Maternal Smoking and Childhood Leukemia and Lymphoma Risk among 1,440,542 Swedish Children

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Abstract

Possible *in utero* effects of maternal smoking on hemopoietic cancer in the offspring have been addressed previously, although the results are inconclusive. In this investigation, we take advantage of population-based registers in Sweden to examine maternal smoking during pregnancy and childhood risk of leukemia and lymphoma. Prospective data were available from 1,440,542 Swedish children born between 1983 and 1997. Proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) controlling for potential confounders. In the study base, 750 hemopoietic cancers occurred across 11 million person-years. Incidence rates per 100,000 person-years were 4.7 for acute lymphocytic leukemia (ALL), 0.45 for acute myelogenous leukemia, and 0.76 for non-Hodgkin's lymphoma. Maternal smoking was associated with a lower risk of ALL (HR, 0.73; 95% CI, 0.58–0.91). On the other hand, there was a higher risk of acute myelogenous leukemia (HR, 1.41; 95% CI, 0.74–2.67) particularly among heavy (≥10 cigarettes per day) smokers (HR, 2.28; 95% CI, 1.05–4.94). The data also suggested a small excess risk of non-Hodgkin's lymphoma (HR, 1.25; 95% CI, 0.76–2.04). Evidence from this large cohort suggests that maternal smoking affects the risk of childhood leukemia and lymphoma in the offspring. The Swedish registries provide unique opportunities to examine this research question, with a design inherently free of selection and recall biases. The apparent protective effect with ALL needs to be explored further and in no way supports maternal smoking as beneficial, given its adverse association with common pregnancy outcomes. (Cancer Epidemiol Biomarkers Prev 2004;13(9):1528–33)

Introduction

The negative effects of cigarette smoking on cancer risk in adulthood are well documented and include convincing evidence of an increased risk of cancer of the lung and larynx (1), bladder (2), esophagus (3), and oral cavity (4). The possible *in utero* effects of maternal smoking during pregnancy on subsequent cancer risk in the offspring have been addressed more recently through epidemiologic studies, although the results are in large part inconclusive (5, 6). With respect to childhood leukemia and lymphoma, several case-control studies have observed a positive effect of maternal smoking during pregnancy on risk of acute lymphocytic leukemia (ALL; refs. 7, 8), acute myelogenous leukemia (AML; refs. 9, 10), and lymphomas (7, 11). Other studies have found no association between maternal smoking and risk of these cancers (7, 12), whereas others still showed some evidence of a protective effect at least for ALL (13-15) and AML (15, 16).

A well-conducted case-control study is an efficient design to examine *in utero* exposure to cigarette smoking and risk of childhood cancer. However, this study design is vulnerable to potential biases, including selection and recall biases, which could account for the diverging results of prior studies. Given the rarity of childhood leukemia and lymphoma, however, a cohort study, which would avoid these potential limitations, is often difficult to undertake with sufficient statistical power.

In the present investigation, we take advantage of existing population-based registers in Sweden to examine the effect of maternal smoking during pregnancy on childhood risk of leukemia and lymphoma among a cohort of 1,440,542 Swedish children born between 1983 and 1997.

Materials and Methods

Study Population. The study base for the present investigation consists of all live births in Sweden between January 1, 1983 and December 31, 1997 that were registered in the population-based Swedish Medical Birth Registry. The Birth Registry includes >99% of all births in Sweden (17). Follow-up data on this cohort were achieved through linkage of the Birth Registry with the Swedish Cancer Registry and the National Cause of Death Registry. Because each Swedish

Received 11/21/03; revised 4/13/04; accepted 4/15/04.

Grant support: Swedish Cancer Society grant 4242-B00-02XBB and Swedish Foundation for International Cooperation in Research and Higher Education grant, supporting collaboration between Karolinska Institutet and Harvard University.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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Table 1. Characteristics of malignant childhood leukemia and lymphoma (*International Classification of Diseases, Seventh Edition* codes 200.0–207.0) in Sweden among cohort of 1,440,542 children born 1983–1997

	International Classification of Diseases, Seventh Edition code	*n*	Rate per 10^5 person-years	Mean (SD) age at diagnosis	% Male
ALL	204.0	505	4.75	3.7 (2.7)	53.7
AML	205.0	48	0.45	3.5 (3.9)	45.8
Chronic myelogenous leukemia	205.1	13	0.12	5.4 (3.8)	53.9
Other leukemias*	206–207	22	0.21	3.6 (3.7)	45.5
NHL†	200, 204.1	81	0.76	5.7 (3.0)	74.7
Hodgkin's disease	201	20	0.19	7.0 (3.7)	75.0
Reticulosis	202	61	0.57	2.4 (2.9)	57.4

*Includes 6 monocytic leukemias and 16 other and unspecified leukemias.
†Includes two chronic lymphocytic leukemia cases classified as NHL.

resident is assigned a national registration number, which is a unique identifier, it is possible to merge national databases.

