Parity, Reproductive Factors, and the Risk of Pancreatic Cancer in Women

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Abstract

Incidence rates for pancreatic cancer are consistently lower in women than in men. Previous studies suggest that reproductive factors, particularly parity, may reduce pancreatic cancer risk in women. We examined parity, breast feeding history, age at first birth, menstrual factors, and exogenous hormone use in relation to pancreatic cancer risk in a prospective cohort study of women. Information on parity and other reproductive factors was ascertained by questionnaires in 1976 and updated biennially. Multivariate relative risks were adjusted for cigarette smoking, body mass index, diabetes, and height. During 22 years of follow-up (1976–1998), 115,474 women contributed 2.4 million years of person time, and 243 cases of pancreatic cancer were identified. Compared with nulliparous women, the relative risk of pancreatic cancer was 0.86 [95% confidence interval (CI), 0.55–1.36] for women with 1–2 births, 0.75 (95% CI, 0.48–1.17) for 3–4 births, and 0.58 (95% CI, 0.34–0.98) for those with ≥5 births after adjusting for other factors. An analysis for linear trend indicates a 10% reduction in risk for each birth (P_trend = 0.008). Other reproductive factors and exogenous hormone use were not significantly related to pancreatic cancer risk. In this large prospective cohort of women, parity was associated significantly with a reduced risk of pancreatic cancer. Additional studies should examine the physiological or hormonal changes underlying pregnancy or childbirth that may explain this finding.

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related mortality among men and women in the United States (1). More than 30,000 people will be diagnosed with this disease, and a similar number will die from this disease in 2002 (2). The median survival for pancreatic cancer is <5 months, and <4% of cases survive 5 years after diagnosis (1). Despite the burden of pancreatic cancer, remarkably little is known about its etiology.

Cigarette smoking is the only consistently identified modifiable risk factor for pancreatic cancer. However, the RR for current cigarette smokers is ~2.5, and only ~25% of cases in the United States are attributable to smoking cigarettes (3). Therefore, much of the incidence of pancreatic cancer must be related to other factors.

Among the few consistent epidemiological features of pancreatic cancer is a lower incidence rate in women than in men. This incidence difference appears to be independent of differences in cigarette smoking patterns by gender and could be explained in part by reproductive factors. Prior studies have reported inverse (4–7) associations between increasing parity and the risk of pancreatic cancer. In addition, inverse associations with older age at menarche (6), younger age at first birth (5), and older age at first birth (8) have also been reported. Furthermore, in a small case-control study among postmenopausal women, increased duration of oral contraceptive use and younger age at first birth were associated with decreased risk of pancreatic cancer (4). However, other analyses of oral contraceptive use have failed to find any association (4–6, 9, 10). Studies of postmenopausal hormone use suggest null (4, 6, 9, 11) or weakly positive (5) associations with pancreatic cancer risk. Although results are inconsistent, previous work indicates a possible role for selected reproductive factors, and parity in particular, in the risk for developing pancreatic cancer.

We examined the relationship among reproductive factors, postmenopausal hormone and oral contraceptive use, and the risk of pancreatic cancer in a large, prospective cohort study of women. All of the exposure information was measured before the diagnosis of pancreatic cancer thereby avoiding biases that may result from collecting these data retrospectively from patients or proxy respondents.

Materials and Methods

Cohort. The NHS is an ongoing cohort study established in 1976 with 121,701 responses to a mailed questionnaire from married registered nurses in the United States 30–55 years of age. Detailed information on individual characteristics and behaviors was obtained from the questionnaires at baseline and

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3 The abbreviations used are: RR, relative risk; NHS, Nurses’ Health Study; BMI, body mass index; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.
Prospective Study of Parity and Pancreatic Cancer

