Original Contribution

Smoking Cigarettes before First Childbirth and Risk of Breast Cancer

Mina Ha1,2, Kiyohiko Mabuchi1, Alice J. Sigurdson1, D. Michal Freedman1, Martha S. Linet1, Michele Morin Doody1, and Michael Hauptmann3,4

1 Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD.
2 Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, Korea.
3 Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD.
4 Bioinformatics and Statistics, Netherlands Cancer Institute, Amsterdam, The Netherlands.

Received for publication July 31, 2006; accepted for publication January 5, 2007.

Inconsistent epidemiologic findings on cigarette smoking and female breast cancer risk may reflect insufficient assessment of smoking onset and amount relative to reproductive events. To determine the risk of breast cancer associated with smoking during different periods of reproductive life, the authors evaluated 906 incident breast cancer cases in a nationwide cohort of 56,042 female US radiologic technologists (1983–1998) who responded to two questionnaire surveys. After they accounted for age, birth cohort, and established breast cancer risk factors, smoking-related breast cancer risks differed by smoking during three reproductive time periods (p = 0.003), with a statistically significant 3% increase per pack-year of smoking between menarche and first childbirth (relative risk = 1.03, 95% confidence interval: 1.02, 1.05) and no significant association for smoking after first childbirth. Risk also increased with younger age at smoking initiation (p-trend = 0.06), after adjustment for pack-years of smoking before and after first childbirth, indicating an independent effect of age at smoking initiation. The findings from this study suggest that sensitivity of the female breast to tobacco carcinogens is increased during adolescence and early adulthood but decreases after first childbirth, when most breast tissue has terminally differentiated.

breast neoplasms; reproduction; smoking

Female breast cancer is not widely accepted as a smoking-related malignancy (1, 2) because most previous studies provided little or no evidence for an association (3). However, several recent studies suggest that smoking at young ages may increase breast cancer risk (4–6). It can be postulated that breast cancer risks differ according to smoking at young ages versus smoking later in life because tissue susceptibility to carcinogenic effects of tobacco smoke may vary according to age or physiologic characteristics during different periods of a woman’s reproductive life.

MATERIALS AND METHODS

We used data from the US Radiologic Technologists study. The study follows a cohort of 146,022 (106,953 female) radiologic technologists residing in the United States who were certified by the American Registry of Radiologic Technologists for at least 2 years between 1926 and 1982. Study population and methods are described in detail elsewhere (7, 8). Briefly, the cohort is mostly female (73 percent) and Caucasian (95 percent) and has been followed up through annual recertification with the American Registry of Radiologic Technologists and linkage with national address and mortality databases. During 1983–1989, all 132,454 (98,233 female) subjects located and alive were mailed a baseline questionnaire, followed by a second questionnaire administered during 1994–1998. Of 98,233 women eligible, 69,524 responded to the baseline questionnaire (71 percent response). For 67,645 female

Correspondence to Dr. Mina Ha, Department of Preventive Medicine, Dankook University College of Medicine, San 29 Anseo-Dong, Cheonan, Chungnam 330-714, Korea (e-mail: minaha@dankook.ac.kr).
responders who were cancer free (except for nonmelanoma skin cancer) when they completed the baseline questionnaire, we assessed breast cancer incidence in a subcohort of 54,522 women who responded to a second questionnaire in 1994–1998 (81 percent response) and 1,520 women who died between 1983 and August 1998; 11,603 women were lost to follow-up. First primary breast cancers during follow-up were identified from self-reports in the second questionnaire (n = 781). We sought pathology reports or medical records to confirm the breast cancer self-reports. Because 99.4 percent of self-reported breast cancers were confirmed among technologists for whom these medical records could be obtained (8), we included self-reported breast cancers even if medical records were unavailable (n = 155). In addition, 125 possible breast cancer diagnoses were ascertained among the 1,520 women who died during follow-up from the underlying or contributing causes of death identified on death certificates (before 1993) or National Death Index Plus records (since 1993). For deceased cases, the date of diagnosis was approximated by subtracting from the date of death the average breast cancer survival time based on 1973–2000 data from the Surveillance, Epidemiology, and End Results Program, stratified by 5-year categories of age at death.

We obtained information on cigarette smoking from the answers to the following five questions in the baseline questionnaire: Have you smoked at least 100 cigarettes during your entire life? How old were you when you started smoking? Do you smoke cigarettes now? How old were you when you stopped smoking? On the average, how much do you or did you smoke each day? A smoker was defined as a woman who had smoked at least 100 cigarettes in her lifetime. Former smokers had stopped smoking more than 2 years before the baseline questionnaire. We used pack-years (number of packs of cigarettes smoked per day times number of years of smoking) up to the time of response to the baseline questionnaire to estimate cumulative tobacco smoke exposure.