Information on incident leukemia and lymphoma cases in the cohort came from the Swedish Cancer Registry, established by the National Board of Health and Welfare in 1958. Swedish law mandates and regulates physicians and pathologists, who confirm the diagnosis of cancer, to report on every newly diagnosed malignant tumor to the Swedish Cancer Registry. Since the early 1980s, all notifications of cancer diagnosis have been sent directly to one of six regional cancer registers, each of which has a strictly defined catchment area. All case reports are verified for completeness at the regional registries and subsequently computerized. Incidence statistics from the six regional registries are pooled in the Swedish Cancer Registry.

Information on all deaths in the cohort was available from the National Cause of Death Registry. The registry includes dates of death from specific causes, which is obtained from death certificates and coded according to the standards of the *International Classification of Diseases, Eighth, Ninth, and Tenth Editions*. Medical certification is carried out by the attending physician or coroner, with use of both clinical records and autopsy reports. This registry, which was established in 1961, maintains date and cause of death for >99% of residents who died after this year.

Among the 1,591,271 Swedish live births between 1983 and 1997, we excluded 3,627 (0.2%) infants who died within the first week of birth and 1,475 (0.1%) with Down syndrome. We excluded from the analysis an additional 97,905 (6.2%) births with missing information on maternal smoking, 47,573 (3.0%) with other missing covariate data, and 149 (0.01%) with erroneous follow-up information. Thus, the sample size of the final cohort for this analysis was 1,440,542 (90.5%) Swedish births during 1983 to 1997.

Data Collection. The Birth Registry includes standardized information from antenatal, obstetric, and neonatal medical records. During the first antenatal visit, normally at 8 to 12 gestational weeks, information from a standardized questionnaire is recorded by a nurse midwife. Information on maternal smoking during the first trimester has been collected routinely since 1983. Women were asked the number of cigarettes that they smoked, which was coded on the questionnaire as 0, 1 to 9, or ≥10 cigarettes per day. Additional covariate data include maternal demographic data, reproductive history, and birth characteristics and outcomes. Through linkage with the Education Registry, years of formal education attained as of December 31, 1998 were obtained from Statistics Sweden. Information on mother's country of birth was provided through linkage to the Immigration Registry and stratified into Nordic (Sweden, Denmark, Norway, Finland, and Iceland) or non-Nordic country of birth.

Lymphoma and Leukemia Cases. The incidence of lymphoma and leukemia (*International Classification of Diseases, Seventh Edition* codes 200–207) in the cohort was based on information provided by the Swedish Cancer Registry. Information available from the Swedish Cancer Registry includes date of diagnosis, malignancy, histologic subtype (WHO/HS/CANC/24.1 Histology Code), basis of diagnosis, and death from cancer. Observation time of the cohort was calculated from date of entry into the cohort (birth date) until the occurrence of a diagnosis of any primary lymphoma or leukemia cancer, or censoring since diagnosis of another cancer, death, or end of the observation period (December 31, 1997).

Statistical Analysis. The relation between maternal smoking and risk of childhood lymphoma or leukemia in the offspring was assessed using information on time to cancer event, which accounts for different amounts of follow-up time in the cohort. First, the incidence rates of cancer in the entire cohort were estimated by dividing the number of cases that occurred during follow-up by the total number of person-years at risk for a given level of exposure. Proportional hazard models using Proc PHREG in SAS version 8.2 were used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of hemopoietic cancers, given smoking status, comparing nonsmokers as the reference. To assess whether the dose of cigarettes increased or decreased risk in a linear fashion, we calculated statistical tests for trend. The following covariates were evaluated as potential confounders: maternal age (categorically: ≤19, 20–24, 25–29, 30–34, ≥35 years), maternal education (categorically: ≤9, 10–11, 12, ≥13 years), parental status (cohabitating/not cohabitating), residence at birth (town or rural/large city), maternal birthplace (Nordic/non-Nordic), parity (categorically: 1, 2–3, ≥4), birth year (ordinal), and baby's gender (male/female). Because of concern that

birth weight (ordinally) and gestational age (categorically: <32, 32–36, ≥37 weeks) potentially could be considered on the causal pathway, we controlled for these variables in a secondary analysis.

