Appendix 3

Review of papers since 2000 relating risk of lung cancer to potential confounding variables

INDEX

		Page
A.	FRUIT, VEGETABLES AND DIETARY FAT CONSUMPTION	A3-1
B.	AIR POLLUTION	A3-18
C.	ALCOHOL	A3-19
D.	EDUCATION	A3-23
E.	INCOME	A3-25
F.	OBESITY	A3-28
G.	OCCUPATION	A3-31
H.	PHYSICAL ACTIVITY	A3-38
I.	SOCIOECONOMIC FACTORS	A3-40
J.	CONCLUSIONS	A3-41
	REFERENCES	A3-42

A. FRUIT, VEGETABLES AND DIETARY FAT CONSUMPTION

1. Balder [1]

This was a case-control study nested within a prospective study in the Netherlands. The prospective study was on males and females, but the paper reports on males only. Table 5 on page 488 gave the RR and 95% CI for lung cancer per increment in 1 SD in factor score for dietary patterns, stratified by smoking status and histologic type of cancer and adjusted for age and energy. For never smokers there were 52 cases of lung cancer in a person time of 2,452, giving for "Salad vegetables pattern" values an RR of 1.21 (0.94 – 1.56), for Cooked vegetables pattern 0.84 (0.63-1.12) and for Pork, process meat and potatoes pattern 0.51 (0.33 – 0.77). Note there was a negative RR for smokers and former smokers for "Salad vegetables pattern," with values of 0.77 (0.65 – 0.90) and 0.90 (0.80 – 1.01) respectively.

2. Brennan [2]

This was a multicenter case-control study involving centers in countries in Europe (3 from Germany and 1 each from Sweden, France, Spain, UK and Italy) concentrating at looking at the effect of diet on lung cancer in non-smokers. The results, given in Table 2 on page 52, were for fruits and vegetables, males and females combined, adjusted for age, sex and center, with results divided into thirds. Particular results of interest were:

	Tertile 1	2	3	Linear trend
Fruit	1.0 139/273	0.9 (0.6-1.3) 124/251	1.0 (0.6-1.5) 212/371	0.81
Fresh vegetables	1.0 46/83	0.9 (0.7-1.1) 180/362	0.7 (0.5-1.0) 110/237	0.09

[Here and subsequently summary tables show odds ratios or relative risks (95% CIs) and numbers of cases/controls (or at risk) by level of dietary exposure, with p-values for linear trend where available.]

In Table 3 on page 53 results are given for consumption of meat, fish and dairy products, with particular results:

	Tertile 1	2	3	Linear trend
Eggs	1.0 110/206	1.0 (0.6–1.6) 154/306	0.9 (0.8–1.1) 232/519	0.63
Cheese	1.0 113/222	0.9 (0.7–1.2) 164/331	0.7 (0.5–1.0) 219/477	0.01
Butter	1.0 65/194	1.2 (0.9–1.5) 21/49	1.3 (0.9–1.9) 88/207	0.24
Margarine	1.0 98/189	0.7 (0.4–1.1) 19/53	0.7 (0.6–0.8) 57/208	0.05

It can be noted that combinations of protective foods often produced extra protection – with eating vegetables and cheese having an OR of 0.6 (0.5 – 0.7).

Individual results for particular centers have been reported by Nyberg [3] and Jöckel [4]. The results from Nyberg were used in our previous work on estimating the effects of confounding.

For estimating odds ratios the authors made use of what they called a "sandwich estimator" with reference made to a paper by White [5].

3. Breslow [6]

This paper was based on analysis of a cohort created by linking the US NHIS data with the National Death Index. All results were based on models using all the data, adjusting for sex and smoking, so data were not available for non-smokers on their own. It is worth noting that 41.8% were men, 47% were never smokers, 21% were ex-smokers and that when checking for interactions between the variables and smoking, there was only a significant effect for alcohol. Although there was no interaction, taking the results as applicable to never-smokers would not agree with our

previous work. Results for quartiles of consumption are given in Table 2 on pages 423 and 424. Particularly of interest were:

	Quartile 1	2	3	4	Linear trend
Fruit	1.0 35/39,880	1.2 (0.7–1.9) 46/41,087	0.8 (0.4–1.4) 31/39,865	0.9 (0.5–1.6) 42/39,893	0.489
Vegetables	1.0 36/40,478	1.0 (0.6–1.8) 38/41,474	1.3 (0.8–2.0) 49/41,078	0.9 (0.5–1.5) 35/41,088	0.786
Dairy produce	1.0 51/39,138	0.9 (0.5–1.4) 50/46,437	0.7 (0.4–1.2) 33/36,161	0.5 (0.3–0.8) 22/40,562	0.009
Added fats	1.0 31/40,763	1.1 (0.6–1.9) 38/39,894	1.0 (0.5–2.1) 36/39,447	1.2 (0.7–2.0) 52/42,152	0.603
Alcohol	1.0 52/47,779	0.7 (0.4–1.3) 23/31,894	1.0 (0.6–1.6) 32/41,061	1.3 (0.8–2.0) 50/41,026	0.101

4. Chan-Yeung [7]

This paper reports on a case-control study in Hong Kong. Unfortunately all the results are for smokers and non-smokers together, though there are values adjusted for smoking. These are given in Table 4 on page 137 and it is interesting to note that there seems to be an increase in OR for increasing consumption of vegetables and fruits and a decrease for increasing amounts of fatty food:

Women	ORs are adjusted for educational status and smoking		
	<15 p/wk*	15-30 p/wk	30+ p/wk
Fruit	1.0	0.58 (0.27–1.22)	1.25 (0.65–2.44)
	<45 p/wk	45-65 p/wk	65+ p/wk
Green vegetables	1.0	2.11 (0.91–4.86)	1.74 (0.86–3.52)
	<70 p/wk	70-100 p/wk	100+ p/wk
Fruit, tubers and green veg	1.0	1.60 (0.74–3.47)	1.86 (0.89–3.90)
	<1 p/wk	1-2 p/wk	>2 p/wk
Fatty food	1.0	0.94 (0.45–1.96)	0.45 (0.20–1.02)

*p/wk = portions/week

5. Darby [8]

This paper reported on diet in relation to smoking and lung cancer based on a very large case-control study in the UK. However, "there were only 26 subjects with lung cancer in the study who had never smoked, which was too few to provide useful data on diet and lung cancer among never smokers". It is also worth mentioning the footnote to Table 1 on page 729 which states "The number of males with lung cancer who were lifelong non-smokers is atypically low and should not be used to estimate relative risk. See Peto et al (2000) for further details." [9] Checking the Peto (2000) paper they seem to use the data from non-smokers in CPS II as the numbers of non-smokers is so small, but they don't seem to give a clue as to why the numbers are so small!

This paper shows no significant decreases in lung cancer risk for increasing consumption of vegetables or green vegetables. However, estimates of intake of carotene, carrots and tomatoes all showed some decreasing effects. Butter and milk showed some increase in risk with increasing dose while margarine showed decreasing risk with dose. The authors speculate about some extra confounder not being measured. They do also say "It is clear that the commonly observed association between carotene rich foods and lung cancer risk is partially confounded by smoking, since it is well established that smokers have a lower intake of carotene rich foods than non-smokers (Margetts and Jackson, 1993)." [10] and see also Margetts 1996 [11].

