Reproductive History and Cutaneous Malignant Melanoma: A Comparison between Women and Men

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To evaluate whether previously observed associations between parity and cutaneous malignant melanoma (CMM) risk in women reflected a biologic mechanism or resulted from uncontrolled confounding by lifestyle factors associated with parity (e.g., patterns of sun exposure), the authors investigated the effect of reproductive history (parenthood) on CMM risk in both women and men. Using information from Danish national registers (1968–2003), the authors established a population-based cohort of more than 3,500,000 persons with information on parenthood and CMM. Relative risks were estimated using Poisson regression models. Overall, number of children was significantly associated with a woman’s risk of CMM ($p = 0.004$), with the lowest risk being seen among women with many births. Women aged 25 years or older at their first birth had a 24% (95% confidence interval: 16, 33) higher risk of CMM than younger women. Ten or more years after the birth of her youngest child, a woman had a 15% (95% confidence interval: 5, 27) higher risk of CMM than she did in the first 10 years. Similar results were observed in men. The similarity of effects for men and women suggests that lifestyle factors, rather than exposure to pregnancy hormones, may be responsible for the observed associations between reproductive history and CMM risk in women.

Abbreviations: CI, confidence interval; CMM, cutaneous malignant melanoma; RR, relative risk.

Various physical and lifestyle characteristics (e.g., fair skin phenotype, increased number of raised nevi, high degree of freckling, blond hair, an inability to tan, lifetime intermittent intense sun exposure, sunburns during childhood) are established risk factors for cutaneous malignant melanoma (CMM) (1–7). However, some studies have suggested that a woman’s reproductive history may affect her risk of CMM, leading to speculation that in women, the development of CMM might also be influenced by the hormonal changes occurring during pregnancy. Nevertheless, this hypothesis has not been supported by all studies examining the relation between reproductive history and CMM risk. For example, while some studies have shown that women who have had many livebirths have a lower risk of CMM than women who have had few or no livebirths (8, 9), others have found no association between parity and CMM risk (10–13). Unfortunately, most studies have been limited by small sample sizes. However, a large case-control study (4,779 cases) conducted by Lambe et al. (8) found that women with more than two livebirths had a decreased risk of CMM compared with nulliparous women, with a risk reduction of 8 percent for each additional child. Furthermore, women who gave birth to their first child after age 20 years were at greater risk of developing CMM than women who first gave birth at a younger age (<20 years); the risk increased 16 percent for each 5-year increase in age at first birth.

Rather than reflecting a true causal link between hormonal changes associated with pregnancy and CMM risk, previously reported associations between CMM risk in women and aspects of reproductive history could simply
have resulted from uncontrolled confounding by lifestyle factors such as sun exposure patterns (14). For example, it is plausible that patterns of sun exposure vary with number of children; it could be argued that people without children have more leisure time and consequently more frequent and prolonged sun exposure than people with children, and that the more children one has, the less time one spends in the sun, particularly on any given occasion. In addition, because it is predominantly sunburns at young ages that are associated with CMM (15), it is conceivable that having a first child at a young age could result in less exposure to sun during a critical risk period. Consequently, we conducted a large cohort study to investigate the relation between reproductive history (aspects of parenthood: number of children; age at the first child’s birth, and time since the birth of the youngest child) and CMM risk in both men and women. Findings similar to those reported by Lambe et al. in women but not in men would support the hypothesis that exposure to pregnancy hormones (and the timing of that exposure) influences a woman’s risk of CMM. However, similar findings in men and women would make an underlying hormonal mechanism unlikely, suggesting rather that lifestyle factors closely associated with the number of children a person has are responsible for previously observed associations between reproductive history and CMM risk.

MATERIALS AND METHODS

Data sources

Danish Civil Registration System. All residents of Denmark are registered in the Civil Registration System, a computerized national civil register that was established in 1968 to replace individual municipal paper registers (16). The system’s records are updated daily and contain demographic information on each person living in Denmark, including name, sex, address, civil status, date and place of birth, citizenship, and kinship (links between parents and their children). The Civil Registration System also tracks vital status and emigration from Denmark; people who die, emigrate, or disappear remain in the system, and the date of death, emigration, or disappearance is recorded. (Date of disappearance is defined as the date on which the state officially determines that a person’s whereabouts are unknown, usually 1–2 years after the person’s last contact with state services.)

