

Maternal Lung Cancer and Testicular Cancer Risk in the Offspring

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Abstract

It has been hypothesized that smoking during pregnancy could increase the offspring's risk for testicular cancer. This hypothesis is indirectly supported by both ecological studies and studies of cancer aggregations within families. However, results from analytical epidemiological studies are not consistent, possibly due to methodological difficulties. To further study the association between smoking during pregnancy and testicular cancer, we did a population-based cohort study on cancer risk among offspring of women diagnosed with lung cancer. Through the use of the Swedish Cancer Register and the Swedish Second-Generation Register, we identified 8,430 women who developed lung cancer between 1958 and 1997 and delivered sons between 1941 and 1979. Cancer cases among the male offspring were then identified through the Swedish Cancer Register. Standardized incidence ratios were computed, using 95% confidence intervals. We identified 12,592 male offspring of mothers with a subsequent diagnosis of lung cancer, and there were 40 cases of testicular cancer (standardized incidence ratio, 1.90; 95% confidence interval, 1.35–2.58). The association was independent of maternal lung cancer subtype, and the risk of testicular cancer increased stepwise with decreasing time interval between birth and maternal lung cancer diagnosis. Our results support the hypothesis that exposure to cigarette smoking *in utero* increases the risk of testicular cancer.

Introduction

Testicular cancer is the most common cancer in young men, and the incidence is increasing epidemically (1). Little is known about the causes, but exposures during the fetal period are likely to be instrumental (2). Due to the parallel trends of female smoking-associated cancers and testicular cancer, maternal smoking during pregnancy has been suggested as a risk factor (3), but because the exposure occurs up to five decades before the disease, valid assessment of exposure is challenging. For instance, because mortality is more than tripled among female smokers compared with nonsmokers (4), retrospective

studies in which mothers are interviewed can be expected to underestimate smoking prevalence.

In retrospective studies, smoking during pregnancy has not been found to be a significant risk factor of testicular cancer (2, 5–7). However, a positive association between parental lung cancer and testicular cancer in the offspring has been suggested in four of five studies (7–11), and in two of these studies, the association was confined to the mothers (7, 8). Given that smoking is the predominant cause of lung cancer, these reports suggest that smoking during pregnancy may play a role in testicular carcinogenesis. To further study the association between maternal lung cancer and testicular cancer risk in the offspring, we did a cohort study on sons of women later diagnosed with lung cancer.

Materials and Methods

Setting. All residents in Sweden alive after 1947 have a unique national registration number, referred to in all medical records and official registries. Through the use of the national registration number, it is possible to link information from several databases together.

The Swedish Cancer Register has collected information about all cases of cancer in Sweden since 1958. Only histologically verified cancers are included in the register, and the sensitivity is over 98% (12). To enable comparisons over time, the Cancer Register includes all newly diagnosed cancers according to the seventh revision of International Classification of Disease in a four-digit code. The Cancer Register also provides a three-digit code (PAD code) used by the diagnosing pathologists with information on histopathological diagnosis (13). Through the use of the PAD code, information on histopathological subtype of cancers at different sites can be obtained for cancers diagnosed before the introduction of more detailed classification systems.

The Swedish Second-Generation Register, created by Statistics Sweden, provides information on vertical and horizontal first-degree relatives for residents born 1941 or later, and adoptions and other nonbiological relations are specified (14). To be included in the register, relatives have to have been alive in 1960 or born thereafter. Through the use of the Second-Generation Register, relatives of patients identified in the Cancer Register can be identified, allowing for studies of familial aggregations of cancer within the Swedish population.

The Cohort. We used the Cancer Register to identify all women with a diagnosis of lung cancer during the period 1958 through 1997. By linkage to the Second-Generation Register, we could then identify the offspring of these women. Eligible were sons born between 1941 and 1979 whose mothers had one of the following lung cancer subtypes: adenocarcinoma; small cell carcinoma; squamocellular carcinoma; anaplastic carcinoma; or mesothelioma. Only sons whose birth dates preceded the maternal date of diagnosis were included. The sons were then linked back to the Cancer Register to obtain information on cancer occurrence during the years 1958 to 1997.

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Table 1 Women with lung cancer and their sons by maternal birth year, maternal year of lung cancer diagnosis, and lung cancer subtype, and sons by birth year

	Mothers	%	Sons	%
All years	8,430	100	12,592	100
Maternal birth year				
1895–1909	554	6.6	647	5.1
1910–1919	2,259	26.8	3,142	25.0
1920–1929	2,981	35.4	4,690	37.2
1930–1939	1,718	20.4	2,747	21.8
1940–1949	834	9.9	1,258	10.0
1950–1961	84	1.0	108	0.9
Maternal year of lung cancer diagnosis				
1958–1969	352	4.2	396	3.1
1970–1979	1,139	13.5	1,402	11.1
1980–1989	3,219	38.2	4,475	35.5
1990–1997	3,720	44.1	6,319	50.2
Maternal lung cancer subtype				
Adenocarcinoma	3,146	37.3	4,629	36.8
Small cell carcinoma	1,181	14.0	1,891	15.0
Anaplastic carcinoma	2,226	26.4	3,255	25.8
Squamocellular carcinoma	1,707	20.2	2,566	20.4
Mesothelioma	170	2.0	251	2.0
Birth year of sons				
1941–1949			4,915	39.0
1950–1959			4,441	35.3
1960–1979			3,236	25.7