6. Feskanich [12]

This paper investigates fruit and vegetable consumption and risk of lung cancer by examining the women in the Nurses' Health Study (NHS) and the men in the Health Professionals' Follow-up Study. This gave sufficient numbers to be able to look at men, women, smokers and non-smokers separately. Table 4 gives RRs for total fruits, vegetables and fruits + vegetables for the various groups.

NHS Women Never Smokers	OR are adjusted for age, follow-up cycle, total energy intake and availability of diet data		
	Tertile 1	2	3
Total fruits	1.0	Not given	0.34 (0.16–0.72)
Total vegetables	1.0	Not given	0.94 (0.46–1.91)
Total fruit + veg	1.0	Not given	0.58 (0.28–1.18)

7. Hirvonen [13]

This paper was based on a large cohort study of men aged 50 – 69 years, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (ATBC). Enrolment took place in southwestern Finland between 1985 and 1988 and was restricted to men who smoked at least 5 cigarettes a day at the time of the questionnaire. This report was looking at flavonol and flavine intake in relation to cancer in smokers. Table 5 on page 793 does give relative risks for vegetables, fruit, berries, tea and wine, all of which show reductions with increasing consumption. However as this is only in smokers it will not be included in our files.

8. Holick [14]

This is another report on the ATBC study in Finland. Table 3 gives results for Fruits, vegetables and fruits + vegetables, but this is still a study on smokers only and will not be added to the database.

9. Hu [15]

This is a report on a case-control study in non-smoking women in Canada, with the data collected between 1993 and 1997. Detailed tables for vegetables and fruit are given in Table 2 on page 132 and for beverages are given in Table 3 on page 133. In particular there are the following RRs, adjusted for 10 year age, province, education, social class and total energy:

	Quartile 1	2	3	4	Linear trend
Total fruit	1.0 46/119	0.8 (0.4–1.5) 34/122	0.9 (0.5–1.6) 39/120	1.1 (0.6–2.0) 38/118	0.83
Total vegetables	1.0 40/118	1.3 (0.7–2.4) 49/138	1.3 (0.6–2.6) 29/98	1.4 (0.7–3.0) 41/127	0.37
Total veg, fruit and juices	1.0 42/121	1.1 (0.6–2.1) 46/121	1.0 (0.5–1.9) 29/120	1.3 (0.6–2.6) 42/120	0.63
French fries or fried potatoes	1.0 59/184	0.8 (0.5–1.4) 45/165	1.7 (1.0–3.0) 53/120		0.05
Tea (cups per week)	0 1.0	1–7 0.6 (0.3–0.9)	>7 0.4 (0.2–0.7)		0.0008
Alcohol (servings per week)	0 1.0	1 0.8 (0.5–1.4)	>1 0.8 (0.5–1.2)		0.25

Data on occupational exposure to asbestos, oil, pesticides, herbicides, radiation sources and wood dust are given in Table 4 on page 134.

Note that this data set was also reported on by Johnson [16], though in that paper they only used those cases with a relatively complete history of residential passive smoke exposure.

10. Jansen [17]

This paper looks at some of the data from the Seven Countries study, a cohort study in men aged 40 – 59, initiated between 1958 and 1964. Dietary intake of the Finnish, Italian and Dutch survivors was assessed in 1970 and information on survival was available up to 1995. Table 1 gives some baseline figures for current and non smokers (never + ex), but the main results in Table II gives results only for smokers. Figures 2a and 2b give relative risks of lung cancer for nonsmokers, light and heavy smokers by consumption of (a) fruit and (b) vegetables, relative to heavy smokers with a low consumption of the dietary variable considered. This gives relative risks for nonsmokers of 0.07, 0.07 and 0.14 for fruit consumption and 0.1, 0.17 and 0.1 for vegetable consumption. No CIs are available for these figures, but there is an impression of a fall in risk for heavy smokers (1, 0.47, 0.4 for fruit, 1, 0.92 0.64 for

vegetables) but not for nonsmokers. However, there were only 38 lung cancer deaths in nonsmokers, of which only 10 were in never smokers.

11. Kreuzer [18]

This paper is based on a case-control study in Germany conducted between 1991 and 1996, but looking specifically at the non-smoking women. Data for RRs for lung cancer in relation to the consumption of fruits, vegetables, meat, fish and dairy products are given in Table IV on page 710. These are adjusted for age and region. In particular:

	Nev/lm/lw/w[a]	Sw	Daily	Linear trend
Fruit	1.0 17/34	0.55(0.28–1.09) 36/98	0.66 (0.37–1.19) 177/403	0.94
Fresh vegetables	1.0 22/43	0.57 (0.33–0.99) 147/326	0.45 (0.25–0.82) 60/165	0.03
Meat	1.0 16/63	1.57(0.90–2.75) 142/311	1.61 (0.90–2.89) 72/157	0.44
Sausages	1.0 30/71	0.99 (0.60–1.62) 81/182	0.99 (0.61–1.62) 120/279	0.43

	Nev/lm/lw	W	Sw/Daily	Linear trend
Eggs	1.0 52/102	0.68 (0.44–1.05) 70/186	0.69 (0.46–1.05) 107/245	0.22

	Nev/lm	Lw/w/sw	Daily	Linear trend
Milk	1.0 78/159	0.98 (0.67–1.45) 81/160	0.65 (0.44–0.95) 72/215	0.16

[a] Nev, never; lm, less than monthly; lw, less than weekly; w, weekly; sw several times weekly

Note that Table V gives some odds ratios for various occupations.

12. Liu [19]

This study reported on data from two large cohort studies in Japan, the first for men and women aged 40-59, interviewed in 1990 and the second for men and women aged 40 – 69, interviewed in 1993. Follow-up was to the end of 1999. Table 3 on page 353 gives RRs for lung cancer by food consumption for never and ever smokers separately. The relevant data for never smokers (males and females combined) adjusted for age, gender, area, sports, frequency of alcohol intake, BMI, vitamin supplement use, salted fish and meat and pickled vegetables, were:

	Low	Middle	High	Linear trend
Fruit	1.0 25/110627	1.17 (0.25–5.48) 26/143425	2.09 (0.56–7.83) 55/189726	0.22
Vegetables	1.0 28/130452	0.96 (0.37–2.45) 31/150722	1.37 (0.79–2.37) 47/162604	0.20
Veg + fruit	1.0 24/121244	1.34 (0.52–3.42) 32/149661	1.95 (0.84–4.52) 50/172873	0.17

Note that the authors claim that references Mayne [20], Brennan [2], Nyberg [3] and Feskanich [12] have showed strong protective effect of diets high in fruit and vegetables for lung cancer.

13. Michaud [21]

This paper investigates specific carotenoids and risk of lung cancer by examining the women in the Nurses' Health Study and the men in the Health Professionals' Follow-up Study. These data have already been looked at for vegetable and fruit consumption in Feskanich [12] given above. In this study subjects who never smoked had a 63% lower incidence of lung cancer for the top compared to the bottom quintile of α-carotene, RR 0.37 (0.18 – 0.77).

