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Background Paper

Parental Tobacco Smoke and Childhood Cancer

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ABSTRACT

We have identified more than 30 studies on the association between exposure to maternal tobacco smoke during pregnancy and cancer in childhood and have combined their results in meta-analyses based on a random effects model. The results of the meta-analyses suggest a small increase in risk of all neoplasms (relative risk [RR] 1.11, 95% confidence interval [CI] 1.00-1.23, based on 11 studies) and leukaemia (RR 1.14, 95% CI 0.90-1.44, 7 studies), but not in risk of central nervous system (CNS) tumours (RR 1.04, 95% CI 0.92-1.18, 12 studies). Results for other specific neoplasms were sparse, but for no type of tumour did the available data suggest a strong association. No clear evidence of dose-response was present in the studies that addressed this issue. The results on exposure to maternal tobacco smoke before or after pregnancy are too sparse to allow a conclusion. The results on tobacco smoke from the father suggest an association with brain tumours (RR 1.22, 95% CI 1.05-1.40, based on 10 studies) and lymphomas (RR 2.08, 95% CI 1.08-3.98, 4 studies), while the data are too sparse for the other neoplasms. For the results on exposure from either maternal or paternal smoke, bias and confounding can not be ruled out with confidence. Further studies are needed to confirm the hypothesis that parental tobacco smoke is a weak risk factor of childhood cancer. Eleven studies provided results on risk of lung cancer in adulthood and childhood passive smoking exposure: they do not provide evidence of an increased risk (summary RR 0.91, 95% CI 0.80-1.05).

INTRODUCTION

Cigarette smoking has been identified as a major source of preventable morbidity and premature mortality (1). During the last 15 years, attention has been focused on the potential health effects of environmental tobacco smoke (ETS) (2). ETS is composed of tobacco smoke emitted from the end of a burning tobacco product (sidestream smoke) plus the smoke as well as the portion of inhaled (mainstream) smoke which is exhaled by the smoker. Although the composition of mainstream smoke and ETS are not identical, the latter appears to include most of the tobacco combustion by-products, notably the carcinogens (3, 4).

There is evidence that exposure to ETS causes lung cancer (2, 5) and ischaemic heart disease (6, 7), while the effects of ETS on cancers in adulthood other than of the lung, and on non-neoplastic respiratory diseases in adults are still a matter of discussion (2, 8, 9). There is also evidence that ETS is harmful for children. In particular, ETS exposure is causally associated with lower respiratory tract infections, fluid in the middle ear, symptoms of upper respiratory tract irritation, some reduction in lung function, additional episodes and increased severity of symptoms in children with asthma, and occurrence of asthma in previously asymptomatic children (8).

The potential carcinogenic effect of ETS on children has not been clarified. Paternal smoking may cause mutations in the spermatogonia (10). Smoking by either parent may affect the developing foetus transplacentally, or subsequently the developing child. Studies in animals suggest that some effects of exposure in early life may not be apparent until adult life (11).

METHODS

We reviewed all epidemiological studies on childhood cancer, as tobacco smoking has in many studies been recorded as a potential confounder rather than the primary exposure of interest; we also used some recent reviews (12, 13). Most studies were carried out in Western Europe and North America, where cigarettes are the most commonly used tobacco product.

There are problems in distinguishing between transgenerational, transplacental and direct effects of exposure to ETS, i.e., between the effects of preconceptional, prenatal and postnatal exposure to tobacco smoke. Mothers and fathers who smoke during pregnancy have usually smoked before, and continue to smoke after the birth. Moreover, due to the concordance of

smoking habits in married couples (14), children who are exposed to maternal smoking might also be exposed to paternal smoking. However, in most studies results have been reported on ever paternal and maternal smoking or on smoking during the index pregnancy. We combined these sources of exposure and based our review mainly on these results. Whenever possible, however, we have separated the effect of preconceptional smoking and of smoking after the index birth.

In addition, we have reviewed the studies of lung cancer among non-smokers, in which the effect of childhood exposure to ETS has been addressed. In most of these studies, no distinction is made between preconceptional, transplacental and direct ETS exposure. In several studies, on the other hand, a distinction is made between exposure to ETS from the mother, the father and, in some cases, other adults.

We have extracted from the available studies information on risk from any exposure to maternal or paternal smoking during pregnancy, as well as quantitative results, expressed as number of cigarettes per day smoked by the parents, which was the quantitative variable more frequently reported. For neoplasms and groups of neoplasms for which risk estimates were available from at least three different studies, we have combined the relative risks (RRs) for any exposure to tobacco smoke into a meta-analysis based on a random effects model (15). When no single risk estimate was available from a study (e.g., results were only available for different subtypes of a neoplasm or for different levels of smoking), we have first combined the results of each study to derive a summary risk estimate. In some cases, we have derived the RR and the confidence interval (CI) from the raw data reported. We have tested for the presence of publication bias by looking at the regression of the logarithm of the RR against the inverse of its variance (16).

RESULTS

Childhood Cancer

Ever exposure to maternal tobacco smoke or exposure during pregnancy

Four cohort studies have been published on cancer risks in children of mothers who smoked during pregnancy (table 1). Neutel and Buck reported the results of a prospective study of the relationship between smoking in pregnancy and cancer in 89,302 new-borns, from Ontario, Canada, and England and Wales (17). For cancer of all sites, the children of smokers had a RR of 1.3 (95% CI 0.8-2.2). This weak excess was accounted for by leukaemia RR 1.8), and solid tumours of sites other than the nervous system (RR 1.5). No evidence of a dose-response relationship with amount of maternal smoking was present.

A significant positive association was found in a study based on 16,193 infants born in Great Britain during one week in 1970 (18). A total of 33 children developed cancer by age 10, nine of whom had leukaemia. The RR associated with the mother smoking 5 or more cigarettes per day throughout pregnancy, compared with not smoking or smoking less than 5 cigarettes per day, was 2.5 (95% CI 1.2-5.1).

In the largest cohort study, from Sweden, there was no increase in the overall risk for cancer in children born to mothers reporting smoking during pregnancy (19). The RRs were similar for both solid tumours and lymphatic and haematopoietic neoplasms, without any dose-response relationship. A RR larger than 1.5 was found for cancers of the endocrine glands, and for myeloid leukaemia, reticulosis, and other lymphatic and haematopoietic neoplasms; none of these excesses was statistically significant. Finally, in a cohort study of over 50,000 US new-borns, no overall association nor dose-response gradient was found for all neoplasms or leukaemia (20).

Case-control studies are summarized in tables 2 (all neoplasms), 3 (lymphatic and haematopoietic neoplasms), 4 (nervous system tumours), and 5 (other types of solid tumours).