reported cancer from a secondary source (other 15% of cases, we obtained confirmation of the self-
ing the diagnosis of pancreatic cancer on 85% of cases. For the
atic cancer. We were able to obtain pathology reports confirm-
medical records or at least to confirm the diagnosis of pancre-
(subject to state regulations) to obtain permission to retrieve
cancer unreported previously, we contacted a family member
attempted to confirm the self-reported cancer with an additional
thology reports. If permission to obtain records was denied, we
asked to report specific medical conditions including cancers
Participants were
quired about pregnancy and number of live births in 1976 and
sequently on the biennial mailed questionnaires until 1984,
when only 329 participants (0.27%) reported new births. Parity
was recorded as the total number of live births. In addition,
participants responded to questions about their age at the time
of their first pregnancy of ≥6 months duration and their age at
menarche. In 1976, women were asked to record the “intervals
of oral contraceptive use starting from first use and continuing
until the present time.” These data were updated every 2 years
until 1982, when <500 women indicated use of oral contra-
ceptives. We classified women as ever or never users of oral
contraceptives and computed their total duration of use in
months. Questions about menopausal status, age at onset of
menopause, and postmenopausal hormone use were asked at
baseline, and updated every 2 years. Women ≥56 years of age
and current cigarette smokers ≥54 years of age were assigned
to postmenopausal status. History and total duration of breast-
feeding was ascertained on the 1986 questionnaire.

Cigarette Smoking History and Other Risk Factors. Smok-
ing status and history of smoking were obtained at baseline, and
in all of the subsequent questionnaires. Current smokers re-
ported the average number of cigarettes smoked per day on
each questionnaire. We categorized participant cigarette-smok-
ing history as “current,” “former,” or “never-smoker” at each
time interval. In addition we computed the cumulative total
number of pack-years smoked among ever-smokers by multi-
plying the average reported number of packs smoked per day by
the number of years smoked in each time period, summing
overall previous time periods.

Baseline height and current weight were reported in 1976.
BMI in 1976 was estimated by dividing the baseline weight in
kilograms by the baseline height in m². In validation subsudies
the correlation between self-reported weight and weight meas-
ured by a trained technician was 0.96 (13). Participants were
asked about history of diabetes at baseline and in all of the
subsequent questionnaires.

Identification of Pancreatic Cancer Cases. Participants were
asked to report specific medical conditions including cancers
that had been diagnosed in the 2-year period before each
follow-up questionnaire. Whenever a participant (or next of kin
for decedents) reported a diagnosis of pancreatic cancer, we
asked for permission to obtain related medical records of pa-
thology reports. If permission to obtain records was denied, we
attempted to confirm the self-reported cancer with an additional
letter or telephone call to the participant. If the primary cause
of death listed on a death certificate was a case of pancreatic
cancer unreported previously, we contacted a family member
(subject to state regulations) to obtain permission to retrieve
medical records or at least to confirm the diagnosis of pancre-
atic cancer. We were able to obtain pathology reports confirm-
ing the diagnosis of pancreatic cancer on 85% of cases. For the
other 15% of cases, we obtained confirmation of the self-
reported cancer from a secondary source (e.g., death certificate,
physician, or telephone interview of a family member). All of
the medical records had complete information on histology
(hospitals were recontacted if the original information sent was
incomplete). In our analyses, associations were examined in-
cluding and excluding cases with missing records. Because no
material differences were observed between these two types of
analyses, we included cases without medical records. After the
exclusion of prior cancers and missing parity information, 243
confirmed incident pancreatic cancer cases were diagnosed

Statistical Analysis. We computed person-time of follow-up
for each participant from the return date of the baseline ques-
tionnaire to the date of pancreatic cancer diagnosis, death from
any cause, or the end of follow-up (June 30, 1998), whichever
came first. Incidence rates of pancreatic cancer were computed
by dividing the number of incident cases by the number of
person-years in each category of exposure. We computed the
RR for each of the upper exposure categories by dividing the
incidence rates in these categories by the rate in the lowest
category.

RRs adjusted for potential confounders were estimated using
Cox proportional hazards regression (14). SAS/STAT PROC PHREG software was used for proportional hazards
regression analysis (SAS Institute Inc., Cary, NC), and the
Anderson-Gill data structure was used to adjust for time-vary-
ing covariates efficiently (15), for which a new data record is
created for every questionnaire cycle at which a participant was
at risk with covariates set to their values at the time that the
questionnaire was returned. To control for confounding by age,
calendar time, and any possible two-way interactions between
these two time scales, we stratified the analysis jointly by age in
5-year categories at start of follow-up and calendar year of
the current questionnaire cycle. Statistical interaction was as-
sessed with likelihood ratio tests comparing models with and
without interaction terms. The variables height, BMI, age at
menarche, age at first birth, and breast feeding history were
analyzed with baseline values only. All of the other variables
were treated as time varying in the analysis and updated bien-
ially. For these analyses height was categorized into quintiles.
Cigarette smoking status was categorized as five groups; quar-
tiles of pack-years smoked among ever-smokers were com-
pared with the reference category never-smokers. We con-
trolled for the presence or absence of a history of diabetes in
multivariable models, updating biennially (16, 17). Categories
for breast feeding history were created based on previous anal-
yses in this cohort (18). The categories for parity were selected
for consistency and comparability with prior literature on parity
and cancer risk. The category of ≥5 births corresponds to the
widely used definition of “grand multiparity.” On the basis of
previous analyses in this cohort (19), participants were catego-
ized into five groups of baseline BMI in 1976 using whole
number cut points including widely used definitions of over-
weight and obesity (20, 21). Tests for linear trend were per-
fomed using continuous values for the independent variable.
All of the statistical procedures were performed using SAS
version 8. All of the Ps are based on two-sided tests. The
Human Research Committee at the Brigham and Women’s
Hospital approved the NHS.