14. Miller [22]

This study was a large prospective investigation of diet and cancer, the European Prospective Investigation Into Cancer and Nutrition (EPIC). It involved 478,021 individuals recruited from 10 European countries, who completed a dietary questionnaire during 1992 – 1998, with follow-up to December 1998 or 1999. Some centres had additional active follow-up to June 2002. Table V on page 274 gave RRs for lung cancer by quintiles of fruit and vegetable consumption for life-long nonsmokers. The relevant data for sexes combined, adjusted for weight, height, sex and centre are:

	Quintile 1	2	3	4	5	Linear trend
Total fruit	1.0 13 / -*	1.02 (0.48-2.16) 19 / -	0.64 (0.29-1.42) 14 / -	1.19 (0.59-2.39) 32 / -	0.33 (0.13-0.83) 10 / -	0.2429
Total vegetables	1.0 18 / -	0.56 (0.24-1.28) 10 / -	1.14 (0.56-2.33) 20 / -	0.98 (0.47-2.04) 21 / -	0.99 (0.45-2.21) 19 / -	0.6741

* Number of controls not given

15. Miller [23]

This was an earlier report than that given above in (14) and thus has been superseded.

16. Mulder [24]

This is another report on the Seven Countries Study already referred to above in Jansen [17]. This time an attempt was made to estimate dietary consumption for all of the cohorts involved. This involved making various assumptions for each of the countries, but it did increase numbers to a state where analyses involving non-smokers could be given. The following RRs for 25-Year lung cancer mortality in never smokers, adjusted for average age and energy intake are given in Table IV on Page 668:

	Unit of change = change of 10% of the average dietary intake over the 16 cohorts	RR (CI)
Fruit	13 g	0.99 (0.93–1.04)
Total vegetables	18 g	0.86 (0.67–1.08)
Total fat	12 g	0.96 (0.75–1.27)

17. Neuhouser [25]

This paper described an analysis of the data from the β-carotene and Retinol efficacy Trial (CARET) in the US run from 1989 to 1996. Follow-up had been continued to 2003 and the analysis examined the effects of fruits and vegetables in the subjects' diet as opposed to the supplements of β-carotene and retinol that the treatment arm of the trial had been given. The study was restricted to people thought to be of high risk of lung cancer, that is heavy smokers or asbestos exposed people. As such it has no information for non-smokers, though it is interesting to note that they did find a reduction in risk with increasing fruit and vegetables, but only in the arm of the trial not given the supplements.

18. Ozasa [26]

This paper was based on the Japan Collaborative Cohort (JACC) Study, a prospective trial established in 1988 – 1990 with follow-up for deaths continued until the end of 1997. It contained both males and females aged between 40 to 79 from 45 areas in Japan. Table V on Page 1266 gave details of hazard ratios for lung cancer deaths using Cox proportional hazard models for female, nonsmokers divided by various dietary factors. In particular we have the following RRs adjusted for age and parental history of lung cancer:

	≤1-2/w	3-4/w	Almost every day	Linear trend
Vegetables (Green-leafy)	1.0 23/130087	1.19(0.68–2.09) 27/118378	1.35 (0.79–2.30) 35/126081	0.26

	≤1-2/m	1-2/w	3-4/w+	Linear trend
Oranges	1.0 8/42090	0.95(0.38–2.34) 12/68271	1.18 (0.54–2.57) 53/223275	0.053
Fried foods	1.0 15/96003	1.47(0.79–2.70) 35/165130	1.91 (0.98–3.72) 24/83589	0.056

19. Rachtan [27]

This describes a case control study of lung cancer in Polish women in Cracow. Cases were women admitted to hospital between 1 March 1991 and 31 December 1997. From Table 1 on Page 390 we learn that 54 cases and 251 controls never smoked. There was also the impression of an effect of vodka drinking as well as of smoking. Thus in Table 3 on Page 392 ORs for lung cancer are given for non-smoking non-drinkers and for non-smoking vodka drinkers separately for extremes of consumption of vegetables, fruits and margarines. In particular:

	Non-smoking non-drinkers	Non-smoking vodka drinkers
Total cases/controls	23/179	31/72
Carrots	5+ times/wk (vs rarely) 0.10 (0.03–0.36)	5+ times/wk (vs rarely) 0.05 (0.01–0.37)
Other vegetables	Every day (vs rarely) 0.10 (0.01–0.75)	Every day (vs rarely) 0.25 (0.05–1.19)
Fruits	0.38 (0.15–0.98)	0.30 (0.11–0.78)
Margarine	3+ times wk (vs rarely) 0.19 (0.07–0.54)	3+ times/wk vs rarely 0.23 (0.09–0.60)

20. Rylander [28]

This paper relates to a case control study of lung cancer in West Sweden undertaken from 1989 to 1994. Cases were 75 years and younger and of Scandinavian birth. Results for lung cancer risk for non-smoking men and women (combined) are given in Table III on Page 741 for quartiles of vegetable consumption, and in Table IV on Page 742 for fruit consumption. The quartiles for females were defined as 0–4, 4.1–8.9, 9.0–14.1 and >14.1 times/week for vegetables and 0–7.4, 7.5–11.9, 12.0–14.9 and >14.9 times a week for fruit. The results for vegetable/fruit consumption, adjusted for age, gender, ETS at home or work and fruit/vegetable consumption, were as follows:

	Quartile 1	2	3	4
Vegetables	1.0 15/75	0.92 (0.42–1.91) 17/95	0.51 (0.21–1.26) 9/100	0.37 (0.15–0.97) 8/114
Fruit	1.0 9/82	1.76 (0.71–4.36) 16/83	1.38 (0.55–3.74) 15/109	0.99 (0.36–2.74) 9/110

Note that in the paper the number of controls in Quartile 1 was given as 2 for fruit in Table IV. Checking the number of controls in Tables I and III the value 82 would allow the marginal tables to correctly add up to 384. This value also makes sense in terms of the relative risks and so that is the value that has been used.

21. Schabath [29]

This paper described a case-control study looking at the effect of photestrogens on lung cancer risk. These are plant-derived nonsteroidal compounds with weak estrogen-like activity. The cases and controls were US residents, with cases drawn from The University of Texas Cancer Center between July 1997 and October 2003. Table 3 on Page 1497 gives the top five food sources for each phytoestrogen examined, with 77% of phytosterol beta-sitosterol and 89% of ligan precursors matairesinol coming from tea (mainly black tea). Table 6 gave risk of lung

cancer for non-smokers by quartiles of different phytoestrogens, adjusted for age, sex, ethnicity, education, income, body mass index and total energy:

	Quartile 1	2	3	4	Linear trend
Total phytosterols	1.0 87/72	0.63 (0.36–1.09) 55/73	0.57 (0.34–0.97) 63/73	0.63 (0.37–1.07) 61/72	0.06
Total isoflavones	1.0 75/72	0.72 (0.42–1.23) 61/73	0.81 (0.47–1.41) 68/73	0.53 (0.30–0.93) 62/72	0.25
Total ligans	1.0 71/72	0.89 (0.52–1.53) 69/73	0.73 (0.43–1.25) 65/73	0.66 (0.38–1.14) 61/72	0.06

As such these results are more indicative of some extra underlying substances that have yet to be examined fully than values to be added to the database.

22. Shen [30]

This paper described a case-control study looking at the effect of dietary folate intake and lung cancer risk in former smokers. The cases were taken from a sequential sample of confirmed lung cancer cases in The University Texas Cancer Center from July 1995 to July 2001. Significant reductions in lung cancer were seen for increasing levels of food folate, but as these findings were only given for ex-smokers they cannot be included in our database.

23. Shibata [31]

This study is of a cohort of men living in a retirement community in California in the US, followed up from June 1981 to December 1989 (the Leisure World Study). No results were given just for nonsmokers, though adjusted RRs showed small non-significant *increases* in risk of lung cancer with increasing fruit and vegetable consumption. No effect was seen with β-carotene.

