Reproductive History and Stage of Breast Cancer

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A woman's reproductive history influences her risk of breast cancer. The authors hypothesized that reproductive history also influences stage of disease at the time of diagnosis. The authors analyzed a population-based cohort of 1.5 million Danish women born between 1935 and 1978 for whom individual information on births was available. Between 1978 and 1994, 10,790 incident cases of breast cancer in women under 60 years of age were identified. Nulliparous women compared with parous women and women with a late age at first birth compared with an early age were at significantly increased risk of being diagnosed with a large tumor and with cancer that had spread to regional lymph nodes. However, such an association was not seen for women diagnosed with a small tumor and women with cancer that had not spread to regional lymph nodes. Reproductive history did not appear to influence the time interval from first symptoms to first physician visit ("patient delay") or the time interval from first physician visit to surgery ("doctor delay"). The authors conclude that reproductive history is associated both with incidence of breast cancer and with stage of the disease at diagnosis, indicating possible influences on tumor progression and growth rate. Intensified awareness is warranted to achieve earlier diagnosis among nulliparous women and women with a late age at first childbirth, with the hope of improving their prognosis. Am J Epidemiol 1999; 150:1325–30.

It is well established that a woman's reproductive history influences her risk of breast cancer. In particular, parity and age at first childbirth are considered strongly related to the risk of breast cancer (1). However, studies addressing these issues have almost exclusively dealt with breast cancer as a single entity. Thus, little is known about the possible effect of these reproductive factors on tumor biology (tumor progression, metastatic potential, etc.) as reflected in stage of the disease at diagnosis.

We hypothesized that parity and age at first childbirth not only are related to the risk of developing breast cancer but also are associated with the stage of breast cancer at diagnosis. We used a large population-based cohort with detailed information on reproductive history and tumor characteristics to evaluate whether parity and age at first birth are related to tumor size or axillary nodal spread at diagnosis.

MATERIALS AND METHODS

Population registries

Since April 1, 1968, the Civil Registration System in Denmark has assigned an individually unique national registration number to all citizens. This number permits accurate linkage of information obtained from different registries. The Civil Registration System also keeps updated information on vital status, emigration, and dates of live births.

The Danish Breast Cancer Cooperative Group started a series of national prospective studies in 1978 to systematically evaluate breast cancer treatment programs. A detailed description of the group's breast cancer registry has been given elsewhere (2, 3). The Cooperative Group collects detailed information on breast cancer cases at diagnosis, including the size of the tumor and the number of positive nodes. During a limited time period (1977–1981), the Cooperative Group collected additional information such as whether the tumor had been discovered by the woman herself, the date on which the woman experienced the first symptom(s) of her disease, and the date of the woman's first consultation with a medical doctor (4).
Through a linkage between the Danish Breast Cancer Cooperative Group and the Danish Cancer Registry, the Cooperative Group was found to have information on 94 percent of all breast cancer cases reported to the Danish Cancer Registry. The Danish Cancer Registry is considered close to complete regarding incident cases of malignant neoplasms diagnosed in Denmark since 1943 (5); world-standardized breast cancer rates in Denmark during the periods 1978–1982, 1983–1987, and 1988 onward were 64.8, 69.5, and 74.6 per 100,000 women, respectively (6).

**Study cohort**

A research parity database was established from the Civil Registration System that included all women born between April 1, 1935, and March 31, 1978, as described previously (7, 8). Based on each person's identifiable number from the Civil Registration System, a linkage was performed with the Danish Breast Cancer Cooperative Group data to obtain information on invasive primary breast cancers registered during the period January 1, 1978–September 30, 1994.

**Statistical analyses**

The possible impact of reproductive history on the incidence of breast cancer of a specific size or a particular nodal status was investigated in a follow-up study in which data were analyzed by log-linear Poisson regression (9). Each stage-specific subtype of breast cancer was analyzed separately. All women entered follow-up for each of the stage-specific breast cancer diagnoses on January 1, 1978, or on their 12-year birthday, whichever came last. The at-risk period continued until first diagnosis of breast cancer (at whatever stage), death, emigration, or September 30, 1994, whichever occurred first. Pregnancies occurring after a diagnosis of breast cancer were not included in the study. Incidence rate ratios are referred to here as relative risks. Adjustment was made for attained age (12–24, 25–29, 30–34, ..., 50–54, and >54 years), calendar period (1978–1982, 1983–1987, 1988–1992, and 1993–1994), parity (0, 1, 2, 3, and ≥4 live births), and age at first live birth (nulliparous and 12–19, 20–24, 25–29, 30–34, and >34 years). All variables were treated as time-dependent variables. The effects of the confounders were allowed to differ according to stage, making it possible to take into account the fact that temporal trends and other effects could differ by size and nodal status. Testing for effect modification by attained age was performed with age categorized as <45 years versus ≥45 years. Analyses were performed using the SAS procedure PROC GENMOD (10).

