Short Communication

Childbearing and the Risk of Hodgkin’s Disease

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Abstract

The causes of Hodgkin’s disease remain incompletely known, but a higher incidence in men than in women has prompted an interest in the role of female sex hormones and reproductive history. Available epidemiological data are, however, contradictory. We analyzed possible associations between parity, age at first birth, and the risk of developing Hodgkin’s disease by a linkage between the Swedish Cancer Register and a nationwide Fertility Register. Among women born between 1925 and 1972, 917 cases with Hodgkin’s disease and concomitant fertility information were identified. For each case patient, five age-matched controls were randomly selected among women in the Fertility Register. Conditional logistic regression was used to estimate odds ratios of Hodgkin’s disease associated with a birth. We found a slightly and nonsignificantly reduced risk of Hodgkin’s disease in ever-parous compared with nulliparous women. Among parous women, the number of children was unrelated to risk, whereas there was some evidence of an increased risk with late age at first birth in women under age 45 at diagnosis. No clear temporal relations between childbearing and subsequent risk were discernible in any parity or age group. Although uncontrolled confounding might have affected our results, they do not indicate that hormonal or immunological changes associated with childbearing play a role in the development of Hodgkin’s disease.

Introduction

The etiology of Hodgkin’s disease, a malignancy of the immune system, remains incompletely known. Young adult age, high socioeconomic status, small number of siblings, certain occupational exposures, EBV infections, and genetic susceptibility have all been linked to this lymphoma (1, 2). The bimodality of the age-specific incidence curve, present in both sexes, suggests that this lymphoma may be a heterogeneous entity depending on age of clinical onset (3, 4). Another salient feature of Hodgkin’s disease, the higher adult incidence in men than in women, cannot fully be explained by socioeconomic factors or occupational exposures. The incidence of Hodgkin’s disease in Sweden has declined by about 3% in men and 1% in women per year since the early 1970s, a decrease that has been most pronounced in older age groups. In 1992, the age-adjusted incidence rates in men and women were 2.1 and 1.7 per 100,000, respectively (5).

The gender difference in incidence, which varies by age, has prompted an interest in the role of reproductive and hormonal factors (6). Evidence of both an elevated (7) and a reduced risk of Hodgkin’s disease (8–11) in parous compared with nulliparous women has been reported. Other studies have found no clear risk-modifying effects of parity (12, 13). The possible transient effects of a pregnancy, as well as the influence of age at first birth, on the risk of Hodgkin’s disease are unclear and remain incompletely investigated (6).

Our aim was to examine possible associations between parity and age at first birth and the risk of Hodgkin’s disease in a large population-based cohort in Sweden. Validity and precision were optimized by the use of linked register data comprising 917 women diagnosed with Hodgkin’s disease with concomitant fertility information.

Subjects and Methods

Population Registers. Our study was based on data from two Swedish registers, the Fertility Register and the Cancer Register. In each register, female residents in Sweden can be identified through an individually unique national registration number assigned to every Swedish citizen in 1947 and thereafter at birth. Since 1947, immigrants receive their national registration number at time of first residency.

The Fertility Register is originally based on women born between 1925 and 1960 who were resident citizens of Sweden at the time of the 1960 Census. For these women, reproductive data (number and dates of live births) during the period 1943–1960 were collected retrospectively at the Census. Later birth cohorts of Swedish women have been added continuously, with the women’s own live births being recorded annually via vital statistics records. For the purpose of the present study, the Fertility Register was updated through 1990 and included almost 3.4 million live births recorded from 1943 among women born 1925–1972 (~2.3 million). The quality of data concerning number and dates of birth is generally high (14). In the oldest cohorts, mainly women born 1925–1929, fertility may be underestimated because children born before 1943, those not living with their mother, and those who died before the 1960 Census were not recorded. There might also be a slight overestimation of fertility between 1943 and 1960 because adopted and foster children were included in the retrospectively collected information. From 1961 and onwards, only biological children were included. Dates of death and emigration among registered women are recorded yearly in the Fertility Register, although no information is available on socioeconomic factors.