24. Skuladottir [32]

This paper is based on men and women in the prospective cohort study "Diet, Cancer and Health" initiated by the Danish Cancer Society. Recruitment was between December 1993 and May 1997, with follow up with the Danish Cancer Registry obtained to the end of 2001. Table 2 on Page 5 suggests a lower intake of fruits and vegetables for current smokers than for never smokers – 109 vs 164.9 g/day for fruits and 138 vs 169.4 g/day for vegetables. When looking at the lung cancer risk by fruit/veg consumption there was a very large decrease in risk for increasing consumption when smoking was not allowed for, which was ameliorated by adjusted for various indices of smoking. However there was still indications of an effect when rates where fully adjusted for smoking. There were only nine non-smoking cases and so no separate data on nonsmokers were available.

25. Takezaki [33]

This paper concerned a 14 year population based prospective study in Japan with particular interest in fish consumption. The study started in April 1985 and follow-up was until December 1999 and was for all male residents aged 40 or more and female residents aged 30 or more in the Aichi Prefecture. Only 38 lung cancer cases were seen in the males and 13 in the females. There seemed to be a very large reduction in lung cancer risk with increasing levels of fish consumption. No data were available just for non-smokers.

26. Voorrips [34]

This paper relates to the Netherlands Cohort Study on diet and cancer, a prospective cohort study started in September 1986. The study was of men and women aged 55–69 originating from 204 municipalities with computerized population registries. After 6.3 years of follow-up over 1000 lung cancer cases were identified. Analyses were carried out using a case-cohort approach – finding a sub-cohort to match the cases of lung cancer. Table 7 on Page 113 gave RRs for lung cancer by

quintiles of fruit or vegetable consumption for never smokers. The relevant data, adjusted for highest educational level, family history of lung cancer, age and sex, were:

	Quintile 1	2	3	4	5	Linear trend
All fruit 62 cases	1.0	0.9 (0.4–2.3)	0.7 (0.3–1.9)	0.7 (0.3–1.7)	1.4 (0.6–3.2)	0.44
All vegetables 57 cases	1.0	1.1 (0.4–3.1)	2.1 (0.8–5.6)	2.3 (0.9–5.8)	1.8 (0.7–4.7)	0.06

Note that the paper claims inverse associations with lung cancer, but for non-smokers the effects are, if anything, of an increasing risk with increasing consumption.

27. Voorrips 2 [35]

This is a second paper on the Netherlands Cohort Study mentioned above (26) [34]. This paper concentrated on antioxidants, such as α-carotene and β-carotene, and folate intake. Table 5 gave RRs for lung cancer for never smokers by tertiles of intake, adjusted for highest educational level, family history of lung cancer, age and sex:

Cases: n=35 Subcohort: n = 203	Tertile 1	2	3	Linear trend
α-carotene	1.0	1.32 (0.46–3.79)	1.61 (0.61–4.21)	0.27
β-carotene	1.0	2.35 (0.83–6.65)	1.98 (0.75–5.26)	0.14
Lutein,zeaxanthin	1.0	0.83 (0.29–2.35)	1.35 (0.56–3.26)	0.42
β-cryptoxantin	1.0	0.50 (0.18–1.41)	0.86 (0.36–2.06)	0.76
Lycopene	1.0	0.92 (0.32–2.65)	1.54 (0.61–3.90)	0.26
Vitamin C	1.0	0.72 (0.26–1.99)	0.67 (0.25–1.79)	0.39
Vitamin E	1.0	0.80 (0.32–2.02)	0.67 (0.26–1.67)	0.32
Folate	1.0	1.04 (0.39–2.77)	1.09 (0.44–2.72)	0.82

Though there seems to be little going on in non-smokers, risk did seem to reduce for current smokers, with β-cryptoxantin, Vitamin C and folate showing highly significant decreases in risk with increasing consumption.

28. Wright [36]

This paper looks at the effect of dietary carotenoids and vegetables on lung cancer risk in women, using the Missouri Women's Health Study. This was a case control study in the US of women with incident primary lung cancer, aged between 35 and 84, undertaken between 1 January 1993 and 31 January 1994. Table 4 on page 91 gave ORs separately for never and former smokers combined and for current smokers. It seems clear the effects are less strong in the never and former smokers than in the current smokers, but there are no data available for the never smokers to add to our database.

29. Zhong [37]

This paper relates to a population-based case-control study examining links between lung cancer and green tea consumption for women in Shanghai in China. The study used incident cases of lung cancer diagnosed between February 1992 and January 1994 with the controls randomly selected from the Shanghai residential registry, frequency matched to the expected age distribution of the cases. Table 2 on Page 698 gave RRs for lung cancer for non-smokers and smokers separately and by amount of tea consumed. The following results for non-smokers, adjusted for age, income, number of years of exposure to environmental tobacco smoke at work, high-risk occupation, family history of lung cancer, intake of dietary vitamin C, cooking food at high temperature, and respondent status, were given:

Cases: n=35 Subcohort: n = 203	Non-regular	1-500 (g/year)	501-1500 (g/year)	>1500 g/year
Green Tea	1.0 431/481	0.80 (0.45–1.42) 27/37	0.62 (0.36–1.08) 30/47	0.46 (0.22–0.96) 13/29
Other Tea	1.0 431/481	0.29 (0.05–1.52) 3/7		

Note that:

a) no effect was found in smokers

b) smokers drank less tea than non-smokers

c) no important associations were found with other dietary items such as fat and protein.

d) the authors mentioned nine other studies of tea and lung cancer, five of which showed no meaningful association [38-42], two significant increases, Tewes [43] and Kinlen [44], and two significant decreases with increasing consumption, Ohno [45] in Japan with an RR for women of 0.38 (0.12 – 1.18) and Mendilaharsu [46] in Uruguay with an RR for heavy drinkers of black tea of 0.34 (0.14 – 0.84). Note that the papers showing significant increases did not look at nonsmoking women only.

e) In Table 3 of their paper they produce a very interesting sensitivity analysis looking at the confounding effect of active smoking and green tea drinking. A high odds ratio of 1.69 for risk of lung cancer due to green tea drinking reduced to 1.23 when adjusted for number of cigarettes, to 1.09 when adjusted for pack years and to 0.94 when adjusting for pack years using techniques that allow for continuous variables.

30. Seow [47]

This extra paper was discovered by PNL checking papers on ETS and Lung Cancer. This paper is based on a hospital based case-control study of women in Singapore in China. The data were gathered between April 1996 and December 1998. Table II on page 368 gives RRs for smokers and for non-smokers by various dietary factors. In particular, we are given the following RRs for all lung cancer for lifelong non-smokers, adjusted for age, place of birth and first-degree relative with history of cancer (yes/no):

	Tertile 1	2	3	Linear trend
Total vegetables	1.0 62/208	0.93 (0.62–1.40) 63/232	0.78 (0.51–1.20) 51/223	0.3
Fruits	1.0 71/198	0.63 (0.41–0.97) 54/235	0.60 (0.39–0.93) 51/230	0.03
Soy foods	1.0 80/209	0.57 (0.38–0.86) 51/232	0.53 (0.34–0.81) 45/221	<0.01

B. AIR POLLUTION

1. Zhou [48]

This paper describes results of a small case-control study in Shenyang, China. It does not separate out results for non-smokers.