Follow-Up and Analysis. We followed our cohort to emigration, death, or December 31, 1997, whichever occurred first. Because the Second-Generation Register is based on censuses from 1960 onward, and individuals deceased before 1960 are not included, starting date for our follow-up was January 1, 1960. The expected number of cancer cases in our cohort was calculated through age- and time period-specific incidence rates for the Swedish background population provided by the Cancer Register. The SIR,² *i.e.*, the observed:expected ratio, for testicular cancer could then be computed. For statistical analysis we used SAS software package (15).

Results

Between 1958 and 1997, 22,702 women with lung cancer were reported to the Cancer Register. Of these, 21,384 women fulfilled our inclusion criteria of lung cancer subtype, and 11,696 women delivered a total of 24,602 children during the period 1941–1979. Of the mothers, 8,430 delivered a total of 12,592 sons. The mothers and sons are presented in more detail in Table 1.

There were 40 cases of testicular cancer among the sons. Of these, 14 were seminomas, 25 were nonseminomas, and 1 was of unknown histology. Compared with the background population, sons of women with lung cancer were at increased risk of testicular cancer (Table 2). The SIR for testicular cancer was 1.90 (95% CI, 1.35–2.58), and the increased risk was not confined to any particular histopathological subtype of maternal lung cancer. Apart from maternal mesothelioma, for which the risk estimate was statistically highly unstable, the lowest point estimate for testicular cancer risk was found for a maternal diagnosis of adenocarcinoma, and the highest point estimate for testicular cancer risk was found for a maternal diagnosis of

Table 2 Observed and expected cases of testicular cancer, SIRs, and 95% CIs among sons of women later diagnosed with lung cancer according to birth period, histopathological subtype, maternal lung cancer subtype, and time interval between birth and maternal lung cancer diagnosis

	Observed	Expected	SIR	95% CI
All	40	21.1	1.90	1.35–2.58
Birth year				
1941–1949	15	8.2	1.82	1.02–3.00
1950–1959	14	8.8	1.60	0.87–2.68
1960–1979	11	4.1	2.69	1.34–4.82
Testicular cancer subtype				
Seminoma	14	10.1	1.39	0.76–2.33
Nonseminoma	25	10.7	2.34	1.51–3.45
Maternal lung cancer subtype				
Adenocarcinoma	12	7.7	1.57	0.81–2.74
Small cell carcinoma	6	3.2	1.86	0.68–4.05
Squamocellular carcinoma	9	4.3	2.07	0.95–3.94
Anaplastic carcinoma	11	5.5	2.01	1.00–3.60
Mesothelioma	2	0.42	4.82	0.58–17.4
Time interval between son's birth and maternal lung cancer diagnosis (yrs)				
0–19	4	1.5	2.67	0.73–6.83
20–29	11	5.1	2.17	1.08–3.88
30–39	15	8.3	1.80	1.01–2.97
40–56	10	6.2	1.61	0.77–2.97

squamocellular carcinoma. Maternal lung cancer overall entailed an increased risk for testicular nonseminomas (SIR, 2.34; 95% CI, 1.51–3.45) as well as seminoma (SIR, 1.39; 95% CI, 0.76–2.33), although the latter estimate was lower and nonsignificant.

We also assessed whether the increased risk of testicular cancer was dependent on duration in time between offspring's birth and maternal lung cancer diagnosis, and the risk increased consistently with shortening interval between birth and maternal lung cancer diagnosis (Table 2).

Discussion

In this study we could demonstrate that sons of women diagnosed with lung cancer were at increased risk of testicular cancer. The risk was consistent for all histopathological subtypes of maternal lung cancer, and it increased with decreasing time interval between birth and maternal lung cancer diagnosis.

The increased risk of testicular cancer among sons of women with lung cancer could be genetic in origin, or it could be attributable to environmental exposures. Because the risk of testicular cancer increased stepwise with decreasing time interval between birth and maternal lung cancer diagnosis, we consider a genetic cause less likely. An environmental explanation for our findings is also more consistent with the reports of an increased risk for lung cancer among mothers, but not fathers, of testicular cancer patients (7, 8).