Results
We examined baseline characteristics of women in our cohort
by categories of parity (Table 1). Both age and BMI increased
modestly with increasing parity. Women in higher categories of
parity were less likely to smoke at baseline and more likely to
be former smokers than nulliparous women. There were no apparent differences in height or age at menarche across categories of parity. However, with increasing parity, women who had a younger age at first birth, were more likely to have breast-fed and for a longer duration, and were less likely ever to have used oral contraceptives. Finally, with increasing parity we observed a lower prevalence of menopause at baseline, a lower prevalence of current postmenopausal hormone use, a shorter total duration of postmenopausal hormone use, and an older age at onset of menopause. We assessed the relationship between the risk of pancreatic cancer and various reproductive factors (Table 2). During 2,476,165 person-years of follow-up we identified 243 cases of pancreatic cancer. With increasing parity we observed a decrease in the RR of pancreatic cancer. After adjusting for potential confounders, women with ≥5 children had a RR for pancreatic cancer of 0.58 (95% CI, 0.34–0.98) compared with nulliparous women. In an analysis of linear trend, the RR for pancreatic cancer decreased ∼10% per birth (P_trend = 0.008). In analyzing other reproductive factors, we found no significant relationships between age at menarche, menopausal status, and age at menopause, and the risk of pancreatic cancer. In analyzing potential confounders of the parity relationship, women who had their first child after age 30 appeared to experience a small increased risk of pancreatic cancer (multivariate RR = 1.43; 95% CI, 0.87–2.35). However, the point estimate for this association is imprecise, and the test for linear trend with increasing age at first birth was not statistically significant (P_trend = 0.44). Furthermore, breast feeding for >23 months was weakly associated with a reduction in risk for pancreatic cancer, and similarly the test for trend was not significant (P_trend = 0.47). With the addition of parity to the multivariate model the weak associations observed for both age at first birth and breast feeding were additionally attenuated. In contrast, when including age at first birth and breast feeding in the multivariate model, we continued to observe a significant inverse relation between number of births and the risk of pancreatic cancer in parous women (multivariate RR per live birth = 0.88; P_trend = 0.02) indicating that neither breast feeding nor age at first birth confound this association.

We assessed the use of exogenous hormones in relation to pancreatic cancer risk (Table 3). We observed no overall relationship between the use of postmenopausal hormones or oral contraceptives and pancreatic cancer risk. After adjusting for potential confounders, current users of postmenopausal hormones had a RR of 1.21 (95% CI, 0.83–1.76), and former users had a RR of 1.19 (95% CI, 0.82–1.74) when compared with never-users of postmenopausal hormones. Furthermore, women who used oral contraceptives had a slightly elevated although similar risk of pancreatic cancer to women who never used oral contraceptives regardless of the duration of use. The multivariate adjusted RR for comparing women who had used oral contraceptives for >8 years to nonusers was 1.23 (95% CI, 0.74–2.04; P_trend = 0.54). Adjusting for oral contraceptive use did not materially change the RR for parity.

