancer studies she reviewed, five found a statistically significant protective effect, four found effects in the protective direction but not significant, and two

have reported no effect. Thornton (1993), in a brief review of 14 lung cancer studies reached essentially the same conclusion, namely that the results are quite consistent in demonstrating a negative association. Block (1991) notes that it may be unproductive to stop thinking in terms of "Is it vitamin C or carotenoids" that are protective. She considers it very likely that both are needed, and that "all the nutrients packaged together in fruits and vegetables are synergistic and provide optimal benefit when all are present in optimal quantities".

A number of studies have also looked at the relationship between vitamin E and cancer risk. A recent review by Knekt (1993) cited eight epidemiological studies of lung cancer which have been in agreement with the hypothesis that vitamin E has anticarcinogenic properties, providing protection as a free radical scavenger. He considered that the fact that nine studies have reported no association may be due to several factors, such as small numbers of lung cancer cases, insufficient range of vitamin E concentrations, and weak representativeness of vitamin E measurements. He also noted that smoking may modify the vitamin E requirement, thus obscuring the relationship of vitamin E to lung cancer.

Over 50 years ago, Tannenbaum (1942) demonstrated in animal experimental studies that a high-fat diet could increase risk of cancer. Since then, dietary fat as a possible cause of human cancer has been given attention in numerous epidemiological studies, particularly in relation to cancer of the breast and colon, where a very strong international correlation can be seen between risk of these cancers and indices of fat consumption. Wynder et al (1987)

pointed out that there was also a strong international correlation between lung cancer risk and fat consumption, and suggested that the dramatic rise in lung cancer risk in Japan since World War II may have been correlated with their switching from a traditional low-fat Japanese diet to a high-fat Western diet. Goodman et al (1992) reviewed evidence from epidemiological studies citing six which have reported a positive association between risk of lung cancer and a diet high in cholesterol or fat, and also reported new results from a study in Hawaii which were consistent with a positive relationship between lung cancer and dietary fat. At first sight, reports in various studies of a negative relationship of serum cholesterol with cancer risk might appear to conflict with the hypothesis that dietary fat intake increases risk of lung cancer. Law (1992), in a review of the evidence here, points out that most of the association can be explained by pre-clinical cancer depressing cholesterol levels. Although there is still a weak negative association between cholesterol levels and cancers observed after a period of follow-up long enough to exclude this explanation, Law believes it can be explained by smoking lowering high density lipoprotein (HDL) cholesterol. The prospective serum studies showing a negative relationship with cancer risk measured only total cholesterol, and a positive relationship of lung cancer risk with low density lipoprotein (LDL) cholesterol, increased by eating fatty food, is not excluded.

Generally, the literature seems quite conclusive in indicating that dietary factors are implicated in the aetiology of lung cancer. It is perhaps less easy to determine which specific dietary factors

are the most important. The evidence seems to be stronger as regards the negative relationships with fruit and vegetables, beta-carotene and vitamin C than it is as regards the negative relationship with vitamin E and the positive relationship with dietary fat. However it should be pointed out that there are strong inter-correlations between consumption of the various dietary items, and it is difficult to be completely certain which of the dietary items are most important or indeed whether all the associations reported with lung cancer necessarily indicate a causal relationship. It is difficult, if not impossible, to find comparison groups of individuals who differ only in respect of the dietary item under consideration, and multiple regression analyses do not, for various reasons, necessarily remove the possibility of an observed relationship being an artefact due to confounding by another dietary item (see e.g. Kolonel (1993)). Despite these reservations, the hypothesis that a diet high in antioxidants protects against lung cancer seems to enjoy considerable scientific support.

2. Evidence has recently accumulated that diet is an important risk factor for lung cancer specifically in non-smokers

In their review of the evidence on fruit and vegetables, Block et al (1992) note that "in a number of studies, significant effects have been found even within strata of smokers or non-smokers". However, in the studies she cites for lung cancer, the great majority of the cases studied were for smokers, and numbers of cases in non-smokers were often very small. Results were often not reported separately for non-smokers and, even when they were, were usually not statistically significant. For example, in the study of Seventh-Day Adventists by Fraser et al (1991), there were only 25 lung cancers in never smokers, and although risk of lung cancer was estimated to be about four times lower in those who ate fruit three or more times a week than in those who ate fruit less than three times, this difference was not statistically significant.