SUMMARY FOR AIR POLLUTION

There are no relevant data provided. Incorporating air pollution into the scheme of things would in any case be extremely difficult given the numerous indicators of air pollution.

C. ALCOHOL

1. Benedetti[49]

This paper reports on two population case-control studies in Montreal, one in men and the other in both sexes. Table 5 on p 475 gives results within strata of smoking, defined as light, moderate and heavy smokers. For men, the light category included smokers, but for women the light category was defined as never smokers. Only the results for women are relevant.

Women Study II	OR adjusted for age,respondent status,ethnicity,SES and schooling/n cases		
	Never	1-6	7+ drinks/wk
Total alcohol	1.0/25	0.2(0.0-0.6)/3	1.1(0.4-3.3)/5
Wine	1.0/27	0.2(0.1-0.6)/3	0.7(0.2-0.5)/3
	Never	1+ drinks/wk	
Beer	1.0/31	0.5(0.3-0.9)/2	
Spirits	1.0/29	0.8(0.5-1.5)/4	

2. Boffetta[50]

This paper compares the incidence of various cancers (including lung) in 182667 patients with a hospital discharge of alcoholism with that of the national population. The analyses do not relate to smoking or ETS at all, data on which would not have been available on the patients. ETS is not even mentioned in the paper.

3. DeStefani[51]

This paper describes a case-control study in Uruguay. Table 2 presents results relating ml ethanol per day to risk, with various adjustments for smoking, but no results are given for never smokers. Only 4 never smokers had lung cancer.

4. Djoussé[52]

This paper presents long-term follow-up results from the Framingham study. Results relating risk to alcohol intake are only presented for the whole population with adjustment for smoking, and not for never smokers alone.

5. Freudenheim[53]

This paper describes a case-control study in western New York. While Table 2 presents results adjusted for smoking, no results for never smokers alone are given.

6. Nishino[54]

This paper describes long-term follow-up (from 1988-1999) of men aged 40-79 living in Japan. Table 3 on p 53 presents some results for never smokers.

Drinking	Person-years	No. of deaths	HR*
Never	13368	5	1.00
Ever	36575	13	1.22 (0.43-3.45)
Current <25 g/day	21297	7	1.10 (0.35-5.31)
25-49.9 g/day	9607	1	0.37 (0.04-3.18)
≥50 g/day	3331	1	1.15 (0.13-9.98)
Ex-drinkers	2339	4	4.20 (1.12-15.72)

* Adjusted for age, family history of lung cancer, intake of green-leafy vegetables, oranges and fruits other than oranges

7. Zang[55]

This paper describes results from a case-control study conducted between 1969 and 1994 in hospitals in 8 US metropolitan areas. Controls excluded patients with smoking or alcohol related illnesses. Table 4 on p 365 presents odds ratios (adjusted for BMI, age and current cigs/day) for males only for <1 vs ≥5 whiskey-equivalent current daily alcohol intake of 1.1 (0.9-1.3) for current smokers only based on 874 cases and of 1.2 (1.0-1.4) for current and never smokers combined based on 911 cases. Whether it is possible to obtain valid estimates of the odds ratio for never smokers could be investigated. Table 7 on p 366 also presents results relating current alcohol use to lung cancer in non-smokers. The number of cases considered (53) seems far too low to include ex-smokers (judging by data in Table 1 implying there were over 1000 lung cancers in ex-smokers) and one can probably assume the data were for never smokers. These are:

Whiskey-equivalent ounces per day	Odds ratios adjusted for age and BMI*	Cases
0	1.0	23
1-5.9	1.2 (0.7-2.1)	26
6+	0.7 (0.2-2.0)	4

* Inferred from final paragraph of p 361

8. Rachtan[56]

This is the same case-control study of Polish women as considered under diet (study 19) but the paper is a different one. The controls were next-of-kin of patients without tobacco-related cancer. The relevant results for lifelong non-smokers are given in Tables 5, 6, 7 and 8 on pp 124 and 125.

	Cases	Controls	OR (95%)*
Average intake of vodka (g/wk)			
0	23	179	1.00
<100	25	69	2.26 (1.06-4.85)**
≥100	6	3	15.0 (2.34-96.00)**
Any	31	72	3.47 (1.88-6.39)
Amount of alcohol (g/wk)			
<1	23	198	1.00
≥1-4	15	37	3.89 (1.82-8.32)
≥4-8	7	9	8.76 (2.81-27.29)
≥8	9	7	12.06 (3.94-36.91)

Grams per wk	Mean for cases	Mean for controls	p
Vodka	11.7	1.9	0.0000
Wine	18.3	4.6	0.0219
Beer	25.9	5.5	0.4690
Total alcohol	6.7	1.3	0.0000

* Odds ratios are adjusted for age except where indicated by **

** Adjusted for age, passive smoking, consumption of milk, butter, margarine, cheese, meat, fruit, vegetables, carrots, spinach, siblings with cancer, tuberculosis, place of residence, occupational exposure to coal and other dusts, rubber, acid mist, solvents, metals and other chemicals

SUMMARY FOR ALCOHOL

Of the 8 papers provided, 4 are of no use for the project. The other 4 papers are all based on small numbers of cases in drinking never smokers (8 in study 1 – Benedetti[49], 13 in study 6 – Nishino[54], 30 in study 7 – Zang[55] and 31 in study 8 – Rachtan[56]), with the

Rachtan study having results very different from those in the other studies. Given that the literature on lung cancer and alcohol generally shows little or no association once smoking is adjusted for[57] it seems a waste of effort to try to include alcohol as an additional factor in the analyses.

D. EDUCATION

1. Braaten[58]

This paper describes results from follow up to 2001 of Norwegian women responding to an extensive questionnaire in 1991/2 or 1996/7. The results given in Tables 2 and 3 on pp 2594 and 2595 only relate to the whole population and not to never smokers.

2. Chan-Yeung[7]

This study has already been considered under diet (study 4). No results relating education to lung cancer risk are given for never smokers.

3. Dreassi[59]

This is not an epidemiological study at all, but an ecological analysis fitting time trends in socioeconomic factors to time trends in lung cancer. No data on smoking are used.

4. Huisma[60]

This paper describes analyses based on national databases which linked vital registries to population censuses. Data on smoking were not collated or analyzed.

5. Louwma[61]

This paper describes results from a Dutch prospective study followed up from 1991 to 1998. Analyses relating education to lung cancer risk are not presented separately for never smokers.

6. Mackenbach[62]

As with Huisma (no 4), this paper describes analyses based on national databases for which smoking information was not available.

7. Martikainen[63]

This paper describes results of a follow-up study of Finnish male smokers that took part in a randomized trial of alpha-tocopherol and beta-carotene. There were no never smokers in this study.

8. Regidor[64]

This paper describes results based on a study in Spain involving mortality registry records and linked population census data. Smoking was not considered in the study, presumably as data were not available in the mortality records.

9. Ruano-Ravina[65]

This paper describes the results of a population-based case-control study conducted in Spain. Although there are some limited results for never smokers, they relate to occupation not education and will be considered elsewhere.

10. Steenland[66]

This paper describes detailed results relating education to mortality from a variety of causes based on the well known CPS-I and CPS-II studies. While results are presented adjusted for smoking, no results are given specifically for never smokers.

SUMMARY FOR EDUCATION

None of the references provided under the heading education add anything new to the data considered in the original analyses. However, there are data in references considered later (see income study 1 – Gorlova[67] and study 2 – Mao[68]).