In two studies (23, 27) there was evidence of a dose-response relationship between overall cancer risk in the offspring and the number of cigarettes smoked per day by the mother during pregnancy (table 2); the interpretation of one of these studies (23), however, is limited by the selection of children with juvenile diabetes as controls. In this study, the increased risk and the linear trend remained significant only for acute lymphocytic leukaemia (ALL), accounting for about half of the cases (table 3). John and co-workers conducted a case-control study of childhood cancer (ages 0-14 years) diagnosed in Denver, Colorado (25). Information on smoking by both parents and other household members was obtained for 223 cases and 196 controls, with 63% participation rate. After adjustment for paternal education, maternal smoking during the first trimester of pregnancy was associated with an increased risk for all cancers combined, ALL, and lymphomas.

No strong association was found between maternal smoking during pregnancy and overall childhood cancer in the remaining case-control studies (21, 22, 24, 26) (table 2). McKinney and Stiller reported the results from a multicentre English study of childhood cancer (22). For each of 555 cases, two age- and sex-matched controls were selected. There was no evidence of an increased risk of cancer in the children of mothers who smoked in pregnancy. Detailed analysis restricted to leukaemia and lymphoma also failed to show a positive association between maternal smoking during pregnancy and increased risk (50) (table 3). A small increase in risk of all childhood neoplasms with no evidence of a dose-response relation was reported by Buckley and colleagues (21). A slight increase in risk was associated with maternal smoking during pregnancy in the two remaining studies (24, 26), one of which, from Sweden, partially overlapped with the cohort study described above (19).

The meta-analysis of the 11 studies providing a RR for maternal smoke and overall cancer risk resulted in a summary RR of 1.11 (95% CI 1.00-1.23). There were no discrepancies among the results of the four cohort studies (RR 1.15, 95% CI 0.77-1.72) and those of the seven case-control studies (RR 1.11, 95% CI 1.03-1.20). There was no evidence of publication bias ($p = 0.73$).

With respect to lymphatic and haematopoietic neoplasms, except in the studies by Sterjnfeldt (23) and John (25), no strong association was found, in any study, with either leukaemia, or leukaemia and non-Hodgkin's lymphoma (NHL) combined (table 3). Among the studies which looked at specific neoplasms, an association was suggested with acute non-lymphocytic leukaemia (AnLL) and NHL in an Italian study (29). The results of the meta-analysis were 1.03 (95% CI 0.90-1.17) for all lymphatic and haematopoietic neoplasms (9 studies), 1.13 (95% CI 0.85-1.49) for either NHL or all lymphomas (6 studies), 1.14 (95% CI 0.90-1.44) for either all leukaemias, acute leukaemia or ALL (7 studies). There was however evidence of publication bias in the available results on lymphomas ($p = 0.04$): as it can be seen in table 3, studies with large number of cases tended to show null results (21, 27), while studies with small number of cases were consistently positive (23, 25, 29), leaving open the possibility that small null or negative studies have not been reported.

No clear association between maternal smoking during pregnancy and tumours of either the central nervous system (CNS) or the brain has been found in most studies that addressed this association (Table 4): positive and negative results tend to balance. The summary RR estimated via the meta-analysis was 1.04 (95% CI 0.92-1.18, 12 studies), with no evidence of publication bias. When specific tumours of the CNS were considered, a positive association with neuroblastoma was found in an American study (37), while two other neuroblastoma studies did not confirm this finding (27, 33): the meta-analysis of the three studies yielded a RR of 1.25 (95% CI 0.78-2.00). The only available study of retinoblastoma found a non-significant increase in risk from maternal smoking for the heritable form but not for the non-heritable form (34).

No association between Ewing's sarcoma and maternal smoking during pregnancy was suggested in the only fully reported study in which this neoplasm was assessed (44). However, in a study reported only in abstract form (45), a positive association was found for smoking of both parents (table 5).

There was no association between maternal smoking during pregnancy and either kidney cancer or Wilms tumour (21, 22, 23, 27, 46), hepatoblastoma (47), bone cancer (27), rhabdomyosarcoma (48, 49) or soft tissue sarcomas in general (25, 48) (table 5). In one of the three studies of Wilms tumour looking at dose-response (23), the risk increased with increased amount of maternal smoking. The results of the meta-analysis for kidney cancer or Wilms tumour was 0.95 (95% CI 0.76-1.19, 5 studies).

Exposure to maternal tobacco smoke before pregnancy

Three studies of brain neoplasms reported results separately for maternal smoking before and during the index pregnancy. The odds ratios (ORs) were 0.9 (95% CI 0.4-2.1) (25), 0.4 (95% CI 0.1-1.3) (39) and 0.8 (95% CI 0.6-1.0) (43). One of these studies reported also results from preconceptional exposure to maternal smoke for other neoplasms (25): lymphomas (OR 1.9, 95% CI 0.7-5.2), ALL (OR 2.1, 95% CI 1.0-4.3) and STS (OR 1.2, 95% CI 0.5-3.0): for the three neoplasms, the risks are similar to those estimated for exposure during pregnancy (tables 3 and 5). The OR of leukaemia from maternal smoke before the index pregnancy was reported in a further study to be 1.0 (95% CI 0.8-1.3) (28).

Exposure to maternal tobacco smoke after pregnancy

No risk estimates were reported on the risk of childhood cancer from exposure to maternal smoke after birth as distinguished from in-utero or preconceptional exposure. As stated above, several of the studies reviewed in the section on exposure during pregnancy assessed ever smoking status of the mother, which likely includes mothers smoking before, during and after the index pregnancy. These studies however are not relevant to assess the effect of ETS exposure during pregnancy for that of transplacental exposure to tobacco components and metabolites.

Exposure to paternal tobacco smoke

The cancer risk in children following exposure to tobacco smoke from the father has been addressed in fewer studies than in the case of exposure from the mother. These studies are summarized in table 6.

Stewart and colleagues (53) found that only a slightly higher proportion of fathers of children with childhood cancer of any type were reported to be smokers than those of control children. In the study by John et al. (25), 105 children were exposed to paternal smoking only. Weak associations with paternal smoking prior to birth in the absence of maternal smoking were found for all cancers combined, ALL, lymphomas, and brain tumours.

There are however several exceptions. A very strong association (RR, adjusted for socio-economic status: 6.7; 95% CI: 1.0-43) between NHL and paternal smoking prior to the child's birth, without dose-response relation, was found in an Italian study (29). As already mentioned, a positive association between rhabdomyosarcoma and the father ever having smoked cigarettes was reported in a small study in North Carolina (52). However, a second, larger case-control study did not confirm these results; the cases comprised 322 children with rhabdomyosarcoma; RRs of 1.0 (95% CI: 0.7-1.4), 1.0 (95% CI: 0.7-1.4) and 0.9 (95% CI: 0.7-1.3) were found for paternal smoking during the year preceding or at the time of the index child's diagnosis, after the child's birth and at the time of diagnosis, respectively (49, 54). In a study of retinoblastoma, a non-significant association was found for the heritable form but not for the non-heritable form, a pattern similar to the one found for maternal smoke (34).