Exceptionally, Knekt et al (1993) reported a number of significant associations between diet and lung cancer incidence in non-smokers. In one of his studies 5254 subjects in Finland completed a dietary history and were followed up for up to 19 years, during which 121 lung cancers were seen, 26 in non-smokers. Among non-smokers, being in the lowest tertile of consumption was associated with a significant increased risk of lung cancer (compared to being in the highest tertile of consumption), for fruits and berries (RR = 6.8, 95% CI = 1.6-29.7), margarine (7.1, 1.6-31.6), and marginally for vitamin E (3.3, 1.0-11.3). Near significant increases were seen for beta-carotene (2.8, 0.8-10.0) and vitamin C (3.1, 0.9-10.7). In his other study, 144 lung cancer

cases, 22 non-smokers, were compared with 270 age-sex matched controls who had serum samples stored some years before. Again comparing tertiles, low consumption, among non-smokers, was associated with a significantly increased risk of lung cancer for vitamin E (6.6, 1.3-33.5), and with non-significant increases for beta-carotene (2.6, 0.7-8.9), retinol (4.4, 0.9-21.5), and selenium (1.6, 0.5-5.5). Non-smokers with all four micronutrients in the lowest tertile had a lung cancer risk that was 12.1 fold higher (95% CI 1.3-115.8) than non-smokers with no micronutrients in the lowest tertile.

A major source of data on lung cancer risk in non-smokers are those studies that have investigated possible effects of ETS. Because interest in this area is specifically on risk in lifelong non-smokers, such studies have typically collected data on much larger numbers of lung cancers in non-smokers than is the case for most of the studies to which Block et al (1992) referred. A number of these have collected data on diet. Below we summarize the relevant data:

1. Hirayama (1984), has presented detailed results from his large long-terms Japanese prospective study giving the joint relationship of lung cancer risk in non-smoking women to age, smoking by the husband, occupation and daily/non-daily consumption of green-yellow vegetables, based on 200 cases of lung cancer. From this table I have estimated that the age-adjusted relative risk for non-daily/daily consumption of green-yellow vegetables is 1.28 (95% CI 0.94-1.73). Elsewhere

Hirayama (1990), reported graphically relative risks among non-smokers of 1.00, 1.37 and 1.97 for respectively daily, occasionally and rare/none consumers of green-yellow vegetables, but did not give the statistical significance of this trend.

2. Gao (1987), based on a case-control study conducted in Shanghai, reported that, compared with those in the highest quartile (I) of consumption of carotene-rich foods, relative risks of lung cancer of 0.6(95% CI 0.5-0.8), 0.5(0.4-0.7) and 0.5(0.3-0.6) for those in quartiles II, III and IV. These results were for smokers and non-smokers together, but the authors note in the text that "the patterns were generally similar for smokers and non-smokers".

3. Shimizu (1988), based on a study conducted in Japan involving 90 non-smoking women with lung cancer and their age-matched controls, found no real evidence of a relationship between risk of lung cancer and frequency of various food items, including fruit and green-yellow vegetables.

4. Koo (1988) reported detailed results relating to diet in a study of Hong Kong Chinese women involving 88 lung cancer patients and 137 controls who had never smoked tobacco. Risks were presented in relation to tertiles of frequency of consumption of a range of different food items and nutrient levels, and were adjusted for age, number of live births and education. Compared with women in the high tertile, women in the low tertile had significantly increased risks of lung cancer for retinol (R=2.41, trend $p<0.05$), vitamin C (R=2.11,

$p<0.05$), fresh fruit ($R=2.39$, $p<0.01$) and "good diet" ($R=2.31$, $p<0.01$), a "good diet" being based on consumption of cruciferous vegetables, leafy green vegetables, carrots, beans/legumes, tofu/soy products, soup, milk and fresh fish. An increased risk for beta-carotene ($R=1.37$) was not statistically significant.