We assessed whether the relationship between parity and pancreatic cancer risk was homogeneous across strata of potential effect modifiers. In particular we evaluated the relationship by strata of cigarette smoking (ever/never), and BMI (<25/≥25), and physical activity in 1980 (vigorous exerciser/otherwise). Tests for interaction showed no evidence for effect modification by any of these factors (Ps for interaction with

Table 1  Baseline characteristics of women in the NHS by categories of parity

<table>
<thead>
<tr>
<th></th>
<th>Nulliparous</th>
<th>1–2 Births</th>
<th>3–4 Births</th>
<th>≥5 Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of individuals (%)</td>
<td>8,599 (7.3)</td>
<td>42,178 (35.7)</td>
<td>49,562 (42.0)</td>
<td>17,765 (15.0)</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>43.0 (7.6)</td>
<td>41.2 (7.7)</td>
<td>43.2 (6.8)</td>
<td>45.6 (5.7)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5</td>
<td>23.4</td>
<td>23.6</td>
<td>23.9</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.64</td>
<td>1.64</td>
<td>1.64</td>
<td>1.63</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>35.0</td>
<td>33.2</td>
<td>32.8</td>
<td>32.8</td>
</tr>
<tr>
<td>Former</td>
<td>21.2</td>
<td>23.2</td>
<td>23.7</td>
<td>23.6</td>
</tr>
<tr>
<td>Never</td>
<td>43.5</td>
<td>43.4</td>
<td>43.2</td>
<td>43.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>2.3</td>
<td>1.9</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>12.4</td>
<td>12.4</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Age at first birthb (years)</td>
<td>N/A</td>
<td>26.1</td>
<td>24.3</td>
<td>20.6</td>
</tr>
<tr>
<td>Breast feedingc (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>N/A</td>
<td>4.6</td>
<td>3.8</td>
<td>3.2</td>
</tr>
<tr>
<td>&lt;4 Months</td>
<td>N/A</td>
<td>10.7</td>
<td>9.9</td>
<td>8.8</td>
</tr>
<tr>
<td>4–6 Months</td>
<td>N/A</td>
<td>10.4</td>
<td>10.1</td>
<td>8.8</td>
</tr>
<tr>
<td>7–11 Months</td>
<td>N/A</td>
<td>7.5</td>
<td>8.6</td>
<td>7.4</td>
</tr>
<tr>
<td>12–23 Months</td>
<td>N/A</td>
<td>6.6</td>
<td>12.1</td>
<td>11.9</td>
</tr>
<tr>
<td>&gt;23 Months</td>
<td>N/A</td>
<td>1.7</td>
<td>6.2</td>
<td>13.9</td>
</tr>
<tr>
<td>Oral contraceptive (OC) Use (%) ever</td>
<td>36.6</td>
<td>47.1</td>
<td>46.7</td>
<td>45.4</td>
</tr>
<tr>
<td>Duration of OC use (months)</td>
<td>15.3</td>
<td>22.2</td>
<td>21.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Postmenopausal (%)</td>
<td>37.9</td>
<td>35.5</td>
<td>34.0</td>
<td>32.5</td>
</tr>
<tr>
<td>Postmenopausal hormone (PMH) Usec (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>39.0</td>
<td>44.1</td>
<td>48.3</td>
<td>52.1</td>
</tr>
<tr>
<td>Former</td>
<td>19.1</td>
<td>16.5</td>
<td>15.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Current</td>
<td>28.9</td>
<td>25.6</td>
<td>22.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Duration of PMH usec (months)</td>
<td>29.1</td>
<td>22.4</td>
<td>18.3</td>
<td>15.0</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td>45.9</td>
<td>47.2</td>
<td>47.6</td>
<td>48.0</td>
</tr>
</tbody>
</table>

a All of the values except age and number of participants are age-standardized. Baseline characteristics reported in 1976 except where otherwise noted. Columns may not add to 100% because of missing data.
b Reported to 1984 among parous women.
c Among postmenopausal women.
Prospective Study of Parity and Pancreatic Cancer

From 1976 to 1998, we observed a significantly lower risk of pancreatic cancer risk and higher parity (4–7). These studies were small and, with one exception (4), the results were not statistically significant. However, each reported a $\geq50\%$ reduction in pancreatic cancer risk among women with $\geq4$ or $5$ births. In contrast, two analyses of nationwide registries in Scandinavian populations did not observe inverse associations between parity and pancreatic cancer risk (8, 22). However, these registry-based analyses were unable to control for possible confounding by cigarette smoking in these populations. Furthermore, because these registry studies included cases of pancreatic cancer that were diagnosed $\geq40$ years in the past, the adequacy histological and/or radiological confirmation of these older pancreatic cancers may be limited. However, if the results of these studies are truly null, then some region-specific confounding of parity may explain the observed disparity in results.

The strengths of this study include a prospective design, a relatively large number of cases for this cancer, and detailed information on potential risk factors of pancreatic cancer. The prospective design of this study obviates recall bias and the need for proxy respondents in collecting exposure information.