Information on reproductive and other known risk factors was also obtained from the baseline questionnaire except for menopausal status, which was based on both questionnaires. We used mean reported age at menopause stratified by 5-year categories of age at baseline as an approximation for the 4.7 percent of women for whom information on menopause was missing. We used calendar year that the woman first worked as a radiologic technologist as a surrogate for occupational radiation exposure, since the average level of exposure was higher in earlier years of employment. In previous analyses of this cohort, this measure was found to be the most important radiation-related determinant for elevated risk of radiogenic cancers (9).

Hazard ratios were calculated to estimate breast cancer risk and 95 percent confidence intervals using proportional hazards regression with age as the time scale. Subjects contributed follow-up time from their age at response to the baseline questionnaire to age at diagnosis of breast or any other cancer (except nonmelanoma skin cancer), death, or response to the second questionnaire, whichever occurred first. Women who reported a diagnosis of breast cancer on the second questionnaire or died from breast cancer during follow-up contributed an event, whereas the person-time of all other subjects was censored. Analyses were stratified by 5-year birth cohort intervals to adjust for secular trends. Cumulative pack-years of smoking during different intervals were calculated by dividing lifetime pack-years into periods, and those variables (categorical and continuous for trend tests) were evaluated together in one model. Likelihood ratio tests with two-sided p values were used to evaluate whether dividing lifetime pack-years into time periods fit the data better.

RESULTS

Among the 56,042 female radiologic technologists we studied, mean age at completion of the baseline questionnaire was 37.5 years (range, 22–92). There were 12,372 women who reported being postmenopausal on the baseline questionnaire and 12,376 women who experienced menopause during follow-up. A total of 39,132 (69.8 percent) women were parous (one or more livebirths), and 27,502 (49.1 percent) were cigarette smokers who, on average, began smoking at age 18.3 years (range, 8–79) and had smoked for 13.6 pack-years (range, 0.3–145). Among parous women, mean smoking duration was 6.8 years (range, 1–39) before and 12.9 years (range, 1–59) after first childbirth. Before assessing smoking-related breast cancer risk, we examined risks according to known and suspected risk factors for breast cancer in the study population. As expected, breast cancer risk was significantly increased with increasing age, lower parity, later age at first childbirth, postmenopausal status, presence of family history of breast cancer, increasing alcohol intake, and earlier calendar year starting to work as a radiologic technologist, although the risk was not related to age at menarche, hormone replacement therapy, or body mass index (table 1). Breast cancer risks for former and current smokers, compared with never smokers, were 1.17 (95 percent confidence interval: 0.99, 1.38) and 1.13 (95 percent confidence interval: 0.96, 1.32), respectively.

Among parous women, breast cancer relative risks associated with cumulative pack-years of cigarette smoking before and after first childbirth differed significantly (p < 0.001). There was a significant trend of rising breast cancer risk with cumulative pack-years of smoking before (p-trend < 0.0001) but not after (p-trend = 0.14) first childbirth in the model including separate variables for smoking before and after first childbirth as well as other covariates (figure 1). Risks for 1–3, 4–6, 7–9, and 10 or more pack-years of smoking before first childbirth, compared with not smoking before first childbirth, were 1.01 (95 percent confidence interval: 0.78, 1.31), 1.18 (95 percent confidence interval: 0.87, 1.59), 1.24 (95 percent confidence interval: 0.85, 1.81), and 1.78 (95 percent confidence interval: 1.27, 2.49), respectively, after adjusting for smoking after first childbirth and other covariates. The trend for smoking before first childbirth remained significant after additionally adjusting for age at smoking initiation (table 2).

Relative risks differed significantly according to timing of smoking defined by reproductive events (p = 0.003), with a nonsignificant 6 percent increase per pack-year of smoking before menarche (relative risk = 1.06, 95 percent confidence
interval: 0.76, 1.47), a statistically significant 3 percent increase between menarche and first childbirth (relative risk = 1.03, 95 percent confidence interval: 1.02, 1.05), and a non-significant 1 percent decrease after first childbirth (relative risk = 0.99, 95 percent confidence interval: 0.98, 1.00) (figure 2). The difference in risks per pack-year of smoking before menarche and between menarche and first childbirth was not statistically significant ($p = 0.92$), possibly because
only 0.5 percent of parous women smoked before menarche ($n = 212$) and the range of pack-years was relatively narrow (0.5–10). Risk increased with younger age at smoking initiation ($p$-trend $= 0.06$) after adjustment for pack-years of smoking before and after first childbirth (table 2), suggesting an independent effect of age at smoking initiation.