The relations between reproductive history and factors associated with tumor detection, such as whether the woman had discovered the tumor herself (yes/no), the time interval from first symptom to first physician visit in days (patient delay), and the time interval from first physician visit to surgery in days (doctor delay), were evaluated by means of the Mann-Whitney and χ² tests.

**RESULTS**

**Incidence**

In total, 1,529,512 women were included in the cohort. Of these, 1,000,276 women (65.4 percent) had a total of 2,071,415 births before the end of follow-up: 254,694 women (25.5 percent) had one birth, 494,697 (49.5 percent) had two, 193,250 (19.3 percent) had three, and 57,635 (5.7 percent) had four or more. A total of 10,790 primary invasive breast cancers diagnosed before 60 years of age were detected in this cohort during 22.3 million person-years of follow-up. Table 1 gives the distribution of cases and person-years by age, calendar period, parity, and age at first birth.

**TABLE 1. Distribution of cases of breast cancer and person-years of follow-up by age, calendar period, and reproductive history, Denmark, 1978–1994**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of births</th>
<th>Person-years of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>%</td>
</tr>
<tr>
<td>12–29</td>
<td>158</td>
<td>1.5</td>
</tr>
<tr>
<td>30–39</td>
<td>2,054</td>
<td>19.0</td>
</tr>
<tr>
<td>40–49</td>
<td>6,072</td>
<td>56.3</td>
</tr>
<tr>
<td>≥50</td>
<td>2,506</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td>10,399,000</td>
<td>5,973,000</td>
</tr>
<tr>
<td></td>
<td>4,656</td>
<td>5,850,000</td>
</tr>
<tr>
<td></td>
<td>2,010</td>
<td>6,657,000</td>
</tr>
<tr>
<td></td>
<td>1,295</td>
<td>7,245,000</td>
</tr>
<tr>
<td></td>
<td>9,501,000</td>
<td>581</td>
</tr>
<tr>
<td></td>
<td>1,472</td>
<td>3,469,000</td>
</tr>
<tr>
<td></td>
<td>2,693</td>
<td>6,480,000</td>
</tr>
<tr>
<td></td>
<td>710</td>
<td>3,164,000</td>
</tr>
<tr>
<td></td>
<td>183</td>
<td>648,000</td>
</tr>
<tr>
<td></td>
<td>3,469,000</td>
<td>6.1</td>
</tr>
<tr>
<td>No. of births</td>
<td>1,910</td>
<td>723,000</td>
</tr>
<tr>
<td></td>
<td>4,892</td>
<td>7,700,000</td>
</tr>
<tr>
<td></td>
<td>2,112</td>
<td>6,188,000</td>
</tr>
<tr>
<td>≥4</td>
<td>581</td>
<td>2,390,000</td>
</tr>
</tbody>
</table>
Overall, we documented a significantly lower incidence of breast cancer among ever parous women compared with never parous women (relative risk = 0.87; 95 percent confidence interval: 0.82, 0.92). Among parous women, we found a significantly increasing incidence of breast cancer with increasing age at first birth ($p < 0.0001$) and decreasing parity ($p < 0.0001$) (table 2).

Table 2 shows the associations between these reproductive factors and breast cancer risk according to tumor size. Ever parous women had a significantly lower incidence of larger tumors than nulliparous women; for tumors less than or equal to 20 mm in diameter, we found no such association. In other terms, nulliparous women had a significantly increased risk of being diagnosed with a large tumor compared with parous women (relative risk = 1.69; 95 percent confidence interval: 1.37, 2.04). Among ever parous women (relative risk = 1.01; 95 percent confidence interval: 0.87, 1.16) and among nulliparous women (relative risk = 0.87; 95 percent confidence interval: 0.82, 0.92).