At its inception on April 1, 1968, the Civil Registration System assigned a unique personal identification number to each living person then residing in Denmark. Each child born in Denmark since then has been assigned a personal identification number at birth; all immigrants and temporary residents receive personal identification numbers soon after entering the country. The Civil Registration System and the personal identification number permit virtually complete follow-up of study subjects residing in Denmark, as well as linkage of information from Denmark’s population-based health registers.

Danish Cancer Register. Registration of incident cases of cancer diagnosed in Denmark from 1943 to the present is considered close to complete (17). Hospitals report all cancer cases to the Danish Cancer Register when they are first diagnosed, along with any subsequent changes in the diagnosis. Information is also forwarded to the register when patients first receive treatment. In addition, both pathology and forensic medicine departments report information to the register. All cancer-specific autopsy information is registered, regardless of whether the deceased person was known to have cancer or the cancer was first noted at autopsy. Diagnoses for the time period relevant to our study were registered using International Classification of Diseases, Seventh Revision, codes.

Study population

Establishment of the cohort. Using information from the Civil Registration System, we established a cohort that included all persons born in Denmark during the period 1935–1968 and still alive on April 1, 1968, as well as all those born in Denmark after April 1, 1968. Persons registered in the Danish Cancer Register with a CMM diagnosis before the start of follow-up (see below) were excluded from the cohort.

Identification of CMM cases. CMM cases were ascertained using the Danish Cancer Register. A person was considered to have CMM if he or she had one or more CMM diagnoses (International Classification of Diseases, Seventh Revision, code 190) noted in the register during the follow-up period.

Determination of reproductive history. We obtained information on each person’s reproductive history (number of children, age at each child’s birth, and time since the birth of the youngest child) from the Civil Registration System. (Because the Civil Registration System contains links between parents and their children, it can be used to determine the number of children a person has had and to ascertain each child’s date of birth.)

Statistical analyses

Each study subject was followed from April 1, 1968, or his/her 12th birthday, whichever came later, to the first of the following events: 1) CMM diagnosis; 2) death; 3) emigration; 4) designation as a “missing person” in the Civil Registration System; or 5) the end of follow-up (December 31, 2003). Associations between reproductive history variables (number of children, age at each child’s birth, and time since the birth of the youngest child) and CMM risk were evaluated with log-linear Poisson regression models using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). The estimated rate ratios are referred to hereafter as relative risks. Relative risk estimates were adjusted for attained age (5-year categories) and calendar period (5-year categories). In addition, each estimate was adjusted for the other reproductive history variables. All variables were treated as time-dependent.

Data for men and women were analyzed separately, with the exception that differences in the effect estimates for men and women were evaluated in a model using data from both men and women and including sex-specific effects for all reproductive history variables (i.e., interactions between the variables and sex). In this model, we evaluated whether
there was a sex difference in the effect of a variable by testing for an interaction between sex and the variable.

**RESULTS**

Of the 1,725,627 women in the cohort, 5,688 were diagnosed with CMM during 42,661,863 person-years of follow-up, while 3,908 cases of CMM were diagnosed among the 1,810,548 men in the cohort during 44,404,154 person-years of follow-up. Table 1 shows the distribution of CMM cases and person-years of follow-up in women and men by number of children, age at the first child’s birth, and time since the birth of the youngest child.

At the end of follow-up, 566,705 women and 753,705 men remained childless. Of the women with one or more children at the end of follow-up, 261,078 had one child, 586,303 had two children, and 311,541 had three or more children. Of the men who had fathered at least one child, 259,812, 516,358, and 280,673 had one, two, and three or more children, respectively.