5. Kalandidi (1990) reported detailed results relating to diet in a study of Greek non-smoking women involving 91 lung cancer patients and 120 controls. After controlling for age, years of schooling, interviewer and total energy intake, the authors reported results of a multiple regression analysis in which significant ($p<0.05$) negative association was noted between lung cancer risk and fruit consumption ($RR=0.33$, 95% CI 0.13-0.86, for high to low quantiles of consumption). An almost significant negative association was also noted for vitamin C consumption ($RR=0.67$, 95% CI 0.42-1.05).

The five studies reviewed above, which all relate to Asian or Greek populations, are in general (with the exception of the study by Shimizu) all consistent with the notion that dietary factors affect lung cancer risk in non-smokers. This evidence has recently been considerably augmented by papers published relating to three very large US case-control studies.

6. Candelora *et al* (1992) presented detailed dietary results for a large case-control study in Florida for which ETS results had previously been reported by Stockwell *et al* (1992). Based on

124 non-smoking lung cancer cases and 263 non-smoking controls, they presented a striking variation in lung cancer risk among non-smokers in relation to various indices of diet. Compared with individuals in the highest quartile of vegetable consumption, those in the lowest quartile had an estimated five times greater risk of lung cancer (95% CI 2-10) with the dose-related trend statistic highly significant ($p<0.001$). Significant or near significant trends were also seen in relation to consumption of green and yellow vegetables ($p<0.001$), fruits ($p<0.05$), total carotene ($p<0.001$), beta-carotene ($p<0.1$), alpha-carotene ($p<0.001$), cryptoxanthin ($p<0.05$), vitamin A ($p<0.01$) and vitamin C ($p<0.01$). All these trends were in relation to a reduced risk with increasing consumption.

7. Alavanja et al (1993) presented detailed dietary results for a large case-control study in Missouri for which ETS results had previously been reported by Brownson et al (1992). Based on a total of 429 lung cancer cases (294 lifelong non-smokers and 135 long term ex-smokers), they presented evidence of a striking positive relationship between lung cancer risk and saturated fat consumption. Risks by quintiles were 1.0, 1.65, 1.81, 2.83, and 6.14 (trend $p<0.001$). There were also independent relationships of risk with consumption of beans and peas (negative) and with consumption of citrus fruits and juices (positive), with about a two-fold risk difference between high and low frequency of consumption.

8. Mayne et al (1994) presented detailed dietary results for a

large case-control study in New York State for which ETS results had previously been reported by Varela (1987) and by Janerich et al (1990). Based on a total of 413 lung cancer cases (192 never smokers and 231 long term ex-smokers) and a similar number of matched controls, Mayne et al presented relative risks of lung cancer by quartiles of consumption of a variety of individual food items and selected food groups. Consumption of greens (trend $p<0.01$), fresh fruits ($p<0.01$) and cheese ($p<0.05$) were associated with a significant dose-related reduction in risk of lung cancer, whereas consumption of whole milk ($p<0.01$) was associated with a significant dose-related increase. The authors concluded that dietary beta carotene, raw fruits and vegetables, and vitamin E supplements reduce the risk of lung cancer in non-smoking men and women.

3. There is strong evidence that smokers differ markedly from non-smokers in their diet, and that these differences tend to be in a direction that would predict a higher risk of lung cancer

Quite a large number of studies have compared smokers and non-smokers in respect of various aspects of diet. Without attempting a comprehensive review, results from a number of studies are summarized below.

Fehily et al (1984) studied a general population sample of 493 men aged 45 to 59 from Caerphilly who completed a seven-day weighed dietary record. They noted that there was no difference in energy intake of smokers and non-smokers but in general smokers had lower intakes of vitamins, minerals and dietary fibre. After adjusting for social class smokers were found to have a daily intake of vitamin C, total vitamin A, retinol and beta-carotene that was significantly less than that of non-smokers (including ex-smokers) by respectively 22%, 20%, 18% and 25%. Intake of fat was similar in smokers and non-smokers.