Increasing incidence of breast cancer with increasing parity was significantly associated with a risk for larger tumors. The protective effect of multiparity was significantly stronger for small tumors (<20 mm) than for larger tumors. Indeed, we found no association between number of births and risk of breast tumors above 50 mm in diameter (table 2). Similar associations with reproductive history were found when breast cancer cases were classified by nodal status instead of by tumor size (no positive nodes, 1–3 positive nodes, and ≥4 positive nodes; data not shown). To evaluate whether our results were modified by age, particularly by menopause status, we performed a test for interaction with age categorized as <45 years versus ≥45 years. Our analysis did not show any effect modification by attained age.

The associations shown in table 2 are further illustrated in figures 1 and 2. Here the predicted breast cancer rates (based on the model from table 2) are calculated by tumor size at diagnosis for women aged 50–54 years in 1993–1994, according to their reproductive history. In figure 1, tumor size-specific rates of breast cancer in nulliparous women are compared with rates in uniparous women according to their age at the birth. Having one's first child at a young age slightly increases a woman's risk of being diagnosed with a small tumor, whereas the risks of medium and large tumors are reduced after the first birth. The reduction in medium and large tumors becomes smaller the older the woman is at the time of childbirth. For women aged ≥35 years at their first birth, there is even a small increase in risk. The incidence of tumors less than 21 mm in diameter at age at first birth, there is even a small increase in risk. For women aged ≥35 years at their first birth, there is even a small increase in risk. The incidence of tumors less than 21 mm in diameter at age at first birth, there is even a small increase in risk. For women aged ≥35 years at their first birth, there is even a small increase in risk. The incidence of tumors less than 21 mm in diameter at age at first birth, there is even a small increase in risk. For women aged ≥35 years at their first birth, there is even a small increase in risk. The incidence of tumors less than 21 mm in diameter at age at first birth, there is even a small increase in risk.
FIGURE 1. Predicted breast cancer rates by tumor size at diagnosis in nulliparous and uniparous Danish women aged 50–54 years in 1993–1994, according to age at first childbirth. Prediction is based on the model from table 2 (Denmark, 1978–1994); cases with missing information on tumor size are not included.

Diagnostic delay

For women whose cancer was diagnosed during the period 1978–1982, additional information had been obtained about whether the woman discovered the
tumor herself, about the time interval between the first symptoms' being observed by the woman and her first visit to a physician (patient delay), and about the time interval between the first physician visit and the time of definitive surgery or biopsy (doctor delay) (4). Overall, 93.3 percent of the women had discovered the tumor themselves, and among these women the median patient delay was 9 days. The median doctor delay was 29 days.

A more detailed presentation of the data is given in table 3. We evaluated the associations between the three tumor detection-related variables and the reproductive variables presented in table 2. There was no significant association in any of the nine tests (table 3).

**DISCUSSION**

This study showed that parity and age at first birth are associated not only with the incidence rate of breast cancer but also with the stage of the disease at diagnosis. Whereas nulliparous women versus parous women and women with a late age at first childbirth compared with an early age were at similar risks of having breast cancer diagnosed at an early stage (small tumor, no metastatic spread), nulliparous women and women with a late first birth were at significantly increased risk of being diagnosed with advanced breast cancer (large tumors, extensive metastatic spread to regional lymph nodes). In contrast, multiparity was protective against being diagnosed with a small tumor but not against being diagnosed with a large tumor. These results can be ascribed to differences in tumor progression rates and/or differences in detection rates. Obviously, a large tumor must at some point have been small. Under the assumption that certain tumors grow more rapidly than others, some tumors will stay in the category of small tumors for a shorter time before they move on to become medium-sized and eventually large tumors. Thus, according to one interpretation, nulliparous women and women with a late age at first birth who are at particularly high risk of being diagnosed with large tumors may have tumors with rapid growth potential.

A rival explanation would be that associations exist between reproductive factors and the probability of early tumor detection. For example, differences in detection rates might arise if breast self-examination is more difficult for nulliparous women compared with parous women or more difficult for women with a late age at first birth versus an early age at first birth. The breast tissue of a nulliparous woman is firmer and more homogenous than the breast tissue of a parous woman, which might make detection of a tumor more difficult. However, it is equally conceivable that the nodularity present in a parous woman's breast would make it difficult to distinguish glandular tissue from tumor tissue. Thus, the extent of which and direction in which reproductive factors may influence detection of tumors is difficult to predict. Differential use of mammography according to reproductive history could also cause differences in time of detection. However, the vast majority of women in our study were below age 50. In Denmark, mammography is offered only to women aged 50 years or older and only in a few parts of the country.

