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Original Paper

Cancer in the Offspring of Parents with Lung Cancer

N. Seersholm,[1] H. Hertz[2] and J.H. Olsen[1]

[1]Division for Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, Box 839, DK-2100 Copenhagen Ø; and [2]Paediatric Department, Rigshospitalet, Copenhagen, Denmark

Despite several studies on the role of passive smoking in the development of childhood cancer, particularly leukaemia, lymphomas and brain cancer, no definitive answer has yet been provided. The aim of the cohort study reported here was to analyse the incidence of cancer in the offspring of young lung cancer patients on the basis of the assumption that all of the offspring were exposed passively to smoke. The files of the Danish Cancer Registry provided 3348 cases of lung cancer patients born after 1935, and their offspring ($n = 6417$) were identified through the Danish Population Register. The files of the offspring were then linked with the files of the Danish Cancer Registry and the numbers of cancers observed in the offspring were compared with those expected from national age-specific and calender-time-specific rates. A total of 135 333 person-years was the basis for analysis. Twenty-six cancers were observed, with 30.3 expected, yielding a standardised incidence ratio (SIR) of 0.9 (90% confidence interval (CI), 0.6–1.2). There was no excess of brain tumours, leukaemias or lymphomas. Stratification for sex of the lung cancer patients revealed a non-significantly increased risk for both non-Hodgkin's lymphoma (three cases; SIR = 3.4; 90% CI: 0.9–8.7) and Hodgkin's disease (three cases; SIR = 2.6; 90% CI: 0.7–6.6) in the offspring of female lung cancer patients. These results suggest that there is little evidence of an excess cancer risk in childhood, whether due to passive smoking or to as yet unidentified genetic factors, among the offspring of people who develop lung cancer. However, the results are limited by the fact that exposure was only assessed indirectly, with no measurement of actual cigarette consumption made. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

THE ROLE of passive smoking in the development of cancer in adults has been the subject of a large number of studies, many of which found positive associations with lung cancer [1, 2]. Epidemiological studies on a possible association between childhood cancer and maternal smoking habits during pregnancy [3–9], or passive smoking of the child at home [10–12], have provided no clear answer. Some authors have found increased risks for all types of childhood cancer combined [3, 6, 7] and for specific types of cancer, particularly leukaemia, lymphomas and tumours of the central nervous system [3, 7, 11]. In other studies, no such associations were seen [4, 5, 8–12]. These inconsistent findings may be due to inaccurate assessment of smoking habits, such as recall bias in case–control studies (case mothers recall their smoking habits differently from control mothers) and under-reporting of smoking habits in cohort studies. It is, therefore, uncertain whether there is an association of passive smoking and childhood cancer.

In the present study of the rates of cancer in children of lung cancer patients, we considered registration of lung cancer in an adult to be a strong indication that their offspring were exposed to environmental tobacco smoke. It is estimated that 75–90% of lung cancer cases arising in the Danish population are caused by tobacco smoking [13]. The proportion is even higher in the subgroup of patients with onset of cancer at an early age, suggesting that a diagnosis of lung cancer in relatively young adults can serve as a valid proxy for tobacco smoking [14].

PATIENTS AND METHODS

The parental study group consisted of 3348 individuals who were born after 1935 and notified to the Danish Cancer

Correspondence to N. Seersholm.
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Registry with cancer of the lung diagnosed during the period 1 April 1968 to 31 December 1991. The Central Population Register (CPR) was established in Denmark on 1 April 1968, and all citizens were assigned a unique, 10-digit, personal identification number (also used by the Cancer Registry), which includes six digits for date of birth. All citizens born after 1953 and alive in 1968 are recorded with their parents. If it is assumed that a person begins to give birth after his 18th birthday, it is possible to trace offspring alive in 1968 to all persons born after 1935. The recordings of parenthood are based on legal relationships and it is possible that a few adopted offspring are recorded as biological offspring. By means of computerised record linkage with the files of the CPR, using the identification numbers of the lung cancer patients, offspring alive on or born after 1 April 1968 were selected, with name, identification number and date of death if deceased or date of emigration if they had emigrated from Denmark.