After adjustment for age and calendar period, CMM risk did not differ between nulliparous women and women with one child (for no children vs. one child, relative risk (RR) = 0.99, 95% confidence interval (CI): 0.91, 1.09). In contrast, men who had not fathered any children had a decreased risk of CMM compared with men who had fathered one child (for no children vs. one child, RR = 0.88, 95% CI: 0.79, 0.98). The difference in the relative risks for women and men was statistically significant (p = 0.001).

Associations between number of children and CMM risk in women and men with one or more children are shown in Figure 1. After adjustment for age, calendar period, age at the first child’s birth, and time since the birth of the youngest child, number of children was significantly associated with risk of CMM (women: p = 0.004; men: p = 0.026). Persons of both sexes with two or three children had a slightly increased risk of CMM compared with persons with only one child. In both sexes, having five or more children was

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**FIGURE 1.** Estimated relative risk of cutaneous malignant melanoma by number of children in women and men with at least one child, Denmark, 1968–2003. Relative risk estimates were adjusted for age, calendar period, age at the first child’s birth, and time since the birth of the youngest child; persons with a single child formed the reference group. The estimates for women plotted in the figure are as follows: two children, relative risk (RR) = 1.10, 95% confidence interval (CI): 1.01, 1.19; three children, RR = 1.07, 95% CI: 0.97, 1.18; four children, RR = 0.94, 95% CI: 0.80, 1.11; five children, RR = 0.85, 95% CI: 0.60, 1.20; and six or more children, RR = 0.43, 95% CI: 0.19, 0.95. The estimates for men are as follows: two children, RR = 1.10, 95% CI: 1.00, 1.22; three children, RR = 1.05, 95% CI: 0.93, 1.18; four children, RR = 1.18, 95% CI: 0.99, 1.41; five children, RR = 0.79, 95% CI: 0.52, 1.18; and six or more children, RR = 0.52, 95% CI: 0.23, 1.16.

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**TABLE 1.** Distribution of cases of cutaneous malignant melanoma and person-years of follow-up in women and men, according to number of children, age at the first child’s birth, and time since the birth of the youngest child, Denmark, 1968–2003

<table>
<thead>
<tr>
<th>Reproductive History</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1,725,627)</td>
<td>(n = 1,810,548)</td>
</tr>
<tr>
<td>No. of children</td>
<td>No. of cases</td>
<td>Person-years</td>
</tr>
<tr>
<td>0</td>
<td>1,186</td>
<td>18,199,454</td>
</tr>
<tr>
<td>1</td>
<td>991</td>
<td>6,537,271</td>
</tr>
<tr>
<td>2</td>
<td>2,353</td>
<td>11,794,452</td>
</tr>
<tr>
<td>3</td>
<td>924</td>
<td>4,689,399</td>
</tr>
<tr>
<td>4</td>
<td>193</td>
<td>1,129,236</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>232,513</td>
</tr>
<tr>
<td>≥6</td>
<td>6</td>
<td>79,538</td>
</tr>
<tr>
<td>Time (years) since birth of the youngest child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1,186</td>
<td>18,199,454</td>
</tr>
<tr>
<td>0–4</td>
<td>872</td>
<td>7,988,724</td>
</tr>
<tr>
<td>5–9</td>
<td>659</td>
<td>4,661,865</td>
</tr>
<tr>
<td>10–14</td>
<td>681</td>
<td>3,547,361</td>
</tr>
<tr>
<td>≥15</td>
<td>2,290</td>
<td>8,264,460</td>
</tr>
<tr>
<td>Total</td>
<td>5,688</td>
<td>42,661,863</td>
</tr>
</tbody>
</table>
associated with a decrease in CMM risk. Overall, the association between number of children and CMM risk did not differ between men and women \((p = 0.10)\).

Women and men who had their first child at a very young age \((<20 \text{ years})\) had a decreased risk of CMM compared with those who had their first child at 20–24 years of age (figure 2). As age at the first child’s birth increased, risk of CMM also increased, except in men who were aged 35 years or older when they fathered their first child. Women who delivered their first child when they were 35 or more years of age had a 53 percent greater risk of CMM than women who first delivered at 20–24 years of age; in contrast, the risk of CMM in men fathering their first child at 35 or more years was similar to that of men who fathered their first child at 20–24 years. Overall, both women and men who were aged 25 years or older when they had their first child were at increased risk of CMM compared with younger \((<25 \text{ years})\) first-time parents (for women, \(RR = 1.24, 95 \% \text{ CI: } 1.16, 1.33\); for men, \(RR = 1.21, 95 \% \text{ CI: } 1.12, 1.33\)). The associations between age at the first child’s birth and CMM risk did not differ between men and women \((p = 0.44)\).