Results for parous women stratified by menopausal status were generally very similar but more unstable among premenopausal women because of the smaller number of events. However, the effect of smoking at an early age was pronounced among postmenopausal women (table 2).

For nulliparous women, relative risks for starting to smoke at age $>20$, 18–20, 15–17, and $<15$ years, compared with those for nonsmokers, were 0.97 (95 percent confidence interval: 0.61, 1.54), 1.40 (95 percent confidence interval: 0.96, 2.06), 1.42 (95 percent confidence interval: 0.92, 2.19), and 1.14 (95 percent confidence interval: 0.56, 2.31), respectively, with no significant trend ($p = 0.71$). The relative risk for $\geq10$ or more lifetime cumulative pack-years of smoking, compared with $<10$ pack-years, was 1.31 (95 percent confidence interval: 0.92, 1.87), with no significant trend ($p = 0.88$).

**DISCUSSION**

We evaluated risk of female breast cancer according to cigarette smoking within time windows of a woman’s reproductive life while controlling for the effects of smoking during other time periods. Our results are consistent with the biologic data indicating that the female breast is sensitive to tobacco carcinogens before first childbirth, and possibly especially before menarche, whereas sensitivity decreases after first childbirth, when most breast tissue has terminally differentiated. These findings also suggest that the absence of associations between breast cancer and lifetime smoking in previous studies (3, 10) may be due to a dilution of the effect of smoking before first childbirth by the absence of an effect of smoking subsequent to first childbirth or after young adulthood.

Most previous studies reporting risks for smoking before first childbirth or at young ages analyzed data separately for each period, and they calculated relative risks for smoking before first childbirth or at young ages compared with not smoking before first childbirth or at young ages, respectively (5, 11, 12). The studies that reported elevated breast cancer risks associated with smoking in early life (5, 11) did not control for smoking during other periods. Only one study, to our knowledge, assessed risks associated with smoking during one period by adjusting for effects of smoking during other periods; increasing breast cancer risks with duration of smoking before but not after first childbirth were observed (4). Although the results of studies with and without joint adjustment are not inconsistent, our data (jointly adjusted for smoking prior to and after first childbirth) revealed higher risks than those derived from separately evaluating breast cancer risks associated with cumulative smoking during specific time windows. In addition, evaluating smoking during different time periods in a joint model enabled us to formally test whether smoking-related risks differed by time period of smoking. On the other hand, mutual adjustment for smoking during different periods of life as well as for cumulative pack-years, age at smoking initiation, and attained age may represent “overadjustment” because these variables are correlated. However, we did not experience any indications of collinearity, for example, inflated standard errors, and adjusted risks were generally similar, but somewhat more pronounced, compared with the corresponding unadjusted risks.

Our study is one of the first to evaluate female breast cancer risk in relation to cumulative pack-years of smoking.
by jointly assessing smoking during different periods of reproductive life. We demonstrated that risks from smoking during different periods of reproductive life vary significantly, with the highest risk conferred by smoking before first childbirth. We also found increased breast cancer risk linked with initiation of smoking at young ages, adjusted for smoking before and after first childbirth, suggesting that age at exposure may modify breast cancer risk for parous women independently of the effect of reproductive history.

In the present study, the effect of smoking at an early age was pronounced in women with postmenopausal breast cancer, perhaps reflecting an antiestrogenic effect of smoking. If smoking at an early age malignantly transforms a breast cell, proliferation of the initiated cell could be decelerated in continuing smokers but not in those who quit, explaining a longer latency (13). This possibility is consistent with previous prospective studies that observed higher breast cancer risks for former compared with current smokers (4, 14–16). Our data showed similar patterns.

Although analyses based on duration of smoking produced results generally similar to those based on pack-years, we preferred pack-years because this metric combines intensity and duration and its values have a wider range than duration, which provides more analytic power, especially for smoking exposure within relatively short time intervals.

We did not have information on passive smoking and could therefore not evaluate its effect on breast cancer risk. However, the resulting underestimation of overall tobacco exposure is most likely nondifferential with respect to case status and would not explain our positive findings. Additionally, the observed borderline statistically significant trend for age at initiation was based on smokers only. Any passive smoking exposure would add only marginally to the tobacco carcinogen exposure of this group.