Whichelow et al (1988) studied 9003 adults representatively sampled from England, Scotland and Wales. Compared with non-smokers (including ex-smokers) smokers were found to be highly significantly less likely to eat breakfast, brown bread, and fresh fruit frequently and more likely to consume fried foods frequently.

Morabia and Wynder (1990) compared intakes of various dietary items by smoking status in 2115 white men and 1060 white women who were patients with conditions not related to tobacco or alcohol in hospitals in five US cities. In both sexes there was a very highly

significant tendency for intake of vegetables and of fruit to decrease progressively over the four groups: lifelong non-smoker and current smoker of 1-19, 20-39 and 40+ cigarettes per day.

Cade and Margetts (1991) obtained 24 hour dietary food records from 1115 men and 1225 women aged 35 to 54 in Ipswich, Wakefield and Stoke-on-Trent. Compared with lifelong non-smokers, current smokers were, in both sexes, found to have a significantly reduced intake of the following nutrients: vitamin C (by 16%), beta-carotene (by 30%), and vitamin E (by 13%). Although total fat intake was only slightly higher in smokers, the polyunsaturated/saturated ratio was significantly lower (by 11%).

Bolton-Smith et al (1991) compared daily nutrient intake and serum vitamin values for 79 smokers and 117 non-smokers randomly sampled from general practitioners' registers in Aberdeen and Glasgow. Compared with non-smokers (including ex-smokers) smokers had significantly reduced dietary vitamin C (by 19%), serum vitamin C (by 50%), dietary beta-carotene (by 17%), serum carotene (by 30%), and serum vitamin E (by 9%). Dietary vitamin E did not differ.

Suyama and Itoh (1992) conducted a mail survey on about 3000 Japanese subjects aged 65 years and older. A multivariate analysis of dietary frequency data regarding 15 food items on 931 male respondents suggested that frequency of intake of plant food, including vegetables and fruits, was lower in smokers than in non-smokers.

Margetts and Jackson (1993) obtained seven-day dietary records and blood samples from 1842 men and women representative of England, Scotland and Wales. Compared with non-smokers (including ex-smokers)

smokers were found to eat more white bread, sugar, cooked meat dishes, butter, and whole milk and less wholemeal bread, high fibre breakfast cereals, fruit and carrots. Smokers had lower intakes of polyunsaturated fat, protein, carbohydrate, fibre, iron, carotene and vitamin C. For the same dietary intake of carotenoids, smokers were more likely to have lower circulating serum beta-carotene concentrations than non-smokers. They noted that "smokers are at increased risk of chronic disease because their diets are different and because smoking creates an altered pattern of demand for specific nutrients".

Subar and Harlan (1993) administered a dietary interview, consisting of a 59-item food frequency questionnaire to a representative sample of 22,080 US adults. The 59 food items were selected to include foods which are the major contributors of nutrients in diet. Compared with never smokers, current smokers had significantly lower levels of daily intake of vitamin C (by 22%), carotene (by 8%), folate (by 8%) and fibre (by 10%) and significantly higher levels of fat (by 13%) and saturated fats (by 14%). For these six nutrients, intake varied by amount smoked so that heavy smokers were most discrepant from never smokers. Compared with never smokers, current smokers were also less likely to eat fruit, drink fruit juice, and eat vegetables other than potatoes.

Generally, the results from the papers considered are very consistent in showing that, compared to non-smokers, smokers have diets that are lower in fruit and green vegetables, beta-carotene,

vitamin C and vitamin E, and higher in saturated fat. All these differences are in the direction that would predict a higher risk of lung cancer.

4. Evidence is accumulating that, just as smokers have poorer diets than non-smokers, so do ETS-exposed non-smokers have poorer diets than non-ETS-exposed non-smokers.