Women and men also did not differ with respect to the association between CMM risk and elapsed time since the birth of the youngest child \((p = 0.58)\). In both women and men, risk of CMM increased after 10 or more years had elapsed, compared with the first 10 years (for women, \(RR = 1.15, 95 \% \text{ CI: } 1.05, 1.27\); for men, \(RR = 1.16, 95 \% \text{ CI: } 1.04, 1.29\)) (figure 3).

**DISCUSSION**

Consistent with several previous reports, including a large Swedish population-based case-control study conducted by Lambe et al. (8), we found that high parity, younger age at first birth, and shorter time since the birth of the youngest child were associated with a reduced risk of CMM in women. However, the results for men were remarkably similar to those observed for women; there was a similar risk reduction among men with five or more children, a higher risk of CMM in men who were older when they fathered their first child, and a higher risk of CMM in men with longer intervals since the birth of their youngest child. Previously, Lambe et al. (8) suggested that the observed association between parity and CMM risk in women could be interpreted as a sign that female sex hormones influence CMM development. However, the similarity of our findings in men and women make a hormonal mechanism for CMM development in women unlikely.
and suggest that lifestyle factors might explain the observed associations between reproductive history and CMM risk.

Sun exposure frequency and intensity might explain our findings by being associated with both reproductive history and CMM risk. Differences in sun exposure patterns related to number of children—with the parents of many children having less sun exposure (both overall and at any given time point) than persons with few or no children—could produce a spurious inverse association between number of children and CMM risk. Similarly, if having one’s first child at a young age reduces frequency of sun exposure, intensity of sun exposure, and number of sunburns incurred during a critical risk period, we would expect to observe an association between younger age at first birth and CMM risk.

The observed associations may also be explained by differences in socioeconomic status related to number of children and age at the first child’s birth. For example, having many children at a young age has been associated with low socioeconomic status, which in turn has been associated with a reduced risk of developing CMM (18).

We lacked information on a number of other established physical risk factors for CMM, including skin phenotype, hair and eye color, number of nevi, and number of sunburns incurred during childhood; such information is not included in the national registers in Denmark. However, these factors are unlikely to have been related to the number of children people had and the ages at which those children were born. Thus, from a biologic point of view, these factors are unlikely to have confounded our results.

Unlike men and women with children, childless men and women differ somewhat in their relative risk of CMM. Men who had not fathered a child had a reduced risk of CMM compared with men who had fathered one child, whereas nulliparous women and women with one child had similar risks. This may be due to the fact that Danish men without children are generally of lower socioeconomic status than men with children (19) and the risk of CMM is lower in people of low socioeconomic status than in those of high socioeconomic status (18). In contrast, childless women typically have a relatively high socioeconomic status, which, along with the possibility of longer/more intense sun exposure, confers a higher risk of CMM (19).

We consider our findings to have high credibility because of the size and nature of this study. Our study was a prospective cohort study based on data collected in the entire population of Denmark within a given time period. All information on exposures was registered prior to the development of the outcome. Both exposure and outcome information came from national registers and was accessed via a unique personal identification number that ensured accurate linkage between registers. Finally, all information on which this report was based must be reported by law in Denmark. As a result of these study conditions, our study results were minimally influenced, if at all, by selection bias and differential misclassification.

In conclusion, in this study, associations between reproductive history and risk of CMM were similar in women and men. This finding argues against the previously advanced hypothesis that exposure to pregnancy hormones influences the risk of CMM in women. Instead, the associations may be explained by lifestyle and/or socioeconomic factors associated with reproductive history.

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Conflict of interest: none declared.

REFERENCES