In a large and carefully conducted study from China, an increased risk was found for lymphomas (OR 4.0, 95% CI 1.3-13), with a trend suggested for average amount of smoking, duration of smoking and cumulative consumption (ORs 2.8 [95% CI 0.-13], 1.3 [0.3-5.5] and 5.7 [1.3-26] for 1-5, 6-10 and more than 10 pack-years) (51). In the same study, a dose-response was suggested for acute leukaemia and brain tumours. Out of the numerous other studies of childhood brain tumours and paternal smoking, only a rather small investigation from Australia (39) reported a positive association.

We conducted meta-analyses on paternal smoke and risk of NHL (RR 2.08, 95% CI 1.08-3.98, 4 studies), ALL (RR 1.08, 0.92-1.28, 3 studies) and CNS tumours or brain cancer (RR 1.22, 95% CI 1.05-1.40, 10 studies). While the results for ALL parallel those found for maternal smoke, the pooled risk estimated for both NHL and CNS tumours are higher than the corresponding figures estimated for maternal smoke. For none of the three neoplasms analysed with respect to paternal smoke was there evidence of publication bias.

For only one study results have been reported also for exposure to paternal smoke before and after the index pregnancy (51). A significant dose-response was found among pack-years of cigarettes smoked before conception and risk of all childhood cancers, acute leukaemia and ALL, while a nonsignificantly increasing trend was found for AnLL, lymphomas and brain tumours. The analysis of pack-years smoked by the father after the index birth was not associated with the risk of all childhood cancers, acute leukaemia, AnLL or brain tumours, while a nonsignificantly increasing trend was present for ALL and lymphomas.

Lung Cancer

A total of 11 studies of non-smokers have reported results on lung cancer following childhood ETS exposure (table 7). A nonsignificantly increased risk for ever childhood exposure was reported in a study from Hong Kong (55), two studies from the USA (58, 61) and among women of a further American study (63). The meta-analysis of the results, based on 10 studies provides a summary risk estimate of 0.91 (95% CI 0.80-1.05). A few studies provided results separately for exposure to ETS from the mother and the father (table 7): the summary risk estimates were 0.83 (95% CI 0.72-0.95) for paternal exposure and 0.99 (95% CI 0.78-1.26) for maternal exposure.

Results on lung cancer risk from quantitative ETS exposure, assessed either as smoker-years or pack-years) have been reported in six of the studies listed in table 7. In two American studies risk estimates increased with increasing estimated exposure (58, 61), while the remaining studies did not provide evidence of a positive dose-response relationship (60, 62, 63, 65). No difference in risk according to histological type of lung cancer was reported in the two largest studies (62, 65).

DISCUSSION

The available evidence indicates that the association between exposure to tobacco smoke and cancer in children, if any, is likely to be weak. The results of the meta-analyses suggested an increased risk following maternal smoke on the order of 10%. However, despite the fact that the results of some of the meta-analyses are statistically significant, several arguments caution against the conclusion that a causal association has been established.

The increase in risk is small and is not clearly concentrated in any specific neoplasm: the only neoplasm for which the result of the meta-analysis on exposure to maternal smoke is significant is leukaemia, but this fact might be due to the greater size of the studies involved.

An increase of this magnitude can be easily explained by bias and confounding. Selection bias is unlikely to represent a major problem, since, although not all the available studies were population-based, there was no obvious cluster of positive results among cohort studies, hospital-based case-control studies or population-based case-control studies. Publication or

reporting bias is a special form of selection bias that might affect meta-analyses. The test we have used to assess the presence of publication bias (16) is not powerful when the meta-analysis is based on relatively few studies, as in the case of neuroblastoma and exposure to maternal smoke or NHL and paternal smoke.

Information bias might be a serious problem for the studies reviewed here, particularly in the form of recall bias. Accuracy of recall is crucial in studies of childhood cancer. Mothers of children with cancer might be more prone to remember possible noxious events during pregnancy than mothers of healthy children. Information on smoking status of the mother was not validated in any study. Some authors addressed this limitation by choosing as controls a group of children with a serious disease, such as other types of cancer, because their mothers may be expected to recall past exposures to noxious agents as vigorously as those of the group of cases (23, 66). However, using cancer controls potentially eliminates interviewer and recall bias, but may underestimate the RR if both cancer cases and cancer controls share risk factors (67).

Confounding factors, i.e., variables which related to tobacco smoke exposure and are also independent risk factors for childhood cancer, may be responsible for the overall increased risk. Factors which have been associated with childhood cancers include drugs and chemicals (33), parental occupational exposures (68-70), prenatal exposure to ionizing radiation (71), diet (72), and socio-economic status (73). Most of these factors were not taken into account in the available studies on parental smoke. It is not possible to determine whether this had any impact on the results, as the data often conflict and the relationship with smoking is unclear (12). However, confounding remains a plausible explanation for the observed increased risk.

The overall interpretation of the studies reviewed here is hampered by the crude exposure assessment used, often based on a dichotomous indicator of smoking by the parents, without considering quantitative exposure variables. Most of the studies reporting results for different exposure levels did not provide evidence of a dose-response relationship, which also detracts from a causal interpretation of the summary risk estimates.

The biologic plausibility of the association between tobacco smoke exposure and childhood cancer is of particular interest, since the types of cancer in childhood are different from those of cancers occurring in adults. Epithelial involvement is relatively rare in tumours of childhood, while many of the tumours have features which recall foetal development and therefore are designated 'embryonal' (74). Involuntary smoking is accompanied by exposure to many of the toxic agents generated by tobacco combustion, and the intake of tobacco smoke components - including carcinogens and mutagens - by children has been confirmed in biochemical studies of cigarette smoke during both gestation and childhood (75-77). Although the conventional assay of cytogenetic abnormalities, such as chromosome aberrations and sister-chromatid exchanges, are unable to detect the low exposures of transplacentally exposed new-born children (78), activation of procarcinogens in human foetal and placental tissues has been demonstrated (79), as has smoke-induced damage to DNA in human placenta (80, 81).

Transplacental exposures to carcinogens can cause cancer in humans, as shown by the occurrence of vaginal clear-cell adenocarcinoma in women whose mothers received diethylstilbestrol during pregnancy (82). Animals appear to be especially susceptible to the carcinogenic effects of some of the chemicals found in tobacco smoke when exposure is transplacental (83). Moreover, exposure of rodents to chemical carcinogens during pregnancy may result not only in a high incidence of tumours in progeny of the first generation, but also in an increased tumour incidence in those of subsequent generations (84).