<table>
<thead>
<tr>
<th>Age at which smoking started (years)</th>
<th>All</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers</td>
<td>294</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;20</td>
<td>54</td>
<td>0.97</td>
<td>0.60, 1.57</td>
</tr>
<tr>
<td>18–20</td>
<td>159</td>
<td>1.09</td>
<td>0.64, 1.86</td>
</tr>
<tr>
<td>15–17</td>
<td>113</td>
<td>1.19</td>
<td>0.68, 2.06</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25</td>
<td>1.48</td>
<td>0.77, 2.84</td>
</tr>
<tr>
<td>p-trend†</td>
<td>0.06</td>
<td>0.93</td>
<td>0.05</td>
</tr>
<tr>
<td>Pack-years of smoking before first childbirth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>323</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>&lt;10</td>
<td>241</td>
<td>0.97</td>
<td>0.61, 1.54</td>
</tr>
<tr>
<td>≥10</td>
<td>75</td>
<td>1.39</td>
<td>0.82, 2.35</td>
</tr>
<tr>
<td>p-trend†</td>
<td>0.002</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Pack-years of smoking after first childbirth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>365</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>&lt;10</td>
<td>110</td>
<td>0.89</td>
<td>0.66, 1.21</td>
</tr>
<tr>
<td>≥10</td>
<td>163</td>
<td>0.84</td>
<td>0.63, 1.14</td>
</tr>
<tr>
<td>p-trend†</td>
<td>0.27</td>
<td>0.68</td>
<td>0.35</td>
</tr>
</tbody>
</table>

* Hazard ratios (HRs) were based on proportional hazards models (one model each for All, Premenopausal, and Postmenopausal) with age as the time scale, stratified at baseline for birth cohort in 5-year intervals, and adjusted for alcohol intake, age at menarche, age at first childbirth, parity, family history of breast cancer, hormone replacement therapy, year that a woman first worked as a radiologic technologist, body mass index, and menopausal status. Age at which smoking started and pack-years of smoking before and after first childbirth were modeled in the same model. Pre- and postmenopausal models were based on person-time and events contributed by study participants before and after their menopause, respectively. Nonsmokers were defined as having smoked <100 cigarettes during a lifetime.

† CI, confidence interval.
‡ Test for trend was based on the corresponding continuous variable; for age at which smoking started, the trend test was based on smokers only.
44 percent) and after (40 percent vs. 36 percent) first childbirth among parous women. For all other variables, including age at first birth as well as age at which smoking started and pack-years of smoking overall or before and after first childbirth, the distribution among subjects lost to follow-up and among those included in the analysis differed by no more than 2 percent per category. It seems unlikely that the observed increased risk for smoking before first childbirth is due to the somewhat higher smoking prevalence among those lost to follow-up. If smoking before first childbirth increases breast cancer risk, the rate of breast cancer diagnoses would have been higher among person-time contributed by those lost to follow-up compared with those included in the analysis, resulting in an underestimation of the smoking-related risk.

Information on parity was derived from the baseline questionnaire. Therefore, some breast cancer events may have been misclassified with respect to parity for women if their first full-term pregnancy occurred during follow-up. This possibility could have influenced some secondary analyses in which nulliparous women were considered the reference group. However, the magnitude of the effect is likely small because most women who were nulliparous at baseline were likely to remain so. The age of those women at baseline (mean, 35.5 years) exceeded substantially the age at first childbirth among parous women (mean, 25.2 years), and 95 percent of parous women at baseline experienced their first childbirth before 32 years of age.

During puberty, the female breast undergoes rapid cell proliferation and is mostly composed of undifferentiated tissue. Lobules differentiate during the first full-term pregnancy, which makes them refractory to neoplastic transformation (17). However, the absence of an association between cumulative pack-years of smoking after first childbirth and breast cancer, which is consistent with findings from other studies (3, 4, 6), may not necessarily imply a complete lack of sensitivity of breast tissue after first childbirth but rather reflect competition between the carcinogenic and antiestrogenic effects of smoking (11). Our findings, if confirmed, provide additional support for the importance of smoking prevention among young females, particularly during childhood, adolescence, and young adulthood.

**ACKNOWLEDGMENTS**

This research was supported in part by contracts NO1-CP-51016, NO2-CP-81121, NO2-CP-81005, and NO1-CP-15673 from the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics.

Conflict of interest: none declared.

**REFERENCES**

1. US Department of Health and Human Services. The health consequences of smoking: a report of Surgeon General. Atlanta, GA: US. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office