Cancer incidence and analysis

The records of the offspring were linked to the files of the Cancer Registry by use of the personal identification number [15]. The period of follow-up for cancer occurrence among offspring was from 1 April 1968 or the date of birth if born later through to the date of death, the date of emigration, the date of the 35th birthday, or 31 December 1991, whichever came first. The calculation of person years of follow-up is illustrated in Figure 1. If the offspring developed cancer and died before 1968 they would be missed and we would underestimate the cancer risk. However, on a previous occasion, we have identified the parents of all children in Denmark who were registered with a cancer diagnosed after 1943 [16], and none were present among our lung cancer patients. In 13 families, both parents had lung cancer and for these the cancer risk among the offspring was only counted once. There were no occurrences of cancer in the offspring of these families.

Tumours observed among the offspring were classified according to a modified version of the International Classification of Diseases, Seventh Revision (ICD-7). National sets of incidence data by sex, 5-year age groups and calendar year periods for these tumour categories were applied to the person-years under observation for the offspring to obtain the number of cancers expected had the cohort members experienced the same rates of cancers as those in the general population. The statistical methods were based on the assumption that the observed number of cancer cases follows a Poisson distribution. Significance and confidence intervals for the standardised incidence ratio (SIR), taken as the ratio of observed-to-expected cancers, were calculated using exact confidence limits.

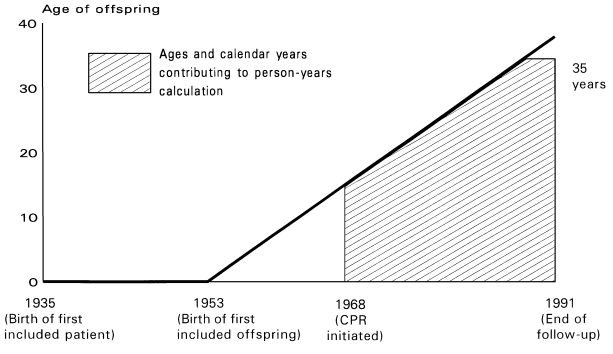

Figure 1. Calculation of person-years of follow-up. The period of follow-up started from 1 April 1968 or later if born after this date and ended at the offspring's 35th birthday, at death, emigration, or 31 December 1991. See text for further explanation.

RESULTS

Of the 3348 (1794 men, 1554 women) lung cancer patients, all diagnosed before age 56 years, 2774 (83%) had a total of 6417 (3325 boys, 3092 girls) offspring born between 1953 and 1991 and before the date of the parents' lung cancer diagnosis. The age distribution among the offspring at the end of follow-up were: 257 between 0 and 9 years, 1338 between 10 and 19 years, 3561 between 20 and 29 years and 1261 between 30 and 34 years. Of the lung cancer patients, 176 were under 35 years of age at diagnosis, 957 were between 35 and 45 years and 2215 were over 45 years. The offspring were followed up for an average of 21.1 years (range, 0–23.7), yielding a total of 135 333 person-years (Figure 1).

An overall total of 26 malignancies were found among the offspring, with 30.3 expected (SIR = 0.9; 90% CI: 0.6–1.2) (Table 1). The incidences of cancers at sites previously reported as being due to parental smoking were not significantly increased: four cases (SIR = 1.0; NS) of leukaemia, three cases (SIR = 0.5; NS) of cancers of the brain and nervous system and eight cases of lymphoma (SIR = 2.1; 90% CI: 1.0–3.7) were found; none of the risks at other sites were significantly elevated. When we stratified for the sex of the offspring, a significantly increased risk for non-Hodgkin's lymphoma was found among girls based on three cases (SIR = 5.7; 90% CI: 1.6–15).

In order to calculate whether there was a different cancer occurrence in the offspring depending on the father or the mother being the lung cancer patient, the analysis was repeated after stratification for the sex of the parents (Table 2). Twenty cancers were observed, with 16.3 expected (SIR = 1.2; NS) among the offspring of female lung cancer patients. A non-significantly increased risk was seen for both

Table 1. *Observed (obs) and expected (exp) numbers of cancers in the* 6417 *offspring of parents with lung cancer, with standardised incidence ratios (SIR) and associated* 90% *confidence intervals (CI)*

Site	Obs	Exp	SIR	90% CI
All malignant neoplasms	26	30.3	0.9	0.6–1.2
Lung	0	0.2	0	0.0–15
Breast	1	0.7	1.5	0.1–6.8
Testis	3	4.2	0.7	0.2–1.9
Kidney	1	0.7	1.4	0.1–6.7
Eye	1	0.4	2.4	0.1–12
Brain and nervous system	3	5.7	0.5	0.1–1.4
Bone	2	1.0	2.1	0.4–6.6
Connective tissue	0	0.6	0	0.0–5.0
Lymphatic and haematopoetic tissues	12	8.0	1.5	0.9–2.4
Non-Hodgkin's lymphoma	4	1.7	2.4	0.8–5.4
Hodgkin's disease	4	2.2	1.9	0.6–4.0
Leukaemia	4	4.2	1.0	0.3–2.2
Other*	3	9.1	0.3	0.1–0.9

*One kidney cancer, one breast cancer, and one cervical cancer.