The comparison of the results of the meta-analyses conducted on exposure to maternal and paternal smoke is problematic. The evidence for maternal smoke points towards a possible

weak effect on lymphatic and haematopoietic organs, which is confirmed by the results on paternal smoke, despite the lack of statistical significance of the latter result. We found evidence of little or no effect of maternal smoke on tumours of the kidney and the CNS, while the results on paternal smoke suggest an effect on NHL and CNS tumours. This difference in target organs, which needs confirmation, might be related to the different mechanism of action of carcinogens in maternal smoke (direct transplacental effects) and in paternal smoke (mainly via preconceptional alterations). The available evidence is inadequate to clearly distinguish between an effect of preconceptional exposure to maternal smoke, in utero exposure and postnatal ETS exposure. One large study from China, however, suggests that preconceptional smoking of the father can contribute to the risk of some neoplasms in the offspring (51).

The available evidence on risk of lung cancer in adulthood following childhood ETS exposure points towards the absence of an increase in risk. The presence of a few positive studies, some of which also reported a positive dose-response relationship, however, suggests caution in concluding that ETS exposure in childhood is not related to subsequent risk of lung cancer.

The harmful effects of active smoking during pregnancy (85), as well as consequences of ETS exposure on children's respiratory health (8), are well established. Apart from lung cancer (5, 8) and ischaemic heart disease (6, 7), the other potential health consequences of tobacco smoke exposure have been less extensively investigated. Overall, there is a suggestion of a weak association between exposure to tobacco smoke during pregnancy and childhood cancer. Bias and confounding, however, can not be ruled out at this stage. Further studies are needed to overcome the practical difficulties of identifying adequate numbers of cases for these rare diseases and the possible limitations of the available epidemiological investigations.

Table 1. Cohort studies of exposure to maternal smoke during pregnancy and childhood cancer

<i>Author & year, Country (Ref.)</i>	<i>Study population</i>	<i>Exposure</i>	<i>Cancer</i>	<i>N</i>	<i>Relative risk (95% CI)</i>
Neutel 1971, Canada, UK (17)	89,302 children 7-10 year follow-up	Mother smoking in pregnancy	All	64	1.3 (0.8-2.2)
Goldging 1990, UK (18)	16,193 children 10 year follow-up	Mother smoking 5+ cigarettes per day during pregnancy	All	33	2.5 (1.2-5.1)
Pershagen 1992, Sweden (19)	497,051 children 5 year follow-up	Mother smoking in pregnancy	All	327	1.0 (0.8-1.3)
			Solid tumours	198	1.0 (0.7-1.3)
			Central nervous system	81	1.0 (0.6-1.6)
		Lymphatic and haematopoietic system	129	1.0 (0.7-1.5)	
Klebanoff 1996, USA, (20)	54,795 children 8 year follow-up	Maternal smoking in pregnancy	All	51	0.7 (0.4-1.2)
			Leukaemia	17	0.8 (0.3-2.1)

Notes:

CI confidence interval

Table 2. Case-control studies of exposure to tobacco smoke from the mother during pregnancy and overall risk of cancer in childhood

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>N cases/controls</i>	<i>Maternal smoking</i>	<i>Relative risk (95% CI)</i>
Buckley 1986 (21)	USA, Canada	1814/720	1-9 cpd	1.3 (0.9-1.9)
			10+ cpd	1.0 (0.8-1.2)
McKinney 1986 (22)	UK	555/1110	1-10 cpd	1.1 (0.8-1.5)
			11+ cpd	0.8 (0.6-1.1)
Stjernfeldt 1986 (23)	Sweden	305/340*	1-9 cpd	1.1 [0.6-1.8]
			10+ cpd	1.6 [1.1-2.3]
Forsberg 1990 (24)	Sweden	69/139	Any smoking	1.1 (0.6-1.9)
John 1991 (25)	USA	223/196	Any smoking	1.3 (0.7-2.1)
Goldging 1992 (26)	UK	195/558	Any smoking	1.2 (0.8-1.8)
Sorahan 1997 (27)	UK	1549/1549	1-9 cpd	1.0 (0.8-1.2)
			10-20 cpd	1.2 (1.0-1.5)
			21+ cpd	1.3 (0.7-2.3)

Notes:

Figures in square brackets were derived from raw data

* diabetic controls

CI confidence interval

cpd cigarettes per day

Table 3. Case-control studies of exposure to tobacco smoke from the mother during pregnancy and risk of lymphatic and haematopoietic neoplasms in childhood

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>Neoplasm</i>	<i>N cases/ controls</i>	<i>Maternal smoking</i>	<i>Relative risk (95% CI)</i>
van Steensel-Moll 1985 (28)	Netherlands	LHP	519/507	Any smoking	1.0 (0.7-1.3)
Buckley 1986 (21)	USA, Canada	ALL	742/720	1-9 cpd	1.0 (0.6-1.5)
		NHL	169/720	10+ cpd	0.9 (0.7-1.1)
McKinney 1986 (22)	UK	Leukaemia	171/1110	1-9 cpd	0.8 (0.3-1.8)
		Lymphoma	74/1110	10+ cpd	1.0 (0.7-1.4)
Stjernfeldt 1986 (23)	Sweden	ALL	157/340*	1-10 cpd	1.0 (0.6-1.7)
		LHP	185/340*	11+ cpd	0.6 (0.4-1.0)
		NHL	16/340*	1-10 cpd	1.9 (0.9-4.0)
Magnani 1990 (29)	Italy	ALL	142/307	11+ cpd	1.0 (0.5-2.0)
		AnLL	22/307	1-9 cpd	1.3 [0.7-2.6]
		NHL	19/307	10+ cpd	[3.4] [2.1-5.7]
John 1991 (25)	USA	ALL	73/196	1-9 cpd	[1.3] [0.7-2.2]
		Lymphoma	26/196	10+ cpd	1.8 [1.2-2.8]
				1-9 cpd	[1.4] [0.3-6.7]
Urquhart 1991 (30)	UK	ALL	142/307	10+ cpd	2.1 [0.7-6.4]
		AnLL	22/307	Any smoking	0.7 (0.5-1.1)
		NHL	19/307	Any smoking	2.0 (0.8-4.8)
Roman 1993 (31)	UK	ALL	73/196	Any smoking	1.7 (0.7-4.5)
		Lymphoma	26/196	Any smoking	1.9 (0.9-4.1)
				Any smoking	2.3 (0.8-7.1)
Sorahan 1997 (27)	UK	LHP	14/51	Any smoking	1.0 (0.3-1.4)
		LHP	54/324	Any smoking	0.5 (0.2-1.2)
		ALL	367/367	Any smoking	1.2 (1.0-1.5)
		Myeloid leukaemia	115/115		1.2 (0.9-1.7)
		Monocytic leukaemia	27/27		1.2 (0.6-2.5)
		Lymphoma	125/125		0.8 (0.5-1.1)

Notes:

Figures in square brackets were derived from raw data

* diabetic controls

ALL acute lymphocytic leukaemia
leukaemia

CI confidence interval

LHP lymphohaematopoietic system

AnLL acute non-lymphocytic

cpd cigarettes per day

NHL non-Hodgkin's lymphoma

Table 4. Case-control studies of exposure to tobacco smoke from the mother during pregnancy and risk of cancer of the nervous system in childhood