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The Swedish Cancer Register started in 1958. All newly diagnosed malignant tumors must be reported to the Register separately by both the clinician and the pathologist or cytologist. Nearly 100% of all diagnosed cancers are recorded (5). All newly diagnosed malignant tumors must be reported to the Register (i.e., over- or underreporting of number of births, is small and confined to the oldest birth cohorts (14). Because of the design and large size of our study, no biological data were available. Instead, parity was considered as a proxy for preg-

nulliparous women as the reference group. All P values were two-sided, and P < 0.05 was considered statistically significant.

Results

The mean age at diagnosis of all case women was 30.5 years with a range of 15–65 years. Sixty-six percent were diagnosed during the latter half of the 30-year follow-up period (Table 1). Table 2 shows the distribution of cases of Hodgkin’s disease and the control series by number of live births and age at first birth. Nulliparity was slightly more common among cases (45.3%) than controls (43.8%).

The relative risk (OR) of developing Hodgkin’s disease was slightly lower in ever-parous compared with nulliparous women (OR, 0.90; 95% CI, 0.75–1.09). Among parous women, however, there was no trend in risk with increasing number of births or with increasing age at first birth (Table 2). After a follow-up of 30 years, there was no trend in risk with increasing age at first birth and the risk of Hodgkin’s disease.

The findings were similar for parity in women under age 45 at diagnosis (data not shown). However, in this age category, there was a significant positive trend (P for trend 0.03) between increasing age at first birth and the risk of Hodgkin’s disease. Compared with women with a first birth before age 20, the estimated risk was twice as high in women with a first birth at age 30 or later (OR, 1.96; 95% CI, 1.15–3.34).

In an analysis of temporal relations between a birth and the risk of Hodgkin’s disease restricted to nulliparous and uniparous women, there was a weak indication of a reduced risk in women with a delivery before age 25 that occurred with several years of delay after the birth. However, overall there was no clear pattern of an increased or decreased risk during the available follow-up time (Table 3).

In a subsequent step, we explored changes in risk after the last birth in uniparous, biparous, and triparous women. Compared with nulliparous women, there were no clear positive or negative trends in risk with time since most recent birth in any of the parity groups (Table 4).

Discussion

Hodgkin’s lymphoma is a disease entity often associated with an immune dysfunction in the affected individual (2, 17). Although it is well established that physiological changes during childbearing modulate the function of the immune system, it is far from clear that they have short- or long-term clinical consequences for a healthy mother (18).

Based on nationwide data covering more than a 30-year period, this is the largest epidemiological study on childbearing and the risk of Hodgkin’s disease reported thus far. Because information on reproductive history was recorded independently of outcome (Hodgkin’s disease), selection and information bias is not an issue. Any nondifferential misclassification of exposure, i.e., over- or underreporting of number of births, is small and confined to the oldest birth cohorts (14). Because of the design and large size of our study, no biological data were available. Instead, parity was considered as a proxy for preg-

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The abbreviations used are: OR, odds ratio; CI, confidence interval.
nancy-associated hormonal, immunological, or other changes that might influence risk.

In this setting, we found little evidence that childbearing plays an important role in the development of Hodgkin's disease. The absence of a clear parity effect is compatible with the results of two recent studies, one Norwegian cohort study (12) and one case-control study from Southern Europe (13). As opposed to two previous reports (10, 13), we found no clear evidence that the risk of Hodgkin's disease varies with time since the most recent pregnancy.

There is no obvious biological explanation to the relationship seen in our study between late age at first birth and the risk of Hodgkin's disease in women age 45 or younger. It cannot be excluded that this finding in an exploratory subgroup analysis was due to chance. According to the two-disease theory, Hodgkin's disease in the young adult may be of a predominantly infectious origin (17). If so, women with late pregnancies might have been exposed more often to the causative agent, possibly by spending more time in the workplace before entering motherhood. To our knowledge, only two previous investigations have found indications of a weak positive association between late age at first birth and the risk of Hodgkin's disease (9, 10), one of which was hampered by its small size and informal design (9).