E. INCOME

1. Gorlova[67]

This paper describes a hospital case-control study in Texas, USA involving 280 never smoking cases and 242 healthy controls who were also never smokers. The controls had never had cancer (except nonmelanoma skin cancer) and were matched on age, sex and ethnicity. Some unadjusted results for income and education are given in Table I on page 1799, but only for sexes combined.

	Cases	Controls	p	RR (95% CI)*
Education (years; mean ± SD)	14.6±3.5	14.1±2.9	0.11	
Income (per year)				
<$40,000	89	59	0.006	1.00
$40,000 to <$75,000	66	88	(trend)	0.50 (0.31-0.79)
$75,000+	101	79		0.85 (0.55-1.32)

*Estimated from numbers

No adjusted results are given. Neither income nor education was included in other analyses so no results adjusted even for age are available.

2. Mao[68]

This paper describes a case-control study in 8 Canadian provinces involving 3280 histologically confirmed lung cancer cases and 5073 population controls. Table 5 on page 814 gives odds ratios for never smokers for education, income and social class, adjusted for age, province, ETS exposure and consumption of vegetables, vegetable juices and meat. Table 2 on page 812 gives number of never smoking controls by sex and the 3 factors.

	Controls	Males OR (95% CI)	Controls	Females OR (95% CI)
Education (years)				
1-8	77	1.0	171	1.0
9-13	271	0.7 (0.3-2.0)	649	0.6 (0.4-0.9)
14+	319	0.9 (0.3-2.4)	430	0.6 (0.4-1.1)
Total	667		1250	
Family income				
High income	124	1.0	172	1.0
Upper middle	198	0.5 (0.2-1.4)	299	1.3 (0.7-2.3)
Low middle	104	1.2 (0.5-3.1)	222	0.8 (0.4-1.6)
Low	92	0.8 (0.3-2.5)	200	1.7 (0.9-3.3)
Total	518		893	
Social class				
I	69	1.0	43	1.0
II	165	1.2 (0.4-3.6)	356	0.9 (0.5-1.5)
IIIN	137	0.7 (0.2-2.2)	404	0.8 (0.5-1.3)
IIIM	155	0.6 (0.2-1.8)	100	0.7 (0.4-1.6)
IV	72	0.6 (0.2-2.4)*	126	1.0 (0.5-1.9)
V	28		42	1.2 (0.5-2.9)
Total	626		1071	

*Social class IV + V combined

According to Table 3, the total numbers of never smoking subjects are:

Males : 45 cases and 680 controls

Females : 161 cases and 1271 controls

but numbers of cases by factor level are not given.

3. Neuberger[69]

This paper describes a case-control study in Iowa women involving 413 lung cancer cases and 614 population controls aged 40-84. Some results of multivariate analyses are shown for the never smokers (56 cases and 414 controls based on Table 1). In the analyses of the total population (Table 2) only family history of kidney and bladder cancer and any lung disease emerged as significant factors. Table 3 presents additional analyses for living cases and controls only. Again only family history of cancer emerged as significant. However, in Table 4 (restricted to those reporting on first-degree relatives only) and Table 5 (further restricted to controls without cancer), asbestos exposure emerged as a factor.

		Cases*	Controls*	OR (95% CI)**
Asbestos exposure	- Table 4	37	413	4.38 (1.10-17.45)
	- Table 5	37	359	5.17 (1.20-22.36)

* Exposed + unexposed

** Adjusted for radon, education and age

The paper provides no relevant results for income.

4. Shaw[70]

This paper describes results of cohort studies in New Zealand based on linking census and mortality datasets. No data on smoking were recorded.

SUMMARY FOR INCOME

The available data on income, from only study 1 – Gorlova[67] and study 2 – Mao[68], the first of which provides only non age-adjusted results for sexes combined, seems too limited to be useful. Education and income are in any case likely to be strongly correlated and we had considerable data for education earlier. Note that the two studies that provide data for income also provide data for education.

F. OBESITY

1. Calle[71]

This paper describes results from 16 year follow up (1982-98) of about 1,000,000 men and women in CPS-II. Results for never smokers are available in Table 3 on page 1633.

	Body Mass Index				
	18.5-24.9	25.0-29.9	30.0-34.9	35.0*	Trend p
Males					
Lung cancer cases	156	179	30*		
Death rate	22.72	23.51	23.45		
RR (95% CI)**	1.00	1.00 (0.80-1.24)	0.93 (0.63-1.39)		0.78
Females					
Lung cancer cases	476	224	78	17	
Death rate	18.71	16.40	19.18	17.51	
RR (95% CI)**	1.00	0.85 (0.73-1.00)	0.99 (0.77-1.26)	0.81 (0.49-1.31)	0.21

* Results are for BMI 30.0+

** Age standardized

2. Eichholzer[72]

This paper describes 17 year follow up (1971/73-90) for cancer of 2974 working men in Basle. Of 87 lung cancers, 22 were in non-smokers. Figure 2 provides graphical Kaplan-Meier plots of survival from lung cancer jointly by smoking status and BMI quartiles. It would be impossible to derive suitable RR estimates from these 8 overlapping and not clearly distinguishable lines. It may well be in any case that their term “nonsmokers” includes former smokers.

3. Jeffreys[73]

This paper describes results of 50 year follow up of British children originally interviewed in 1937-39. No data were recorded on smoking habits and results for lung cancer were only shown for the whole population.

4. Kanashiki[74]

This paper describes results of a case-control study in Japan involving 363 lung cancer cases and 1089 controls selected from mass-screening subjects with no history of cancer and no abnormality on screening. Table 3 on page 1492 presents results for never smokers.

	Body Mass Index			
	<20.8	20.8-22.8	22.9-24.9	25+
Males				
Cases	1	4	3	4
Controls	33	48	36	42
OR (95% CI)*	0.6 (0.1-7.8)	1.1 (0.2-6.3)	1.0	1.8 (0.3-11.0)
Females				
Cases	25	20	35	36
Controls	81	106	87	109
OR (95% CI)*	0.8 (0.4-1.4)	0.5 (0.3-0.9)	1.0	0.9 (0.5-1.5)

* Age-adjusted (not entirely clear from the text, but the ORs and CIs are not the same in all analyses as would be obtained if these were crude ORs)

5. Olson[75]

This paper reports results of follow up (1986-98) of 41,836 Iowa women. 81 lung cancer cases occurred in never smokers. Table 4 on page 612 presents multivariate RRs and CIs for never smokers.

	Body Mass Index				
	≤22.89	22.90-25.04	25.05-27.43	30.69	30.70+
Lung cancer cases	18	19	13	10	16
Person years	50628	60129	61438	62269	63480
RR*	1.00	0.82	0.51	0.35	0.44
95% CI		(0.43-1.57)	(0.24-1.06)	(0.15-0.79)	(0.21-0.95)

* Adjusted for age, physical activity, educational level, beer consumption, height, waist circumference and BMI at age 18 years

Note that as the analysis is adjusted for earlier BMI it is really an analysis of change in BMI.