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>Cancer</i>	<i>N cases/ controls</i>	<i>Maternal smoking</i>	<i>Relative risk (95% CI)</i>
Preston Martin 1982 (32)	USA	Brain tumour	209/209	Any smoking	1.1 [0.7-1.6]
McKinney 1986 (22)	UK	CNS tumour	78/1110	1-10 cpd	1.1 (0.5-2.4)
				11+ cpd	1.0 (0.5-2.0)
Stjernfeldt 1986 (23)	Sweden	CNS tumour	43/340*	1-9 cpd	1.0 [0.4-2.8]
				10+ cpd	0.9 [0.4-2.0]
Kramer 1987 (33)	USA	Neuroblastoma	104/101	Any smoking	1.3 [0.7-2.3]
Bunin 1989 (34)	USA	Heritable retinoblastoma	67/201	Any smoking	2.0 (0.7-6.5)
		Non-heritable retinoblastoma	115/201		1.1 (0.6-2.1)
Howe 1989 (35)	Canada	Brain tumour	74/138	Any smoking	1.4 (0.7-3.0)
Kuijten 1990 (36)	USA	Astrocytoma	163/163	Any smoking	1.0 (0.6-1.7)
John 1991 (25)	USA	CNS tumour	48/196	Any smoking	0.7 (0.3-1.7)
Schwartzbaum 1992 (37)	USA	Neuroblastoma	101/690	1-9 cpd	1.3 (0.4-3.5)
				10+ cpd	1.7 (0.7-2.4)
Gold 1993 (38)	USA	Brain tumour	361/1083	Any smoking	1.1 (0.8-1.5)
McCredie 1994 (39)	Australia	Brain tumour	82/164	Any smoking	0.9 (0.5-1.8)
Bunin 1994 (40)	USA	Astrocytoma	155/155	Any smoking	1.0 (0.6-1.7)
		Primary neuro- ectodermal tumour	166/166		1.0 (0.6-1.7)
Cordier 1994 (41)	France	Brain tumour	109/113	Any smoking	1.6 (0.7-3.5)
Filippini 1994 (42)	Italy	Brain tumour	91/321	1-10 cpd	1.6 (0.7-3.8)
				11+ cpd	1.7 (0.4-6.6)
Norman 1996 (43)	USA	Brain tumour	540/801	Any smoking	1.0 (0.7-1.3)
Sorahan 1997 (27)	UK	CNS tumour	229/229	Any smoking	1.0 (0.8-1.3)
		Neuroblastoma	138/138		0.9 (0.7-1.3)

Notes:

Figures in square brackets were derived from raw data

* diabetic controls

CI confidence interval

CNS central nervous system

cpd cigarettes per day

NA not available

Table 5. Case-control studies of exposure to tobacco smoke from the mother during pregnancy and risk of solid tumours other than cancer of the nervous system in childhood

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>Cancer</i>	<i>N cases/ controls</i>	<i>Maternal smoking</i>	<i>Relative risk (95% CI)</i>
Daigle 1986 (44)	USA	Ewing sarcoma	98/98	Any smoking*	2.2 (NA)
Holly 1992 (45)	USA	Ewing sarcoma	43/193	Any smoking	1.1 (0.5-2.4)
Buckley 1986 (21)	USA, Canada	Kidney cancer	61/720	1-9 cpd 10+ cpd	1.6 (0.6-4.2) 0.9 (0.5-1.8)
McKinney 1986 (22)	UK	Wilms tumour	32/1110	1-10 cpd 11+ cpd	0.9 (0.3-2.6) 1.2 (0.4-3.5)
Stjernfeldt 1986 (23)	Sweden	Kidney tumour	16/340	1-9 cpd 10+ cpd	0.7 [0.1-5.6] 2.5 [0.9-7.2]
Olshan 1993 (46)	USA	Wilms tumour	200/233	1-9 cpd 10+ cpd	0.8 (0.3-1.8) 0.7 (0.4-1.3)
Sorahan 1997 (27)	UK	Wilms tumour Bone cancer	133/133 22/22	Any smoking	1.0 (0.7-1.4) 0.9 (0.4-2.0)
Buckley 1989 (47)	USA	Hepatoblastoma	75/75	1-9 cpd 10-19 cpd 20+ cpd	2.6 (NA) 0.8 (NA) 1.2 (NA)
Magnani 1989 (48)	Italy	All soft tissue sarcomas Rabdomiosarcoma	52/326 36/326	1-15 cpd 16+ cpd 1-15 cpd 16+ cpd	1.0 (0.4-2.4) 0.8 (0.4-2.0) 0.7 (0.3-2.0) 0.8 (0.4-1.8)
Grufferman 1991 (49)	USA	Rabdomiosarcoma	322/322	Any smoking	1.0 (0.8-1.4)
John 1991 (25)	USA	Soft tissue sarcoma	26/196	Any smoking	1.2 (0.5-3.4)

Notes:

Figures in square brackets were derived from raw data

* including paternal smoking

CI confidence interval

cpd cigarettes per day

NA not available

Table 6. Case-control studies of exposure to tobacco smoke from the father during pregnancy and risk of neoplasms in childhood

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>Cancer</i>	<i>N cases/ controls</i>	<i>Paternal smoking</i>	<i>Relative risk (95% CI)</i>
Magnani 1990 (29)	Italy	ALL	142/307	Any smoking	0.9 (0.6-1.5)
		AnLL	22/307		0.9 (0.3-2.1)
		NHL	19/307		6.7 (1.0-43)
John 1991 (25)	USA	ALL	73/196	Any smoking	1.4 (0.6-3.1)
		Lymphoma	26/196		1.6 (0.5-5.4)
		Brain tumour	48/196		1.6 (0.7-3.5)
Filippini 1994 (42)	Italy	Brain tumour	91/321	Any smoking	1.3 (0.8-2.2)
Ji 1997 (51)	China	All cancers	642/642	1-9 cpd	1.5 (1.1-2.3)
				10-14 cpd	1.1 (0.8-1.6)
				15+ cpd	1.5 (1.0-2.3)
		Acute leukaemia	166/166	1-9 cpd	1.6 (0.7-3.9)
				10-14 cpd	0.9 (0.4-1.5)
				15+ cpd	1.9 (0.8-4.6)
		Lymphoma	87/87	1-9 cpd	3.4 (0.8-14)
				11-14 cpd	1.1 (0.3-4.8)
				15+ cpd	3.8 (0.9-17)
		Brain tumour	107/107	1-9 cpd	1.5 (0.5-4.5)
				11-14 cpd	1.6 (0.6-4.7)
				15+ cpd	2.1 (0.6-8.1)
Sorahan 1997 (27)	UK	ALL	367/367	Any smoking	1.1 (0.9-1.3)
		Myeloid leukaemia	115/115		1.0 (0.7-1.3)
		Lymphoma	125/125		1.4 (1.0-1.8)
		Wilms tumour	133/133		1.0 (0.8-1.3)
		Bone cancer	22/22		1.5 (0.7-3.1)
		CNS tumour	229/229		1.2 (1.0-1.5)
Preston-Martin 1982 (32)	USA	Brain tumour	209/209	Any smoking	1.5 [1.0-2.2]
Kramer 1987 (33)	USA	Neuroblastoma	104/101	Any smoking	1.3 [0.7-2.3]
Bunin 1989 (34)	USA	Heritable retinoblastoma	67/201	Any smoking	2.3 (0.8-7.0)
		Non-heritable retinoblastoma	115/201		1.2 (0.7-2.3)
Howe 1989 (35)	Canada	Brain tumour	74/138	Any smoking	1.1 (0.6-2.1)
Kuijten 1990 (36)	USA	Brain tumour	163/163	Any smoking	0.8 (0.5-1.3)