Kravdal and Hansen (12) have suggested that any protective effect of parity may be confined to the nodular sclerosis subtype. We were unable to analyze this theory because information on histological subtypes of Hodgkin's disease was not available in the Cancer Register. A recent assessment shows that about 60% of all cases in Sweden are of the nodular sclerosis subtype. Similarly, an allegedly reduced risk of

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### Table 2
Distribution of 917 women with Hodgkin's disease and 4584 controls by number of live births and age at first birth

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude*</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>OR</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Number of births</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>415</td>
<td>(45.3)</td>
<td>2.008</td>
<td>(43.8)</td>
</tr>
<tr>
<td>Ever-parous</td>
<td>172</td>
<td>(18.8)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td></td>
<td>197</td>
<td>(21.5)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>(1.2)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first birth (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>415</td>
<td>(45.3)</td>
<td>2.008</td>
<td>(43.8)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>94</td>
<td>(10.3)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td>20-24</td>
<td>247</td>
<td>(26.9)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td>25-29</td>
<td>197</td>
<td>(21.5)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td>30+</td>
<td>11</td>
<td>(1.2)</td>
<td>1.091</td>
<td>(23.8)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 3** ORs and 95% CIs of developing Hodgkin's disease in uniparous women, by age and age at first birth compared with nulliparous women

<table>
<thead>
<tr>
<th>Age at first birth (years)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>0.7 (0.4-1.2)</td>
<td>1.0 (0.7-1.4)</td>
<td>0.6 (0.3-1.3)</td>
<td>1.0 (0.6-1.4)</td>
<td>1.0 (0.5-1.6)</td>
</tr>
<tr>
<td>30-39</td>
<td>0.8 (0.2-2.9)</td>
<td>0.6 (0.3-1.4)</td>
<td>0.4 (0.2-0.9)</td>
<td>1.0 (0.6-1.4)</td>
<td>1.0 (0.5-1.6)</td>
</tr>
<tr>
<td>40-49</td>
<td>0.7 (0.1-3.5)</td>
<td>2.5 (0.7-9.6)</td>
<td>1.3 (0.3-5.4)</td>
<td>1.8 (0.3-11.0)</td>
<td>1.0 (0.1-2.9)</td>
</tr>
</tbody>
</table>

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**Table 4** ORs and 95% CIs of developing Hodgkin's disease in uniparous, biparous, triparous, and ever-parous women compared with nulliparous women, by years of follow-up after last pregnancy

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Uniparous</th>
<th>Biparous</th>
<th>Triparous</th>
<th>Ever-parous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1.0 (0.7-1.2)</td>
<td>1.0 (0.6-1.2)</td>
<td>1.0 (0.6-1.2)</td>
<td>1.0 (0.6-1.2)</td>
</tr>
<tr>
<td>0-4</td>
<td>0.9 (0.4-1.0)</td>
<td>0.7 (0.5-1.1)</td>
<td>1.0 (0.6-1.2)</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>10-14</td>
<td>0.7 (0.3-1.5)</td>
<td>0.7 (0.3-1.5)</td>
<td>1.0 (0.6-1.2)</td>
<td>0.9 (0.6-1.2)</td>
</tr>
<tr>
<td>15+</td>
<td>1.4 (0.7-2.6)</td>
<td>1.2 (0.5-1.5)</td>
<td>0.8 (0.6-1.2)</td>
<td>0.8 (0.6-1.2)</td>
</tr>
</tbody>
</table>

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Hodgkin’s disease in women with a history of abortions (19) could not be analyzed due to lack of information in the Fertility Register. Another limitation of our study was the absence of information on possible confounders such as socioeconomic indices, industrial exposures, and occupation. In Sweden, multiparity (more than four children) is not uncommon among both women with a low and high educational level. However, there is strong correlation between high education on the one side and late age at first birth and nulliparity on the other (20). Thus, we cannot exclude that the risk gradient seen between nulliparous and ever-parous women, nor the apparent increased risk with late age at first birth, is confounded by social factors. However, no significant impact of social status was found in a Norwegian study, where the effect of parity was stronger than that of education, occupation, and place of residence (10). Another recent epidemiological study found a protective effect of parity in women of high socioeconomic status only (11). In our study, industrial exposures (for example, wood dust) are unlikely confounders because they are confined largely to male workers.

We conclude that parity does not appear to play an important role in the etiology of Hodgkin’s disease. Our finding of an increased risk of Hodgkin’s Disease in women below age 45 with a history of a late first birth needs to be confirmed in future studies. Our present results are broadly in line with a recent study based on the same data set, showing that childbearing has limited, if any, relevance to the etiology of non-Hodgkin’s lymphoma (21).

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