Table 2. Risk of cancer in offspring stratified by sex of the parent with lung cancer

Site	Father with lung cancer			Mother with lung cancer		
	Obs	SIR	90% CI	Obs	SIR	90% CI
All malignant neoplasms	6	0.4	0.2–0.8	20	1.2	0.8–1.8
Testis	0	0	0.0–1.7	3	1.3	0.3–3.2
Bone	0	0	0.0–6.4	2	4.0	0.7–13
Brain and nervous system	1	0.4	0.0–1.7	2	0.7	0.1–2.2
Lymphatic and haematopoetic tissue	5	1.3	0.5–2.7	7	1.7	0.8–3.2
Non-Hodgkin's lymphoma	1	1.2	0.1–5.8	3	3.4	0.9–8.7
Hodgkin's disease	1	1.0	0.1–4.8	3	2.6	0.7–6.6
Leukaemia	3	1.4	0.4–3.6	1	0.5	0.0–2.4

Hodgkin's and non-Hodgkin's lymphoma but no increased risk for leukaemia or cancers of the brain and nervous system. The median ages at the time of diagnosis of Hodgkin's and the non-Hodgkin's lymphomas were 14 and 23 years, respectively. Six of the offspring of male lung cancer patients had cancers, which was significantly fewer than expected (SIR = 0.42; 90% CI: 0.18–0.83). No specific site was responsible for this decrease in cancer risk.

DISCUSSION

It has been shown in animal experiments that carcinogenic compounds in tobacco smoke cross the placental barrier [16, 17] and the metabolites of several components of tobacco smoke have been measured in the fetal cord blood of mothers who smoked during pregnancy [18]. Therefore, it is possible that childhood cancer could be caused by parental smoking. The findings of the present cohort study of the offspring of a large group of people who had developed lung cancer did not confirm those of previous studies that found passive smoking to be a causative agent of childhood leukaemia, brain tumours and lymphoma. However, we found a non-significantly increased risk of both Hodgkin's lymphoma and non-Hodgkin's lymphoma in the offspring of female lung cancer patients.

A Swedish cohort study [5] and several case–control studies [3, 4, 6, 7] have reported increased risks for childhood lymphoma (subtypes not specified) in the offspring of mothers who smoked during pregnancy, but none of these findings was statistically significant. Two of the studies found increased risks for lymphoma only in children of mothers who smoked fewer than 10 cigarettes daily [4, 5], whereas another case–control study found increasing risks with increasing cigarette consumption [3]. The latter seems to be more biologically plausible, but the study was the target of several critical letters pointing out problems of recall bias and selection of controls [4]. If the two subgroups of lymphomas found in our study are combined, the SIR is significantly elevated to 2.9 (90% CI: 1.3–5.8), but since the two types of lymphoma are so different, we consider it inappropriate to combine them.

Our study has several limitations: exposure was assessed indirectly by assuming that lung cancer patients had smoked heavily since they were teenagers and that the women continued to smoke during pregnancy. If this is not the case for all of the patients, particularly women who can have a high rate of adenocarcinoma, random misclassification of the exposure status will have been introduced, which in turn would attenuate any truly positive (or negative) association. However, this limitation is probably not of major relevance for the chosen study population of relatively young lung cancer patients.

A more serious limitation of the present approach is that the cancers observed in the offspring were compared with the expected number based on cancer rates for the entire Danish population. As approximately 50% of Danish adults smoke, 50% of the children would have been exposed to various levels of environmental tobacco smoke. Therefore, the relative risk for cancer in this study was underestimated and we may have missed an excess risk.

The strength of our approach is that it results in an unbiased assessment of smoking habits, which was a major problem in other studies.

These results, together with other large cohort studies, suggest that there is little evidence of an excess cancer risk in childhood, whether due to passive smoking or to as yet unidentified genetic factors, among the offspring of people who develop lung cancer.

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