Table 6 (cont'd)

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>Cancer</i>	<i>N cases/ controls</i>	<i>Paternal smoking</i>	<i>Relative risk (95% CI)</i>
Gold 1993 (38)	USA	Brain tumour	361/1083	1-19 cpd	0.7 (0.4-1.2)
				20+ cpd	1.1 (0.8-1.5)
McCredie 1994 (39)	Australia	Brain tumour	82/164	Any smoking	2.2 (1.2-3.8)
Bunin 1994 (40)	USA, Canada	Astrocytoma	155/321	Any smoking	1.0 (0.6-1.7)
		Primary neuro- ectodermal tumour	166/321		1.0 (0.6-1.7)
Norman 1995 (43)	USA	Brain tumour	540/801	Any smoking	1.2 (0.9-1.5)
Holly 1992 (45)	USA	Ewing sarcoma	43/193	Any smoking	0.9 (0.4-1.9)
Olshan 1993 (46)	USA	Wilms tumour	200/233	1-9 cpd	0.5 (0.1-1.6)
				10+ cpd	1.1 (0.7-1.8)
Grufferman 1982 (52)	USA	Rabdomiosarcoma	33/99	Any smoking	3.9 (1.5-9.6)
Magnani 1989 (48)	Italy	All soft tissue sarcomas	52/326	1-15 cpd	1.0 (0.4-2.3)
				16+ cpd	0
		Rabdomiosarcoma	36/326	1-15 cpd	0.7 (0.3-1.4)
				16+ cpd	0
Grufferman 1991 (49)	USA	Rabdomiosarcoma	322/322	Any smoking	1.0 (0.7-1.4)

Notes:

Figures in square brackets were derived from raw data

ALL acute lymphocytic leukaemia AnLL acute non-lymphocytic leukaemia

CI confidence interval cpd cigarettes per day

NHL non-Hodgkin's lymphoma

Table 7. Studies of childhood exposure to ETS and lung cancer

<i>Author & year (Ref.)</i>	<i>Country</i>	<i>Gender</i>	<i>N cases/ controls</i>	<i>Paternal smoking RR (95% CI)</i>	<i>Maternal smoking RR (95% CI)</i>	<i>Smoking of any person RR (95% CI)</i>
Koo 1987 (55)	Hong-Kong	F	88/137	-	-	2.1 (0.5-95)
Pershagen 1987 (56)	Sweden	F	77/*	-	-	1.0 (0.4-2.3)
Shimizu 1988 (57)	Japan	F	90/90	1.1 (NA**)	4.0 (NA**)	-
Janerich 1990 (58)	USA	M/F	191/191	-	-	[1.5 (0.8-2.8)]
Sobue 1990 (59)	Japan	F	144/713	0.8 (0.5-1.2)	1.3 (0.7-2.3)	-
Brownson 1992 (60)	USA	F	432/1402	-	-	0.7 (0.5-0.9)
Stockwell 1992 (61)	USA	F	210/301	1.2 (0.6-2.3)	1.6 (0.6-4.3)	-
Fontham 1994 (62)	USA	F	653/1253	0.8 (0.7-1.2)	0.9 (0.6-1.2)	0.9 (0.7-1.1)
Kabat 1995 (63)	USA	M	41/117	-	-	0.9 (0.4-1.9)
		F	69/187	-	-	1.5 (0.9-2.8)
Zaridze 1998 (64)	Russia	F	189/358	0.9 (0.6-1.3)	-	-
Boffetta 1998 (65)	7 countries	MF	650/1542	0.8 (0.6-0.9)	0.9 (0.6-1.5)	0.8 (0.6-1.0)

Notes:

Figures in square brackets were derived from raw data

* cohort study

** excluded from the meta-analysis

CI confidence interval

RR relative risk

REFERENCES

1. Peto R, Lopez AD, Boreham J, Thun M, Heath C, Doll R. Mortality from smoking worldwide. *Br Med Bull* 1996; 52: 12-21.
2. Law MR, Hackshaw AK. Environmental tobacco smoke. *Br Med Bull* 1996; 52: 22-34.
3. O'Neill IK, Brunnemann KD, Dodet B, Hoffman D, eds. *Environmental Carcinogens: Methods of Analysis and Exposure Measurement*, Vol. 9, Passive smoking. IARC Sci. Publ. N. 81, IARC, Lyon, 1987.
4. Löfroth G. Environmental tobacco smoke: overview of chemical composition and genotoxic components. *Mutation Res* 1989; 222: 73-80.
5. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *Br Med J* 1997; 315: 980-88.
6. Steenland K. Passive smoking and the risk of heart disease. *J Am Med Assoc* 1992;267:94-9.
7. Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *Br Med J* 1997; 315: 973-80.
8. U.S. Environmental Protection Agency. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* (Publ. N. EPA/600/6-90/006F). EPA Office of Research and Development, Washington, DC. 1992.
9. Tredaniel J, Boffetta P, Saracci R, Hirsch A. Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases. *Eur Respir J* 1994; 7: 173-85.
10. Evans HJ, Fletcher J, Torrance M, Hargreave TB. Sperm abnormalities and cigarette smoking. *Lancet* 1981; i: 627-9.
11. Draper GJ. General overview of studies of multigeneration carcinogenesis in man, particularly in relation to exposure to chemicals. In: *Perinatal and Multigeneration Carcinogenesis*. Napalkov NP, Rice JM, Tomatis L, Yamasaki H, eds. IARC Sci. Publ. N. 96. IARC, Lyon, 1989, pp. 275-88.
12. Tredaniel J, Boffetta P, Little J, Saracci R, Hirsch A. Exposure to passive smoking during pregnancy and childhood, and cancer risk: the epidemiological evidence. *Paed Perinat Epidemiol* 1994; 8: 233-55.
13. Norman MA, Holly EA, Preston-Martin S. Childhood brain tumours and exposure to tobacco smoke. *Cancer Epidemiol Biom Prev* 1996; 5: 85-91.
14. Lee PN. Lung cancer and passive smoking: association and artefact due to misclassification of smoking habits? *Toxicol Lett* 1987; 35: 157-62.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986; 7: 177-88.
16. Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997; 315: 629-34.
17. Neutel CI, Buck C. Effect of smoking during pregnancy on the risk of cancer in children. *J Natl Cancer Inst* 1971; 47: 59-63.
18. Goldging J, Paterson M, Kinlen LJ. Factors associated with childhood cancer in a national cohort study. *Br J Cancer* 1990; 62: 304-8.
19. Pershagen G, Ericson A, and Otterblad-Olausson P. Maternal smoking in pregnancy: does it increase the risk of childhood cancer? *Int J Epidemiol* 1992; 21: 1-5.
20. Klebanoff MA, Clemens JD, Read JS. Maternal smoking during pregnancy and childhood cancer. *Am J Epidemiol* 1996; 144: 1028-33.
21. Buckley JD, Hobbie WL, Ruccione K, Sather HN, Woods WG, Hammond GD. Maternal smoking during pregnancy and the risk of childhood cancer. *Lancet* 1986; ii: 519-20.
22. McKinney PA, Stiller CA (for the IRESCC group). Maternal smoking during pregnancy and the risk of childhood cancer. *Lancet* 1986; ii: 519.
23. Stjernfeldt M, Berglund K, Lindsten J, Ludvigsson J. Maternal smoking during pregnancy and risk of childhood cancer. *Lancet* 1986; i: 1350-2.
24. Forsberg JG, Kallen B. Pregnancy and delivery characteristics of women whose infants develop child cancer. *APMIS* 1990; 98: 37-42.