Because of the early age at onset of ALL, we examined whether the effect of smoking was constant by age at diagnosis. To accomplish this, we stratified models into risk sets of 0 to 1 (completed), 2 to 4, and ≥5 years of follow-up and estimated the effect of maternal smoking in each risk group. Furthermore, we examined whether the effect of maternal smoking on ALL differed among male and female offspring, comparing the estimates formally with a test for interaction.

Results

This cohort of 1,440,542 children born in Sweden between 1983 and 1997 contributed almost 11 million person-years to the study base. ALL was by far the most common occurring of the leukemias and lymphomas, with an incidence rate of 4.75 per 100,000 person-years (Table 1). The characteristics of non-Hodgkin's lymphoma (NHL) and Hodgkin's disease cases were notably different than ALL and AML, with an older mean age and a predominance of male cases.

In Table 2, we present the prevalence of maternal smoking during pregnancy by demographic, reproductive, and birth characteristics. Overall, 24% of women smoked during pregnancy. The proportion of women smoking during pregnancy was higher among younger women, among those with lower levels of education, and among those born in Nordic countries. Maternal smoking was also associated with preterm birth and lower birth weight. Over the course of the study period, there was evidence of notable decreases in smoking prevalence.

Adjusting for potential confounders, maternal smoking was associated with a 30% lower risk of ALL (HR, 0.73; 95% CI, 0.58–0.91; Table 3). The risk reduction was similar for light (1–9 cigarettes per day) and heavy (≥10 cigarettes per day) smokers. On the other hand, there was evidence that maternal smoking was associated with a higher risk of AML. In particular, children whose mothers smoked ≥10 cigarettes per day during early pregnancy had a >2-fold higher risk of AML (HR, 2.28; 95% CI, 1.05–4.94) compared with women who did not smoke. The data also suggested a small excess risk of NHL, although because of the small number of cases, 95% CIs were wide. In the proportional hazard analyses, further adjustment by gestational age and birth weight did not substantial change the HRs, suggesting that these variables are neither confounders nor on the causal pathway.

In Table 4, we present estimates of the effect of maternal smoking on ALL stratified by age at diagnosis and sex. A decreased risk of ALL associated with maternal smoking was evident for each age at diagnosis (Table 4), although the effect was more consistent among those diagnosed at ages 0 to 1 years. Maternal smoking was associated with a significantly protective effect on risk of ALL among males only, but there was no evidence of a statistical interaction between maternal smoking and infant's sex on risk of ALL (P for interaction = 0.32).

Discussion

Evidence from this large cohort of Swedish children suggests that maternal smoking during pregnancy affects the risk of childhood leukemia in the offspring. The data are consistent with a small protective effect of smoking on risk of ALL and with an excess risk of AML. There is also some evidence that maternal smoking increases the risk of NHL, although small numbers of cases in the cohort prevent definitive conclusions. Although there is no statistical evidence of interaction, the effect of maternal smoking on ALL seems more consistent among male compared with female offspring and slightly stronger for infants during the first year of life.

Table 2. Frequency of smoking during pregnancy by maternal and reproductive characteristics among 1,440,542 Swedish births, Sweden, January 1983–December 1997

	N	Smoking during pregnancy (%)
Maternal age (y)		
≤19	37,243	43.6
20–24	311,861	29.8
25–29	538,653	22.2
30–34	379,602	21.1
≥35	173,183	21.7
Maternal education (y)		
≤9	243,553	43.1
10–11	593,128	28.3
12	177,235	15.7
13–14	252,578	12.3
≥15	174,048	8.4
Parental status		
Cohabitating	1,308,277	22.7
Not cohabitating	71,318	48.4
Town/city		
Large city	383,063	23.6
Town/rural	1,057,479	24.2
Maternal birthplace		
Nordic	1,323,945	24.8
Non-Nordic	116,597	15.4
Parity		
1	584,022	24.0
2–3	753,583	23.4
≥4	102,937	29.4
Multiple birth		
Singleton	1,406,909	24.1
Multiple	33,633	23.5
Offspring sex		
Female	700,348	24.0
Male	740,014	24.1
Gestational age (wk)		
≤31	8,143	31.7
32–36	57,624	28.9
≥37	1,373,847	23.8
Birth weight (g)		
<1,500	7,822	32.1
1,500–2,500	51,340	36.1
2,501–3,500	625,964	29.4
3,501–4,500	703,703	19.1
>4,500	46,871	12.7
Birth year		
1983–1986	343,557	30.3
1987–1990	402,512	26.5
1991–1994	432,496	21.6
1995–1997	261,977	16.1