6. Rauscher[76]

This paper describes results from a case-control study conducted in New York involving subjects who had never smoked more than 100 cigarettes in their lifetime (never smokers). Data on height and weight were complete for 412 pairs of cases (confirmed histologically) and population controls matched on age, sex and district and usually the respondent (subject or surrogate). The results given in Tables 2 and 3 on pp 509-510 for never smokers (only presented for sexes combined) can be summarized as follows:

	Body Mass Index octile							
	1	2	3	4	5	6	7	8
Cases	23	28	25	19	24	20	21	28
Controls	35	31	21	26	17	19	22	17
Crude OR	1.0	1.4	1.8	1.1	2.1	1.6	1.5	2.5

	1	2-7	8
Matched OR (CI)	1.0	1.5 (0.9-2.7)	2.4 (1.1-6.0)
Education adjusted matched OR (CI)	1.0	1.2 (0.6-2.1)	1.8 (0.8-4.5)

SUMMARY FOR OBESITY

Of the 6 papers obtained, 4 include relevant data. The results are, however, extremely conflicting. Study 6 – Rauscher[76] suggests a positive association, as perhaps does study 4 – Kanashiki[74]. Study 5 – Olson[77] shows a negative association but with change in BMI rather than BMI itself, while the largest study, study 1 - Calle[71] shows no association. No reliable adjustment for obesity could be based on these data.

G. OCCUPATION

1. Armstrong[78]

This paper describes a review of 39 studies of risk of lung cancer after exposure to polycyclic aromatic hydrocarbons. The paper notes that only four studies conducted smoking adjustment and there is no mention of any results being available for never smokers.

2. Besso[79]

This paper describes a case-control study of subjects living in a municipality where a smelter was located (but not at the smelter). 316 decedent lung cancer cases were matched to 727 decedents from other causes, with information being obtained from next-of-kin and registry data. Table IV presents results for never smokers for residence in the area near the smelter.

		Never resident	Ever resident
Males	Cases	17	5
	Controls	211	31
	RR(95% CI)*	1.00	2.03 (0.68-6.09)
Females	Cases	43	12
	Controls	128	31
	RR(95% CI)*	1.00	1.03 (0.48-2.20)

* Adjusted for occupation, age and (for men only) period of recruitment

3. Boffetta[80]

This paper presents estimates of lung cancer rates among never smoking male Swedish construction workers, but provides no relative risk estimates in relation to working in this industry, i.e. there is no control group.

4. Durusoy[81]

This paper presents results from a large multicentric case-control study in Central and East Europe. Cases had histologically confirmed lung cancer and controls were mainly hospital patients with non-cancer diseases unrelated to smoking. The study included 48 male and 175 female never smoking cases and 534 male and 505 female never smoking controls. Tables II and III on pp 2545-6 present estimates by risk of two occupational exposures.

Exposure to	Exposed cases	Exposed controls	OR (95% CI)*
Meat aerosols	10	28	1.78 (0.79-4.02)
Live animals	22	89	1.11 (0.64-1.92)

* Adjusted for sex, age and centre

5. Ekberg-Aronsson[82]

This paper describes results from a long-term (1974-1992) prospective study in Malmo, Sweden. Table 3 on p 5 (of the E-publication) gives relative risks by SES among never smokers, and Table 2 on the same page gives numbers at risk.

	Low SES		High SES		
	At risk	RR	At risk	RR (CI)*	Total cases
Men	1496	1.0	1846	3.43 (1.59-7.41)	33
Women	1928	1.0	1928	0.70 (0.20-2.47)	11

* Adjusted for age and marital status

6. Fano[83]

This paper describes results of a case-control study in an industrialised area of Italy. No results are given for never smokers.

7. Guo[84]

This paper describes results of a very large follow-up study in Finland. Although standardized incidence ratios (SIRs) are presented for a large number of occupations, no results are presented for never smokers.

8. Gustavsson[85]

This paper describes the results of a population-based case-control study among men in Stockholm County, involving 1038 incident lung cancer cases and 2359 controls matched on age and year of inclusion in the study, and in part on vital status. Relevant data for never smokers for asbestos exposure are included in Table 2 (p 1018) and Tables 3 and 4 (p 1020).

Asbestos exposure (fibre-years)	Cases	Controls	RR (95%CI)*
None	26	620	1.0
<1 (mean 0.56)	4	51	1.8 (0.6-5.5)
1-2.49 (1.51)	3	26	2.7 (0.7-9.5)
2.5-4.49 (3.44)	1	4	
4.5+ (8.80)	2	4	
1.0+			4.2 (1.6-11.1)
2.5+			10.2 (2.5-41.2)

* Adjusted for age, year of inclusion, residential radon, environmental nitrogen dioxide, diesel exhaust and combustion products

9. Haldorsen[86]

This paper describes an ecological analysis relating lung cancer incidence data and smoking prevalence data by 53 occupational groups. It cannot contribute to our study.

10. Hart[87]

This paper describes 20 year mortality follow-up of 11073 men and 8354 women recruited in the 1970s. Table 2 on p 271 presents some results by social class (non-manual/manual) for never smokers.

	Non-manual			Manual			Ratio of
	At risk	Deaths	Rate	At risk	Deaths	Rate	rates**
Renfrew/Paisley men	457	3	3.9	709	6	4.8	1.23
Renfrew/Paisley women	1629	6	2.3	2030	13	3.3	1.43
Collaborative men	339	0	0.0	247	2	3.3	∞

* Age-adjusted ** Calculated from rates

11. Hart[88]

This paper describes a study linking data from the Scottish mental survey in 1932 and later, Midspan, studies of adults in the 1970s. Smoking was not considered.

12. Hemminki[89]

This paper presents SIRs for cancer in six socio-economic groups based on the Swedish Family-Cancer Database. This database does not contain data on smoking habits.

13. Kjaerheim[90]

This paper describes a case-control study involving 133 lung cancer cases among rock and slag wool (RSW) production workers and 513 matched controls. Although analyses are presented relating exposure to RSW to lung cancer risk adjusted for smoking, no such results are given for never smokers.

14. Li[91]

This paper describes a small case-control study in China involving workers in a rubber factory. Only 9 of the cases were never smokers and no results for never smokers relating to exposure to rubber are presented.

15. Mastrangelo[92]

This paper describes a small case-control study in Italy nested in a cohort study of dairy factors. Only one lung cancer occurred among never smokers (see Table 4 , p 1042).

16. Metcalfe[93]

This paper describes 25-year follow-up of 5577 men recruited from workplaces in the West of Scotland in 1970/73. No results are given for never smokers.

17. Pohlabeln[94]

This paper describes a multicentre case-control study conducted in seven West European countries involving 650 lung cancer cases and 1542 controls, a mixture of community-based controls and hospital-based controls (with diseases unrelated to smoking). All subjects were non-smokers defined as having smoked less than 400 cigarettes in their lifetime. Occupations and industries were classified as known (list A) or suspected (list B) to be associated with lung cancer. The main results are given in Table 4 on p 535.

Occupation	Sex	Cases	Controls	OR(95% CI)
Never A or B	Male	101	366	1.00
Ever A or B		40	165	1.20 (0.76-1.92)
- Ever B, never A		23	107	1.05 (0.60-1.83)
- Ever A		17	58	1.52 (0.78-2.99)
Never A or B	Female	463	942	1.00
Ever A or B		46	69	1.67 (1.10-2.52)
- Ever B, never A		41	59	1.69 (1.09-2.63)
- Ever A		5	10	1.50 (0.49-2.53)

The paper also presents, in Table 2 (p 534, List A) and Table 3 (p 535, List B) numbers of cases and controls and, for the more commonly worked in industries, estimates of OR and CI.

18. Pukkala[95]

This is another paper based on the large Finnish follow-up study; see also study 7 – Guo[84]. No results are presented for never smokers.