25. John EM, Savitz DA, Sandler DP. Prenatal exposure to parents' smoking and childhood cancer. *Am J Epidemiol* 1991; 133: 123-32.
26. Goldging J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *Br Med J* 1992; 305: 341-6.
27. Sorahan T, Lancashire RJ, Hulten MA, Peck I, Stewart AM. Childhood cancer and parental use of tobacco: deaths from 1953 to 1955. *Br J Cancer* 1997; 75: 134-8.
28. van Steensel-Moll HA, Valkenburg HA, Vanderbroucke JP, van Zanen GE. Are maternal fertility problems related to childhood leukemia ? *Int J Epidemiol* 1985; 14: 555-9.
29. Magnani C, Pastore G, Luzzatto L, Terracini B. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. *Tumori* 1990; 76: 413-9.
30. Urquhart JD, Black RJ, Muirhead MJ, Sharp L, Maxwell M, Eden OB, et al. Case-control study of leukemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation. *Br Med J* 1991; 302: 687-92.
31. Roman E, Watson A, Beral V, Buckle S, Bull D, Baker K, et al. Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 years living in West Berkshire and North Hampshire health districts. *Br Med J* 1993; 306: 615-21.
32. Preston-Martin S, Yu MC, Benton B, Henderson BE. N-nitroso compounds and childhood brain tumors: a case-control study. *Cancer Res* 1982; 42: 5240-5.
33. Kramer S, Ward E, Meadows AT, Malone KE. Medical and drug risk factors associated with neuroblastoma: a case-control study. *J Natl Cancer Inst* 1987; 78: 797-804.
34. Bunin GR, Meadows AT, Emanuel BS, Buckley JD, Woods WG, Hammond GD. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. *Cancer Res* 1989; 49: 5730-5.
35. Howe GR, Burch JD, Chiarelli AM, Risch HA, Choi BCK. An exploratory case-control study of brain tumors in children. *Cancer Res* 1989; 49: 4349-52.
36. Kuijten RR, Bunin GR, Nass CC, Meadows AT. Gestational and familial risk factors for childhood astrocytoma: results of a case-control study. *Cancer Res* 1990; 50: 2608-12.
37. Schwartzbaum JA. Influence of the maternal prenatal drug consumption on risk of neuroblastoma in the child. *Am J Epidemiol* 1992; 135: 1358-67.
38. Gold EB, Leviton A, Lopez R, Gilles FH, Hedley-Whyte ET, Kolonel LN, et al. Parental smoking and risk of childhood brain tumors. *Am J Epidemiol* 1993; 137: 620-8.
39. McCredie M, Maisonneuve P, Boyle P. Perinatal and postnatal risk factors for malignant brain tumours in New South Wales children. *Int J Cancer* 1994; 56: 11-5.
40. Bunin GR, Buckley JD, Boesel CP, Rorke LB, Meadows AT. Risk factors for astrocytic glioma and primitive neuroectodermal tumour of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol Biom Prev* 1994; 3: 197-204.
41. Cordier S, Iglesias MJ, Le Goaster C, Guyot MM, Mandereau L, Hemon D. Incidence and risk factors for childhood brain tumours in the Ile de France. *Int J Cancer* 1994; 59: 776-82.
42. Filippini G, Farinotti M, Lovicu G, Maisonneuve P, Boyle P. Mothers' active and passive smoking during pregnancy and risk of brain tumours in children. *Int J Cancer* 1994; 57: 769-74.
43. Norman MA, Holly EA, Ahn DK, Preston-Martin S, Mueller BA, Bracci PM. Prenatal exposure to tobacco smoke and childhood brain tumours: results from the United States West Coast childhood brain tumour study. *Cancer Epidemiol Biomarkers Prev* 1996; 5: 127-33.
44. Daigle AE. Epidemiologic study of etiologic factors in Ewing's sarcoma. Thesis to the University of Minnesota for the degree of Doctor of Philosophy, 1986.
45. Holly EA, Aston DA, Ahn DK, Kristiansen JJ. Ewing's bone sarcoma, paternal occupational exposure, and other factors. *Am J Epidemiol* 1992; 135: 122-9.
46. Olshan AF, Breslow NE, Falletta JM, Grufferman S, Pendergrass T, Robison LL, et al. Risk factors for Wilms tumor. Report from the National Wilms Tumor Study. *Cancer* 1993; 72: 938-44.