None of the papers considered in section 3 compare the diets of ETS-exposed non-smokers and non-ETS-exposed non-smokers. Evidence that their diets might differ materially was first presented by Koo et al (1988) in a further paper based on her study of Hong Kong Chinese women who had never smoked tobacco, which has been referred to already in section 2. Koo et al used the controls from their study to compare women married to smokers with those married to non-smokers on 97 lifestyle variables. They concluded that the women with husbands who had never smoked had healthier lifestyles, being better off in terms of socio-economic status, being more conscientious housewives, eating better diets and with better indices of family cohesiveness. The major dietary differences were that the women married to never smokers more frequently consumed beans/legumes ($p<0.0001$), milk ($p<0.0001$), carrots ($p<0.0003$), cruciferous vegetables ($p<0.001$) and less frequently consumed pickled/salted vegetables ($p<0.0001$), chili ($p<0.0001$), and alcohol ($p<0.0001$). Koo et al did not attempt to estimate differences in intake of beta-carotene or specific vitamins.

Sidney et al (1989) investigated 2142 non-smokers receiving multiphasic health check-ups in Oakland in 1985 who satisfactorily completed questionnaires on smoking, alcohol consumption and diet. Compared with the 1786 non-smokers who reported no ETS exposure, the 356 non-smokers who reported some ETS exposure were found to have a highly significantly ($p<0.001$) lower intake of dietary carotene (6793 vs. 8697 IU/day). The reduction in dietary carotene

in relation to ETS exposure remained highly significant after adjustment for age, sex, race, weight, education and alcohol intake.

Le Marchand et al (1991) described results from a small study conducted in Hawaii in 1986. Eighty-two female non-smokers who were population controls in a lung cancer study completed a questionnaire on diet, alcohol intake and use of vitamin supplements and provided a sample of urine for cotinine analysis. Based on the cotinine analysis, subjects were divided into three groups according to presumed ETS exposure (undetectable, low, high). After adjustment for ethnicity, age, education and alcohol consumption, there were a number of significant relationships between ETS exposure and mean daily nutrient intake. Most notably, ETS exposure was associated with a highly significant ($p<0.001$) reduction in beta-carotene, with levels 5410, 3678 and 2764 in, respectively, the undetectable, low and high ETS exposure groups. Similar negative trends were also seen in vitamin A from foods and in other carotenoids with vitamin A activity, and with daily consumption of various fruits and vegetables, such as carrots, papaya and pumpkin.

Shibata et al (1992) reported results from a prospective study of residents of a retirement community in California. In 1981 data were collected on cigarette consumption and on dietary intake of beta-carotene, via questions on 44 vegetables and fruit items. Among the 5080 men, there was a clear difference in mean daily beta-carotene consumption according to smoking status ($p<0.001$). Compared with never smokers (8505 μg), current smokers had a 27% reduced intake (6178 μg) and past smokers a 9% reduction (7761 μg),

consistent with the findings described above in section 3. Based on data for 4018 spouse pairs, there was a striking correlation ($r = 0.46$, $p = 0.0001$) between beta-carotene intake of the husband and wife. After adjustment for own smoking status, there was a statistically significant ($p = 0.006$) trend of decreasing level of dietary beta-carotene with smoking by the spouse. Among never smokers, marriage to a smoker was associated with a 15% reduction in daily dietary beta-carotene. Exceptionally, in this study, no clear relationship of lung cancer risk to dietary factors was noted after adjustment for smoking habits. However only 125 cases of lung cancer were reported and very few would have been among lifelong non-smokers.

Using the same database for which Whichelow et al (1988) described differences between smokers and non-smokers (see section 2), Thompson and Warburton (1993) investigated differences in diet for never smokers living in smoking households or in non-smoking households. They reported that those individuals living in smoking households consumed fats more frequently, drank more alcohol and were less likely to eat root vegetables and cereal.

A more detailed analysis of the same database, the health and Lifestyle Survey, has been carried out by Thornton et al (1994). They identified 33 lifestyle factors generally associated with adverse health and compared their prevalence in current smokers (by amount smoked), ex-smokers (by time given up), in never smokers living with a smoker (passive smokers) and in other never smokers. Of the 33 risk factors, 27 showed a significantly higher prevalence in heavy smokers than in never smokers, and only two (obesity and

consumption of sweet foods) showed a lower prevalence. For many risk factors, prevalence increased with amount smoked, decreased with time of smoking cessation, and was increased in passive smokers. Dietary risk factors that were increased in passive smokers included high consumption of fried foods ($p<0.001$) and low consumption of fruits ($p<0.01$), salads ($p<0.05$), and breakfast cereal ($p<0.001$).