19. Richiardi[96]

This paper describes results from a case-control study conducted in two areas of Northern Italy. No results are given for non-smokers, it being noted that they were included in the multicentre study by Pohlabeln[94] – see study 17 above.

20. Ruano-Ravina[65]

This paper describes the results of a population-based case-control study conducted in Spain including 163 confirmed lung cancer cases and 241 controls

without neoplasia or respiratory tract disease. Table IV on page 153 presents results for never smokers relating to number of years spent in a "risk profession" as defined by Ahrens and Merletti[97].

Years in risk profession	Cases	Controls	OR (95% CI)*
0	11	77	1.00
1-20	1	12	2.01 (0.19-21.36)
21+	1	18	2.03 (0.18-22.99)

* Adjusted for age and sex

21. Scelo[98]

This paper describes the results of a multicentre case-control study in 7 countries (UK, Central and East Europe), some subjects included in study 4 above[81]. The paper only considers 3 specific exposures (vinyl chloride, styrene and acrylonitrile) and no results are given for never smokers.

22. Sorahan[99]

This paper describes a follow-up study of chrome platers employed in the UK. No results relating employment to lung cancer risk in never smokers are given.

23. Sorahan[100]

This paper describes a follow-up study of nickel-cadmium battery workers employed in the UK. No data on smoking habits were considered.

24. Yiin[101]

This paper describes a follow-up study on UK naval shipyard workers. Smoking history data were not available.

SUMMARY FOR OCCUPATION

Of the 24 papers considered, 17 gave no results at all for never smokers and two[82,87] gave results only for SES – considered later. Three of the studies dealt only with specific occupations and involved small numbers of exposed cases:

Study 2 - Besso[79]	- living near smelter (17 cases)	
Study 4 - Durusoy[81]	- meat aerosols (10 cases)	
	- live animals (22 cases)	
Study 8 - Gustavsson[85]	- asbestos (10 cases)	

Only two studies dealt with more general indices of risky occupation. One, study 20 - Ruano-Ravina[65] included only two exposed cases. Only the large multicentre study, study 17 - Pohlabeln[94] involved moderate numbers – 22 working in List-A occupations and a further 64 working in List-B occupations. While it would be useful to be able to adjust for a general index of risky occupation (such as working in List-A occupations), the data seem too limited to be able to do so.

H. PHYSICAL ACTIVITY

1. Alfano[102]

This paper describes results from a sample of current and former smokers from the Beta-Carotene and Retinol Efficacy Trial and as such includes no results for never smokers.

2. Bak[103]

This paper describes results of follow up (1993/93-2002) of 57,053 persons in a Danish cohort study. As shown in Table 1 on page 441, only 13 lung cancer cases (2 in men, 11 in women) occurred in never smokers and no physical activity results are given specifically for never smokers.

3. Colbert[104]

This paper describes results from a sample of current smokers from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study and as such includes no results for never smokers.

4. Kubik[105]

This paper describes results from a case-control study in Prague women involving 419 lung cancer cases and 1593 controls who were spouses, relatives, or friends of other patients hospitalised at the same department as the cases. 111 of the cases and 933 of the controls were never smokers (less than 100 cigarettes in their lifetime). Results for physical activity for non-smokers are shown in Table 5 on page 140. However this includes those who had quit 20 or more years ago. The results, not shown in detail as they do not strictly relate to never smokers, show no significant trend (after adjustment for age, residence and education) with physical exercise (hours/week, including sport, walking) at any of the three times considered (last 10 years, 1 year before interview, 20 years interview) or with other non-occupational physical activities (e.g. in the garden or house).

It should be noted that Tables 3 and 4 on page 139 include results for non-smokers by other factors (residence, education, 9 food items, 4 beverage items, and 3

alcohol items). Significant associations were noted with urban residence (low risk: 0.41, 0.28-0.61), red meat consumption (high risk: 2.20, 1.07-4.51) and black tea consumption (low risk: 0.67, 0.46-0.99). Again the non-smokers include long-term exsmokers.

5. Mao[106]

This paper describes results from a case-control study of lung cancer in 8 Canadian provinces involving 2128 cases with histologically confirmed lung cancer and 3106 population controls. Table 5 on page 571 gives results for never smokers. Those adjusted for age, residence, education, BMI, caloric intake, vegetable intake, ETS, occupation and alcohol are shown below.

	Total recreational physical activity (metabolic equivalent hours/week)				
	<6.1	6.1 to <15.2	15.2 to <31.4	31.4+	Trend p
Men					
Cases	8	6	8	4	
Controls	88	114	100	118	
OR	1.00	0.53	0.87	0.31	
(95% CI)		(0.17-1.63)	(0.29-2.62)	(0.08-1.14)	
Women					
Cases	28	21	24	27	
Controls	174	198	160	179	
OR	1.00	0.70	0.82	0.80	
(95% CI)		(0.37-1.32)	(0.55-1.90)	(0.54-1.83)	

SUMMARY FOR PHYSICAL ACTIVITY

Of the five studies considered, three provide no useful information at all and two (study 4 – Kubik[105] and study 5 – Mao[106]) find no association, Kubik only in never smokers plus long-term exsmokers.

I. SOCIOECONOMIC FACTORS

1. Battersby[107]

This paper is to do with access to surgery for lung cancer and is irrelevant.

2. Dreassi[59]

As already noted under education, this is an ecological study with no data on smoking.

3. Ekberg-Aronsson[82]

See study 5 under occupation for results for never smokers.

4. Hart[87]

See study 10 under occupation for results for never smokers.

5. Hart[88]

For reasons described under study 11 in occupation, this is irrelevant.

6. Schwartz[108]

This paper describes a study relating stage of diagnosis of cancer to SES and is irrelevant.

7. Tammemagi[109]

This is a study of lung cancer patients only and is not relevant.

8. Tammemagi[110]

Again, this is a study of lung cancer patients only and is not relevant.

SUMMARY FOR SOCIOECONOMIC FACTORS

Of the 8 papers, 6 are irrelevant. Only study 3 – Ekberg-Aronsson[82] and study 4 – Hart[87] provide any relevant data at all, with the Hart study based on very few deaths.

J. CONCLUSIONS

It is clear from sections A and D that there are a number of studies providing information on the relationship of lung cancer risk in non-smokers to fruit, vegetables and dietary fat consumption and to education, additional to those considered earlier [111]. Are there any additional potential confounding variables for which there is sufficient evidence to derive a useful quantitative estimate of the relationship to risk? The relevant data presented in the remaining sections can be summarized as follows:

Section	Potential confounding variable	Sumary of investigation
B.	Air pollution	No data at all.
C.	Alcohol	Only four relevant studies, with conflicting results.
E.	Income	Data very limited; income highly correlated with education.
F.	Obesity	Only four studies, conflicting results.
G.	Occupation	Only five studies, four very small and three of these presenting results only for specific occupation. Only one study is large and deals with risky occupation generally.
H.	Physical activity	Only two relevant studies, neither finding an association.
I.	Socioeconomic factors	Only two relevant studies, one very small.

For none of these seven potential confounding variables are there data which could be used to provide any sort of reliable quantitative estimate of their relationship to lung cancer risk in non-smokers.

As noted in section A (see sections 9 and 29), there are two studies [15,37] that present evidence of a markedly reduced risk of lung cancer in tea drinkers. Although two studies is too few to calculate a very reliable combined estimate, the results are used in some of the analyses in the main report.

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