**Table 2** RRs for pancreatic cancer by reproductive and menstrual factors in the NHS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases/person-years</th>
<th>Age-adjusted RR (CI)y</th>
<th>Multivariate A$^b$ RR (CI)y</th>
<th>Multivariate B$^{bc}$ RR (CI)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>24/174,303</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>N/A</td>
</tr>
<tr>
<td>1–2 Births</td>
<td>86/880,030</td>
<td>0.85 (0.54–1.33)</td>
<td>0.86 (0.55–1.36)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>3–4 Births</td>
<td>101/1,071,530</td>
<td>0.73 (0.47–1.14)</td>
<td>0.75 (0.48–1.17)</td>
<td>0.97 (0.70–1.35)</td>
</tr>
<tr>
<td>5+ Births</td>
<td>32/350,302</td>
<td>0.57 (0.34–0.97)</td>
<td>0.58 (0.34–0.98)</td>
<td>0.64 (0.38–1.05)</td>
</tr>
<tr>
<td><em>P</em>$_{trend}$</td>
<td>0.007</td>
<td></td>
<td>0.008</td>
<td>0.02</td>
</tr>
<tr>
<td>Age at first birth$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;23$ years</td>
<td>42/577,976</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>23–25 years</td>
<td>81/976,853</td>
<td>0.91 (0.63–1.33)</td>
<td>0.94 (0.64–1.36)</td>
<td>0.72 (0.47–1.09)</td>
</tr>
<tr>
<td>26–30 years</td>
<td>69/591,980</td>
<td>1.10 (0.75–1.63)</td>
<td>1.14 (0.77–1.68)</td>
<td>1.05 (0.69–1.60)</td>
</tr>
<tr>
<td>$&gt;30$ years</td>
<td>27/155,053</td>
<td>1.41 (0.86–2.30)</td>
<td>1.43 (0.87–2.35)</td>
<td>1.23 (0.71–2.14)</td>
</tr>
<tr>
<td><em>P</em>$_{trend}$</td>
<td>0.48</td>
<td></td>
<td>0.44</td>
<td>0.68</td>
</tr>
<tr>
<td>Breast feeding$^e$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>71/456,501</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>$&lt;1$ month</td>
<td>19/114,963</td>
<td>0.97 (0.58–1.63)</td>
<td>1.03 (0.61–1.73)</td>
<td>1.08 (0.64–1.84)</td>
</tr>
<tr>
<td>1–3 months</td>
<td>17/127,313</td>
<td>0.82 (0.48–1.41)</td>
<td>0.88 (0.51–1.53)</td>
<td>0.92 (0.53–1.59)</td>
</tr>
<tr>
<td>4–6 months</td>
<td>23/127,180</td>
<td>1.22 (0.75–1.97)</td>
<td>1.26 (0.78–2.05)</td>
<td>1.33 (0.82–2.15)</td>
</tr>
<tr>
<td>7–11 months</td>
<td>12/102,285</td>
<td>0.93 (0.51–1.69)</td>
<td>0.99 (0.54–1.80)</td>
<td>0.95 (0.51–1.78)</td>
</tr>
<tr>
<td>12–23 months</td>
<td>12/128,107</td>
<td>0.70 (0.38–1.31)</td>
<td>0.76 (0.41–1.41)</td>
<td>0.82 (0.44–1.53)</td>
</tr>
<tr>
<td>$&gt;23$ months</td>
<td>6/70,967</td>
<td>0.66 (0.28–1.52)</td>
<td>0.72 (0.31–1.67)</td>
<td>0.86 (0.36–2.02)</td>
</tr>
<tr>
<td><em>P</em>$_{trend}$</td>
<td>0.27</td>
<td></td>
<td>0.47</td>
<td>0.66</td>
</tr>
<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;12$ years</td>
<td>55/496,519</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>12 years</td>
<td>70/753,615</td>
<td>0.94 (0.67–1.35)</td>
<td>0.94 (0.66–1.34)</td>
<td>0.90 (0.55–1.56)</td>
</tr>
<tr>
<td>13 years</td>
<td>71/651,299</td>
<td>1.13 (0.79–1.60)</td>
<td>1.11 (0.78–1.58)</td>
<td>1.11 (0.78–1.58)</td>
</tr>
<tr>
<td>$&gt;13$ years</td>
<td>47/574,731</td>
<td>0.89 (0.60–1.31)</td>
<td>0.84 (0.56–1.25)</td>
<td>0.84 (0.56–1.25)</td>
</tr>
<tr>
<td><em>P</em>$_{trend}$</td>
<td>1.00</td>
<td></td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>14/774,517</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Post</td>
<td>22/91,761,651</td>
<td>1.62 (0.85–3.08)</td>
<td>1.51 (0.71–2.88)</td>
<td></td>
</tr>
<tr>
<td>Age at menopause$^e$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;44$ years</td>
<td>59/524,281</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>44–47 years</td>
<td>38/276,387</td>
<td>0.86 (0.57–1.29)</td>
<td>0.85 (0.56–1.28)</td>
<td></td>
</tr>
<tr>
<td>48–51 years</td>
<td>65/461,721</td>
<td>0.76 (0.53–1.08)</td>
<td>0.77 (0.54–1.10)</td>
<td></td>
</tr>
<tr>
<td>$&gt;51$ years</td>
<td>67/439,262</td>
<td>0.90 (0.63–1.28)</td>
<td>0.95 (0.67–1.35)</td>
<td></td>
</tr>
<tr>
<td><em>P</em>$_{trend}$</td>
<td>0.85</td>
<td></td>
<td>0.97</td>
<td></td>
</tr>
</tbody>
</table>