There are at least three reasons why our results suggest an association between smoking during pregnancy and testicular cancer. First, smoking is the predominant cause of lung cancer (16). In Sweden, the proportion of smokers among females with lung cancer increased from 27% in the beginning of the 1960s to 70% in the following decade, (17), and in a study from 1993, the proportion of female lung cancer attributable to smoking was estimated to be 78% (18). Because about 85% of the cohort were sons of women diagnosed with lung cancer in the 1980s and 1990s, at least three of four mothers with lung cancer would be smokers. Second, when stratifying the analysis on maternal

² The abbreviations used are: SIR, standardized incidence ratio; CI, confidence interval.

lung cancer subtype, the lowest risk of testicular cancer was found for maternal adenocarcinoma, whereas the risk was higher when the mother was diagnosed with squamocellular carcinoma. Although the differences between the two groups were not statistically significant, the finding is consistent with adenocarcinoma being less associated with smoking than is squamocellular carcinoma (16). Third, the testicular cancer risk increased stepwise with decreasing time interval between birth and maternal lung cancer diagnosis. Given an induction period for smoking to cause lung cancer of at least two decades, the proportion of mothers who were active smokers at time of pregnancy will be higher among mothers diagnosed two to three decades after delivery compared with mothers diagnosed more than four decades after the birth of their offspring. It cannot, however, be excluded that the association between smoking during pregnancy and testicular cancer is influenced by other factors associated with smoking habits, such as, for example, alcohol consumption. To disentangle the role of different confounders, analytical studies based on prospective data are needed.

In tobacco smoke, there are at least 55 compounds for which there is "sufficient evidence for carcinogenicity," and the biological pathways through which they act are numerous (19). Besides being a potent carcinogen, tobacco smoke also has other physiological effects; during pregnancy, smoking reduces placental blood flow (20, 21), alters cytochrome P-450 activity in the placenta (22, 23), causes fetal growth retardation (24), and decreases levels of pregnancy estrogens (25). Notably, low birth weight is one of the most consistently reported risk factors for testicular cancer and is also associated with low levels of pregnancy estrogens (2, 6, 25–28). Therefore, potential pathways through which smoking during pregnancy may cause testicular cancer include direct carcinogenic effects through placental passing of carcinogens or an indirect mechanism through the effects on maternal and feto-placental physiology.

One could argue that although the mother was an active smoker before pregnancy, she may have given up smoking while pregnant. However, the importance of smoking cessation during pregnancy was not an issue before 1970, and over 90% of the sons in our study were born before 1970. In fact, in a Swedish study from 1971, it was shown that 97% of the female smokers continued smoking during pregnancy (29). Infants exposed to maternal smoking during pregnancy are also more likely to be exposed to smoke during childhood. However, passive smoking is unlikely to explain our results because active smoking does not increase the risk of testicular cancer (30), and previous reports have found the association between lung cancer and testicular cancer to be confined to the mothers (7, 8).

The results obtained are in line with previous reports of an association between maternal lung cancer and testicular cancer (7–10). Heimdal *et al.* (8) found a doubled risk of lung cancer among mothers of testicular cancer patients, whereas no such increase was found among fathers. Swerdlow *et al.* (7) reported that mothers of men with testicular cancer had a 5-fold increase in lung cancer risk, whereas the relative risk among the fathers was 1.6. This study, however, was based on a limited number of lung cancer cases. In a study by Spermon *et al.* (9), there was an increased risk for respiratory tract cancer among first-degree relatives of men with testicular cancer. In the Swedish setting, the association between parental lung cancer and testicular cancer has been assessed twice before (10, 31). The first study included offspring born in 1941–1955 of parents diagnosed with cancer from 1958 through 1995 (31). This study found no association between maternal lung cancer and testicular cancer

risk. When the study was extended to include both earlier and later birth cohorts, however, a marginally significant association between parental lung cancer and testicular cancer risk in the offspring was found (10). Because parental lung cancer was treated as one entity, rather than separated into maternal and paternal cancer, the smaller magnitude of the association also gives credence to our interpretation of the findings as due to environmental exposures rather than to genetic susceptibility.

Previous studies that have assessed maternal smoking during pregnancy and testicular cancer risk have yielded negative or contradictory results. Three studies have found no association (5, 7, 32), one found a nonsignificant 30% increase in testicular cancer risk if the mother reported ever *versus* never smoking during pregnancy (2), and the most recent study reported an increased risk for nonseminoma among the offspring if the mother smoked 1–11 cigarettes/day during gestation but a decreased risk for higher consumption (6). The same study also reported a negative association between maternal smoking and seminoma in the offspring. Moreover, these studies were case-control studies with retrospective collection of data from mothers of study subjects. Because this design requires equal survival and participation rates among mothers of both cases and controls, and mortality is more than tripled among smokers compared with nonsmokers (4), differential survival or nonresponse could have masked a true effect of maternal smoking. In fact, the study reporting a 30% increase in testicular cancer risk if the mother had ever smoked during gestation was the study with the highest response rate among the mothers (74%), whereas the response rates in the other studies were between 40% and 58%.

Our study was based on data from the Second-Generation Register, which lacks information on the national registration number for about 10% of the infants born in 1941. For deceased people, this figure is even higher: 40–60% of the information on national registration number is missing for those deceased between 1960 and 1990, and 10% thereafter (14). Because men who developed testicular cancer and died are less likely to be included, we may have underestimated the association between maternal lung cancer and testicular cancer risk in the offspring.

In conclusion, we found that a maternal diagnosis of lung cancer increases the risk of testicular cancer in the offspring, and our results suggest that smoking during pregnancy may be the cause. Additional studies on the association between smoking during pregnancy and testicular cancer risk in the offspring that are based on prospectively collected smoking information are warranted because testicular cancer may be, in part, a preventable disease.

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