47. Buckley JD, Sather H, Ruccione K, Rogers PC, Haas JE, Henderson BE, et al. A case-control study of risk factors for hepatoblastoma. A report from the Childrens Cancer Study Group. *Cancer* 1989; 64: 1169-76.
48. Magnani C, Pastore G, Luzzatto L, Carli M, Lubrano P, Teracini B. Risk factors for soft tissue sarcomas in childhood: a case-control study. *Tumori* 1989; 75: 396-400.
49. Grufferman S, Gula MJ, Olshan AF, Falletta JM, Buckley, Pendergrass TW, et al. Absence of an association between parents' cigarette smoking and risk of rhabdomyosarcoma in their children. *Paediatr Perinat Epidemiol* 1991; 5: A17.
50. McKinney PA, Cartwright RA, Saiu JMT, Mann JR, Stiller CA, Draper GJ, et al. The inter-regional epidemiological study of childhood cancer (IRESCC): a case control study of aetiological factors in leukaemia and lymphoma. *Arch Dis Child* 1987; 62: 279-87.
51. Ji BT, Shu XO, Linet MS, Zheng W, Wacholder S, Gao YT et al. Paternal cigarette smoking and the risk of childhood cancer among offspring of nonsmoking mothers. *J Nat Cancer Inst* 1997; 89: 238-44.
52. Grufferman S, Wang HH, DeLong ER, Kimm SYS, Delzell ES, Falletta JM. Environmental factors in the etiology of rhabdomyosarcoma in childhood. *J Natl Cancer Inst* 1982; 68: 107-13.
53. Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. *Br Med J* 1958; i: 1495-508.
54. Grufferman S, Schwartz AG, Ruyman FB, Maurer HM. Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. *Cancer Causes Control* 1993; 4: 217-24.
55. Koo LC, Ho JH, Saw D, Ho CY. Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. *Int J Cancer* 1987; 39: 162-9.
56. Pershagen G, Hrubec Z, Svensson C. Passive smoking and lung cancer in Swedish women. *Am J Epidemiol* 1987; 125: 17-24.
57. Shimizu H, Morishita M, Mizuno K, Masuda T, Ogura Y, Santo M et al. A case-control study of lung cancer in nonsmoking women. *Tohoku J Exp Med* 1988; 154: 389-97.
58. Janerich DT, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, et al. Lung cancer and exposure to tobacco smoke in the household. *N Engl J Med* 1990; 323: 632-6.
59. Sobue T. Association of indoor air pollution and lifestyle with lung cancer in Osaka, Japan. *Int J Epidemiol* 1990; 19: S62-6.
60. Brownson RC, Alavanja MCR, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. *Am J Publ Health* 1992; 82: 1525-30.
61. Stockwell HG, Goldman AL, Lyman GH, Noss CI, Armstrong AW, Pinkham PA, et al. Environmental tobacco smoke and lung cancer risk in nonsmoking women. *J Natl Cancer Inst* 1992; 84: 1417-22.
62. Fontham ET, Correa P, Reynolds P, Wu Williams A, Buffler PA, Greenberg RS, et al. Environmental tobacco smoke and lung cancer in nonsmoking women: a multicenter study. *JAMA* 1994; 271: 1752-9.
63. Kabat GC, Stellman SD, Wynder EL. Relation between exposure to environmental tobacco smoke and lung cancer in lifetime nonsmokers. *Am J Epidemiol* 1995; 142: 141-8.
64. Zaridze D, Maximovitch D, Zemlyanaya G, Aitakov ZN, Boffetta P. Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. *Int J Cancer* 1998; 75: 335-8.
65. Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, et al. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. *J Natl Cancer Inst* 1998; 90: 1440-50.
66. Gold E, Gordis L, Tonascia J, Szklo M. Risk factors for brain tumors in children. *Am J Epidemiol* 1979; 109: 309-19.
67. Linet MS, Brookmeyer R. Use of cancer controls in case-control cancer studies. *Am J Epidemiol* 1987; 125: 1-11.
68. Wilkins JR, Sinks T. Parental occupation and intracranial neoplasms of childhood: results of a case-control interview study. *Am J Epidemiol* 1990; 132: 275-92.

69. Hemminki K, Saloniemi I, Salonen T, Partanen T, Vainio H. Childhood cancer and parental occupation in Finland. *J Epidemiol Community Health* 1981; 35: 11-5.
70. Peters JM, Preston-Martin S, Yu MC. Brain tumors in children and occupational exposure of parents. *Science* 1981; 213: 235-7.
71. Harvey EB, Boice JD, Honeyman M, Flannery JT. Prenatal X-ray exposure and childhood cancer in twins. *N Engl J Med* 1985; 312: 541-5.
72. Preston-Martin S. N-nitroso compounds as a cause of human cancer. In: *The Relevance of N-nitroso Compounds to Human Cancer: Exposures and Mechanisms*. Bartsch H, O'Neill I, Schulte-Hermann R, eds. IARC Sci. Publ. N. 84, IARC, Lyon, 1987; pp. 477-84.
73. Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. In: *Social Inequalities and Cancer*. Kogevinas M, Pearce N, Susser M, Boffetta P, eds. IARC Sci. Publ. N. 138, IARC, Lyon, 1997, pp. 65-176.
74. Marsden HB. The classification of childhood tumours. In: *International Incidence of Childhood Cancer*. Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. IARC Sci. Publ. N. 87, IARC, Lyon, 1988, pp. 9-16.
75. Coghlin J, Gann PH, Hammond SK, Skipper PL, Taghizadeh K, Paul M, et al. 4-aminobiphenyl hemoglobin adducts in fetuses exposed to the tobacco smoke carcinogen in utero. *J Natl Cancer Inst* 1991; 83: 274-80.
76. Greenberg RA, Haley NJ, Etzel RA, Loda FA. Measuring the exposure of infants to tobacco smoke. Nicotine and cotinine in urine and saliva. *N Engl J Med* 1984; 310: 1075-8.
77. Etzel RA, Greenberg RA, Haley NJ, Loda FA. Urine cotinine excretion in neonates exposed to tobacco smoke products in utero. *J Pediatr* 1985; 107: 146-8.
78. Sorsa M, Husgafvel-Pursiainen K, Järventaus H, Koskimies K, Salo H, Vainio H. Cytogenetic effects of tobacco smoke exposure among involuntary smokers. *Mutation Res* 1989; 222: 111-6.
79. Jones AH, Fantel AG, Kocan RA, Juchau MR. Bioactivation of procarcinogens to mutagens in human fetal and placental tissues. *Life Sci* 1977; 21: 1831-6.
80. Everson RB, Randerath E, Santella RM, Cefalo RC, Avitts TA, Randerath K. Detection of smoking-related covalent DNA adducts in human placenta. *Science* 1986; 231: 54-7.
81. Everson RB, Randerath E, Santella RM, Avitts TA, Weinstein IB, Randerath K. Quantitative associations between DNA damage in human placenta and maternal smoking and birth weight. *J Natl Cancer Inst* 1988; 80: 567-76.
82. Vessey MP. Epidemiological studies of the effects of diethylstilboestrol. In: *Perinatal and Multigeneration Carcinogenesis*. Napalkov NP, Rice JM, Tomatis L, Yamasaki H, eds. IARC Sci. Publ. N. 96. IARC, Lyon, 1989, pp. 335-48.
83. Rice JM. Perinatal period and pregnancy: intervals of high-risk for chemical carcinogens. *Environ Health Perspect* 1979; 29: 23-7.
84. Tomatis L, Ponomarev, Turusov V. The effect of ethylnitrosourea administration during pregnancy on three subsequent generations. *Int J Cancer* 1977; 19: 240-8.
85. U.S. Department of Health and Human Services. The health consequences of smoking for women. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health, Washington, DC, 1980.