Table 3. Crude and adjusted HRs for the effect of maternal smoking on leukemia and lymphoma, Sweden, January 1983–December 1997

	Cases (*n*)	Rate per 10^5 person-years	Crude HR	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)
Maternal smoking					
ALL					
No	400	5.93	Reference	Reference	Reference
Yes	105	4.01	0.73	0.73 (0.58–0.91)	0.75 (0.60–0.93)
1–9 cigarettes	61	3.80	0.69	0.68 (0.52–0.89)	0.69 (0.52–0.91)
≥10 cigarettes	44	4.35	0.80	0.80 (0.58–1.10)	0.84 (0.61–1.15)
P for trend			0.016	0.012	0.043
AML					
No	33	0.49	Reference	Reference	Reference
Yes	15	0.57	1.28	1.41 (0.74–2.67)	1.28 (0.65–2.49)
1–9 cigarettes	6	0.37	0.83	0.91 (0.38–2.21)	0.75 (0.29–1.96)
≥10 cigarettes	9	0.89	2.00	2.28 (1.05–4.94)	2.20 (1.00–4.83)
P for trend			0.15	0.084	0.13
NHL					
No	56	0.83	Reference	Reference	Reference
Yes	25	0.96	1.17	1.25 (0.76–2.04)	1.22 (0.74–2.02)
1–9 cigarettes	15	0.93	1.14	1.21 (0.68–2.18)	1.15 (0.63–2.11)
≥10 cigarettes	10	0.99	1.21	1.30 (0.65–2.60)	1.33 (0.66–2.68)
P for trend			0.51	0.38	0.39
Reticulosis					
No	44	0.65	Reference	Reference	Reference
Yes	17	0.65	1.11	1.20 (0.67–2.16)	1.12 (0.61–2.05)
1–9 cigarettes	14	0.87	1.48	1.60 (0.86–3.00)	1.47 (0.77–2.79)
≥10 cigarettes	3	0.30	0.51	0.54 (0.17–1.77)	0.54 (0.16–1.77)
P for trend			0.74	0.855	0.739

*Data adjusted for maternal age, maternal education, maternal birthplace, parity, birth year, and baby's gender.
†Data also adjusted for gestational age and birth weight.

In evaluating the results of the study, there are several strengths to consider. The large size and duration of follow-up provide one of the few opportunities to evaluate the research question of maternal smoking on cancer risk using a cohort design. The Swedish Medical Birth and Cancer Registers include 99% of all births and 96% of cancer cases in Sweden (17, 18), respectively. Using these population-based resources almost eliminates the possibility of selection bias and loss to follow-up.

Maternal smoking in this study was assessed at the time women registered for prenatal care, during the first trimester. In this way, the possibility of recall bias is eliminated. However, we do lack exposure information over the course of pregnancy. Because it is unclear what the critical window of exposure is, we may have some misclassification of this time-varying exposure. For example, ~10% of smokers in Sweden cease cigarette smoking after the first antenatal care visit (19). Thus, if the relevant time window were later in pregnancy, we would have classified a small proportion of unexposed person-time as exposed. Moreover, the societal attitudes toward smoking may have led to underreporting of smoking during pregnancy. Because such misclassification of the exposure is nondifferential, the true associations between maternal smoking and leukemia and lymphoma may be greater than reported.

Because of the study design, there are few limitations to consider. The Medical Birth Register lacks information on some reported risk factors, such as exposure to ionizing radiation, parental occupation, and dietary data. These factors may have differed by maternal smoking status, thus leading to potential residual confounding. Of particular concern may be residual confounding by paternal smoking. Some studies suggest that, among

Table 4. Adjusted* HRs for the effect of maternal smoking on ALL stratified by age at diagnosis and sex, Sweden, January 1983–December 1997

	Age at diagnosis			Gender	
	0–1 y HR (95% CI)	2–4 y HR (95% CI)	≥5 y HR (95% CI)	Male HR (95% CI)	Female HR (95% CI)
Maternal smoking					
No	Reference	Reference	Reference	Reference	Reference
Yes	0.56 (0.31–1.01)	0.83 (0.62–1.11)	0.64 (0.42–0.97)	0.63 (0.46–0.86)	0.85 (0.62–1.16)
1–9 cigarettes	0.57 (0.28–1.15)	0.79 (0.55–1.13)	0.55 (0.32–0.95)	0.63 (0.43–0.92)	0.75 (0.50–1.10)
≥10 cigarettes	0.55 (0.22–1.37)	0.89 (0.59–1.35)	0.78 (0.44–1.40)	0.64 (0.40–1.02)	1.02 (0.66–1.57)
P for trend	0.071	0.33	0.10	0.008	0.59