The reports described above seem consistent in suggesting that:

(i) there are significant differences in diet in relation to ETS exposure;

(ii) these differences are typically in the same direction as seen in relation to active smoking; and that

(iii) the magnitude of the differences in relation to ETS exposure, though smaller than those in relation to active smoking, are not very much smaller.

These results are not unexpected, bearing in mind the likelihood that a husband and wife will share a common diet to quite a considerable extent, a hypothesis given support by the observation of Shibata et al (1992) that dietary intake of beta-carotene of a husband and his wife are strongly correlated.

It is notable that, although there are by now over 30 published studies of the relationship of lung cancer to ETS among lifelong non-smokers, and although (as noted in section 2) some eight of these have reported findings relating diet to lung cancer, only one of these studies (Koo et al, 1988) has been referred to above in this section. The reason is that the great majority of these studies

that have collected data on diet have not presented results comparing diets of non-smokers according to any index of ETS exposure.

An exception to this is the study of Hirayama (1984) which did present a table showing the joint distribution of his lifelong non-smoking female population by green-yellow vegetable consumption (non-daily/daily) by husband's smoking habits, by occupation and by age. Using the data in that table it is possible to calculate age and occupation standardized frequencies of non-daily green-yellow vegetable consumption according to husband's smoking habits. In fact, in these data, there was little difference in frequency for women married to non-smokers (25.4%) and for women married to smokers of 20+ cigarettes a day (24.9%). Although these findings appear to conflict with the findings of the other studies noted above, it should be noted that Hirayama's questionnaire was very brief and no attempt was made to obtain detailed dietary histories, contrasting with the other studies for which results have been cited.

5. The association between ETS and lung cancer is weak

Lee (1993) has recently published a detailed review of 33 epidemiological studies of lung cancer for which results have been separately presented for lifelong never smokers. All of these studies reported results for women, with a further 10 also presenting results for men. Marriage to a smoking husband has been the most commonly used index of ETS exposure and using this index (or in some studies living with a smoker) Lee estimated by meta-analysis a combined relative risk for the 33 studies of 1.17 (95% CI 1.08-1.27) using unadjusted data or 1.14 (95% CI 1.05-1.23) using covariate adjusted data. Lee also estimated that heavy smoking by the husband was associated with a somewhat larger relative risk, estimated approximately at about 1.35. For men, based on far fewer lung cancers, marriage to or living with a smoker was associated with a larger relative risk, but with more variation (unadjusted RR 1.39, 95% CI 0.97-1.99; covariate adjusted RR 1.43, 95% CI 1.02-2.02).

Workplace and childhood ETS exposure are two other indices for which results have been quite frequently reported in epidemiological studies. Based on 14 estimates for each, mainly for women, Lee reported meta-analysis relative risks for these indices which were close to 1.0. (Workplace RR 1.02, 95% CI 0.93-1.12, unadjusted; RR 1.01, 95% CI 0.92-1.10, covariate adjusted. Childhood RR 0.94, 95% CI 0.84-1.05, unadjusted; RR 0.96, 95% CI 6.86-1.07, covariate adjusted).

The general impression of these results is that one is dealing with, at best, a very weak association. For workplace and childhood

ETS exposure the association does not appear to exist at all, while for ETS exposure from a smoking wife the association is not clearly significant. Though the association between lung cancer and smoking by the husband is quite highly significant, it is only quite weak. Relative risks less than 2.0 and especially those less than 1.5 are often cited as being susceptible to bias, and here we are only dealing with a relative risk estimated at less than 1.2.