Finally, behavioral differences according to reproductive history could cause differences in time of detection. For example, parous women and those considering pregnancy may be more frequently in contact with the medical care system, leading to shorter delays in detection in comparison with nulliparous or older women. However, the differences in the effects of reproductive history were the same regardless of age. Furthermore, based on detailed referral information on a subset of the women included in this study, we found

**TABLE 3. Percentage of self-discovered tumors and median patient delay and doctor delay among Danish women diagnosed with breast cancer between 1978 and 1982, according to reproductive history**

<table>
<thead>
<tr>
<th>Parous status</th>
<th>Self-discovered tumor* (%)</th>
<th>Median patient delay† (days)§</th>
<th>Median doctor delay§ (days)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>94</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>Parous</td>
<td>93</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>( p ) for difference</td>
<td>0.78</td>
<td>0.09</td>
<td>0.14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years) at first birth</th>
<th>No. of births</th>
<th>Self-discovered tumor* (%)</th>
<th>Median patient delay† (days)§</th>
<th>Median doctor delay§ (days)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–19</td>
<td>1</td>
<td>92</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>20–24</td>
<td>2</td>
<td>93</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>25–29</td>
<td>3</td>
<td>93</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>30–34</td>
<td>3</td>
<td>93</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>≥35</td>
<td>≥4</td>
<td>92</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>( p ) for difference</td>
<td>0.99</td>
<td>0.98</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

* Information was available for 87% (1,215/1,390) of the cases.
† Time interval from the first symptom to the first physician visit.
§ Time interval from the first physician visit to breast cancer surgery.
¶ Information was available for 87% (1,203/1,390) of the cases.
no evidence of an association between delay in referral or delay in diagnosis and the reproductive factors in question. Therefore, the most likely explanation for our findings is that a woman's reproductive status influences both her risk for tumor development and the biologic features of the tumor, notably its growth potential.

Our prospective analysis was performed in a large population-based cohort, which made selection and information bias very unlikely. A potential limitation of our study was the lack of data on other reproductive factors, such as age at menarche and age at menopause. However, the confounding introduced by lack of adjustment for these variables should have been limited (11). Temporal trends in breast cancer incidence might differ according to tumor characteristics. We took this into account by allowing for different effects of calendar period in the different stage-specific analyses. The cohort included only women who were under age 60 years at the end of follow-up. Therefore, our results were obtained primarily among premenopausal women. However, the effects of reproductive history were the same regardless of age, indicating that the effects may be applicable to both pre- and post-menopausal women.

It is well established that having advanced breast cancer at the time of diagnosis (large tumor, lymphatic spread) is associated with a particularly poor prognosis. Thus, the association with more advanced disease observed for nulliparous women and women with a late age at first birth also gives them a higher risk of lethal disease. In a large cohort of women who had undergone breast cancer treatment, we previously investigated whether the prognostic effect of parity and age at first birth also gives them a higher risk of lethal disease. In a large cohort of women who had undergone breast cancer treatment, we previously investigated whether the prognostic effect of parity and age at first birth also gives them a higher risk of lethal disease. In this study, we adjusted for differences in tumor size and nodal status at the time of diagnosis (in addition to age, histologic grading, treatment regimen, and other factors) (12). Taken together, the two studies illustrate how reproductive risk factors have a further negative effect on the progression rate besides the effects seen as differences in tumor size and nodal status at diagnosis.

In conclusion, these data provide novel evidence that a woman's reproductive status may also influence her stage of breast cancer at diagnosis and thereby her long term disease-specific survival. In particular, nulliparous women and women who give birth to their first child at a late age are at increased risk of being diagnosed with large tumors with extensive metastatic growth and a poor prognosis. Regardless of the underlying biologic mechanism, these results support the development of initiatives to achieve earlier detection of breast cancer, perhaps through a combination of increased awareness and more frequent mammography, in this subset of women who tend to develop more lethal breast cancer.

ACKNOWLEDGMENTS

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REFERENCES