*Data adjusted for maternal age, maternal education, maternal birthplace, parity, birth year, and baby's gender.

nonsmoking mothers, paternal smoking is associated with increased risk of ALL and lymphoma (16, 20). However, in Sweden, paternal smoking is closely associated with maternal smoking (19). Thus, if paternal smoking is associated with increased risk of ALL and NHL also in Sweden, we should have underestimated the protective effect of maternal smoking on ALL and overestimated the effect on NHL.

In this study, mean follow-up time of the cohort is ~8 years, and ~90% of the children were <15 years old at the end of the study. Thus, this study focused on cancers that occurred earlier in the cohort. This observation should be taken into consideration when assessing the generalizability of these findings to malignancies with later age at onset. If the *in utero* effects of smoking play a greater role on later rather than earlier onset cancers (15), then our effect estimates may not be directly applicable to the age groups under study. At least for ALL, our data do not suggest a different effect of smoking by age at diagnosis.

Our results agree with some, but not all, previous studies on the effect of maternal smoking on risk of childhood leukemia and lymphoma. The United Kingdom Cancer Study, which is a nationwide population-based case-control study, evaluated maternal smoking during the second trimester of pregnancy using structured interviews (15). The authors found that maternal smoking was associated with a 24% lower risk of leukemia (P for trend = 0.03). This protective effect was notable for both ALL and AML, however. A large, population-based case-control study undertaken in Germany assessed maternal smoking during the first trimester and found a protective effect for ALL and an increased risk for NHL (14). A meta-analysis based on eight studies, however, found no evidence of an effect of maternal smoking on leukemia (relative risk 1.05; CI, 0.82–1.34; ref. 21).

Few cohort studies examining maternal smoking and risk of childhood hemopoietic cancers have been undertaken. In a study including 54,795 live-born children, there was some evidence of a protective effect of maternal smoking on total leukemia, although the results were not statistically significant (22). In an initial follow-up for the Swedish birth cohort between 1982 and 1987, Pershagen et al. (23) reported no association between maternal smoking and cancers of the lymphatic and hemopoietic system (HR, 1.04; 95% CI, 0.71–1.52). However, in case-control studies nested within the cohort through 1989, there was evidence of a protective effect of ALL (13) and excess risks of AML (10) and NHL (11). Maternal smoking data from the Swedish nested case-control and cohort studies was derived in the same manner as the present study.

Given the inconclusiveness of earlier epidemiologic studies, we can turn to biological plausibility to assess the study findings. First, several components of cigarette smoke, such as benzo[*a*]pyrene and 4-aminobiphenyl, are known to cross the placental membrane and have been detected in the placenta and fetal blood of offspring (24-27). In addition, maternal smoking during pregnancy was positively associated with increased numbers of specific mutations such as deletions in lymphocytes of the offspring (28, 29). Thus, it is biologically plausible that maternal smoking during pregnancy increases the risk of NHL and AML, as observed in our study.

The protective effect of smoking and ALL is more difficult to understand, and little is known about the mechanism by which smoking could exert such an effect. In animal models in which progeny are exposed *in utero* to benzo[*a*]pyrene, a component of tobacco smoke, there is substantial evidence of generalized immune suppression after birth (30-32). In particular, *in utero* exposure to benzo[*a*]pyrene decreases prolymphocytic cells in animals (31) and suppresses B-cell lymphopoiesis and induces pre–B-cell apoptosis in bone marrow cultures (33). Such suppression of immune function could result in a decreased response and lower likelihood of clonal expansion.

Despite the apparent protective effect of smoking on ALL, this study in no way supports that maternal smoking is beneficial. Smoking during pregnancy is linked to several adverse effects, including fetal growth restriction, preterm birth, and perinatal mortality (33-35), outcomes that are significantly more common conditions. This evidence may simply outline a potential mechanism by which ALL could occur.

Clearly, the question of maternal smoking and risk of hemopoietic cancers remains. This study provides supportive evidence of positive associations with AML and NHL and an interesting protective effect with ALL, which needs to be explored further. With additional follow-up time, this unique cohort of Swedish children will help to further elucidate the role of maternal smoking on risk of childhood cancers.

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Cancer Epidemiol Biomarkers Prev 2004;13:1528-1533.