6. Few studies of ETS and lung cancer have taken the possibility of confounding by diet into account

About half of the 33 studies considered by Lee (1993) appear to have collected data on diet, and although eight of them (see section 2) have reported results relating diet to risk of lung cancer, very few of them have attempted to take the possibility of confounding by diet into account when studying the relationship of ETS to lung cancer. It is particularly striking to note that the three large US case-control studies conducted in Florida, Missouri and New York State (see section 2, paragraphs 6-8) each published two papers, one on the role of ETS ignoring diet, and one on the role of diet ignoring ETS!

There actually appear to have been only three studies which have taken the possibility of confounding by diet into account when investigating the relationship of ETS to lung cancer. In one of these Hirayama found that frequency of daily green-yellow vegetable consumption varied little by husband's smoking status (as noted in section 4) and that adjustment for this, or other dietary factors (rice, meat, fish, milk, pickle, miso soup), did not materially affect the ETS/lung cancer relationship. As noted above, Hirayama's questionnaire was very brief and would not be considered adequate by modern standards for detailed investigation of the effects of diet.

In the second, the hospital case-control study of Kalandidi (1990) referred to in section 2, an unadjusted relative risk of 1.92 (95% CI 1.02-3.59) in relation to marriage to a smoker was found to increase to 2.11 (95% CI 1.09-4.08) after adjustment for total energy intake and fruit consumption. Since, in their data, total

energy intake was unrelated to lung cancer risk, and since (as noted in section 2) fruit intake was significantly negatively related to risk of lung cancer, this would seem to imply that in their data marriage to a smoker was associated with an increased consumption of fruit. However no direct data were presented to confirm this point. This would conflict with the results of other studies summarized in section 4. Conceivably, the increase in relative risk after adjustment might be some sort of artefact of their logistic multiple regression analyses. It should be noted that their relative risk estimates before and after adjustment have very wide confidence limits.

The third study which attempted to take potential confounding into account is the large US multicentre hospital case-control study of lifelong non-smoking women for which ETS results were initially reported by Fontham et al (1991). That paper reported a marginally significant 30% increased risk of lung cancer in relation to exposure to ETS exposure from the spouse, and also noted that their extensive questionnaire included data on diet. However diet was not taken into account at all in this paper. In a later paper Fontham et al (1993) noted that "an approximate 30% risk of lung cancer associated with spousal ETS exposure persisted after an additional adjustment was made for the consumption of vegetables (the most significant food or nutrient factor), family history of lung cancer, and employment in high-risk occupations or industries". However no detailed methodology or results were given to support the statement. Although no detailed results relating to diet from this study have been reported, some clue as to why adjustment had little or no

effect can be seen from an abstract of a paper published at a conference (Fontham et al 1992) which noted only small reductions in lung cancer risk in relation to increased dietary intake of vitamin C and alpha-carotene, and no relationship of risk with intake of total vitamin A, vitamin E, total carotenes, or beta-carotene.

In general it can be concluded that the published evidence from the ETS/lung cancer studies does not demonstrate that adjustment for potential confounding by diet has any material effect on the ETS relative risk estimated. However, given the very strong relationship of diet to lung cancer risk seen in the large Florida, Missouri and New York State studies, and given the quite consistent evidence (see section 4) that ETS exposure is associated with a poorer diet, it would be surprising if the picture did not change were appropriate results to be published from these studies.

7. Though confounding by diet has not yet been shown directly to be important in ETS/lung cancer studies, there is strong indirect evidence that it is

Given knowledge of the magnitude of the association of dietary variables with lung cancer risk and with indices of ETS exposure, it is possible to calculate the extent to which confounding by diet might bias the ETS/lung cancer relationship. For example, if one assumes that:

(i) a dietary variable (e.g. low beta-carotene consumption) increases risk of lung cancer by a factor R;

(ii) the prevalence of the dietary variable is PN in non-ETS-exposed non-smokers and PE in ETS-exposed non-smokers; and that

(iii) ETS exposure in fact has no effect on risk of lung cancer,

one can readily calculate that one will observe an apparent relative risk of lung cancer in relation to ETS exposure (B) of:

$$B = \frac{1 + PE(R - 1)}{1 + PN(R - 1)}$$

For example if R = 2, and we have PE = 0.6 and PN = 0.5, the bias B will equal 1.6/1.5 = 1.07. This bias will also multiply any true effects of ETS exposure.

More generally (details not given) it is possible to compute estimates of bias in relation to a dietary variable measured more precisely than present/not present, e.g. as a variable expressed as quintiles or even as a continuous variable.

Some of the authors of the studies considered in section 4 have attempted to produce estimates of bias in this way.

Sidney et al (1989) estimated the extent of confounding of the ETS/lung cancer relationship by carotene intake. Assuming that a decrease in carotene intake between the middle of the highest and the lowest quartiles of carotene risk would double the risk of lung cancer, they estimated that an observed relative risk of 2 for ETS and lung cancer would be reduced to a true relative risk of approximately 1.8 by adjustment for dietary carotene intake. Of course 2 is a completely inappropriate estimate of the observed relative risk of lung cancer in relation to ETS exposure. As already noted 1.15 to 1.20 is a more appropriate estimate for risk relating to smoking by the husband. The bias which Sidney et al (1989) estimate of 2/1.8 = 1.11 would explain a very substantial part of the observed relationship between ETS and lung cancer.

Le Marchand et al (1991) also tried to estimate how much of the ETS/lung cancer relationship could be explained by confounding by beta-carotene consumption, and came to very similar conclusions. Based on the observation, in their own case-control study, that women in the lowest quartile of beta-carotene intake had a risk of lung cancer 2.7 times that of those in the highest quartile of intake, they estimated that failure to adjust for beta-carotene as measured would result in a 10% overestimate of the ETS/lung cancer relative risk. Failure to adjust for the actual level of beta-carotene (i.e. taking measurement error of beta-carotene into account) would result in a 13% overestimate. In other words, an observed ETS/lung cancer relative risk of 1.13 could, according to these data, be wholly explained by confounding by beta-carotene.

Thornton et al (1994) presented data comparing age and sex adjusted prevalence of various dietary factors in lifelong non-smokers living or not living with a smoker. Using these data and various assumptions about the relative risk of lung cancer associated with these dietary factors, it is possible to estimate the magnitude of potential confounding by bias.

	Prevalence in non-smokers		Estimated bias assuming R =		
	Not living with smoker	Living with smoker	1.5	2.0	5.0
High fried food consumption	37.0%	50.2%	1.06	1.10	1.21
Low fruit consumption	34.3%	38.7%	1.02	1.03	1.07
Low salad consumption	49.8%	55.5%	1.02	1.04	1.08

R is the relative risk assumed in relation to the dietary factor.

As noted in section 2, a number of studies have shown quite strong relationships of diet to lung cancer in non-smokers, with relative risks in the range 2-5 or more. Bearing in mind that bias from multiple dietary factors may be substantially greater than that from individual dietary factors (see Thornton et al, 1994 for discussion), the results shown in the table above certainly add further support to the notion that a substantial part of the association of spousal smoking with lung cancer risk may be an artefact arising from confounding by diet. While there are other sources of bias in epidemiological studies of ETS and lung cancer (e.g. due to misclassification of active smoking status, confounding

by non-dietary risk factors, recall bias, publication bias, and inaccuracies in determining exposure, diagnosis, and confounding variables), there seems quite good reason to believe confounding by diet to be of quite major importance. It is one of the reasons "for suspecting that the observed effects of passive smoking on lung cancer may be partly, or even entirely, due to bias" (Peto, 1992).

8. Unless proper adjustment for dietary differences is conducted, reports of an association between ETS and lung cancer are uninterpretable

One major conclusion from the material considered here is that since there is good evidence that diet can have an important confounding effect on the ETS/lung cancer relationship, and since diet has hardly ever been taken into account in the ETS studies (only three out of 33 have even tried to do so), it is difficult, if not impossible, to assess validly the overall data. In order to start to interpret the association, it is vital that adjustment for diet be taken into account. Even then there will be problems, bearing in mind the well known difficulties of obtaining accurate data on diet.

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N.B. Numbers on left indicate sections in which the papers are cited.