CI denotes 95% CI.

$^a$ Multivariate A$^b$ RRs adjusted for age (5-year categories), time period (calendar year), cigarette smoking (quartiles of pack-years), diabetes (yes/no), BMI (cut points: 23.0, 25.0, 27.0, 30.0), and height (quintiles). Multivariate B$^{bc}$ RR adjusted for “Multivariate A” factors and all other variables in column, and is limited to parous women with follow-up from 1986.

$^b$ Results for “breast feeding” among parous women with follow-up from 1986.

$^c$ Results for “age at first birth” among parous women.

$^d$ Results for “age at menarche” among parous women.

$^e$ Results for “age at menopause” among postmenopausal women.

Discussion

In this prospective cohort study of 115,474 women followed from 1976 to 1998, we observed a significantly lower risk of pancreatic cancer with increasing parity. Women who had $\geq5$ births had a 42% lower risk than nulliparous women, and the analysis of linear trend suggests that each birth confers an $\sim10\%$ reduction in the risk of pancreatic cancer among women in our cohort. This observation was independent of the effect of other known risk factors and reproductive variables, and was not modified by cigarette smoking, BMI, or physical activity.

Prior studies of the relationship between parity and pancreatic cancer have mainly reported risk ratios that were similar in direction and magnitude to our findings. Among studies with high rates of pathological confirmation of disease, four case-control studies have reported inverse associations between pancreatic cancer risk and higher parity (4–7). These studies were
Moreover, the prospective collection of data ensures that any errors in reporting will be nondifferential between cases and noncases, and, therefore, attenuate, rather than exaggerate, our estimates of the true RRs. Finally, because follow-up rates are high, differential follow-up is unlikely to have had an important influence on these results (23). Because this is a study of predominantly white women, the generalizability of our findings to nonwhite populations may be questioned. However, in previous studies, race and ethnicity have not substantially modified the influence of other known or suspected risk factors for pancreatic cancer.

The mechanism whereby parity may influence the risk of pancreatic cancer remains uncertain. Previous studies of reproductive factors have focused on the role of estrogen exposure in the etiology of cancer of the pancreas. In rats, estradiol decreases and testosterone increases the occurrence of experimentally induced pancreatic cancer (24). If decreased estrogen exposure is responsible for the inverse association we observe with parity, we would expect to observe similar associations between pancreatic cancer risk and other estrogen-related variables. However, our data do not support a strong role for other predictors of endogenous estrogen exposure. Consistent with other studies (4–6, 9, 10), two major sources of exogenous estrogen, oral contraceptives or postmenopausal hormones, were not strongly related to the risk of cancer of the pancreas. Therefore, among the multitude of physiological changes that occur during and after pregnancy and childbirth, some factor other than estrogen may underlie the influence of parity on pancreatic cancer.

An increasing body of literature has highlighted the role of the IGF axis in the development of cancer (25). IGFs promote cellular proliferation and inhibit apoptosis (26), and higher circulating levels of IGFs have been reported to increase the risk of breast (27), prostate (28, 29), lung (30, 31), and colorectal (32–35) cancers. The effect of IGFs is moderated through the availability of IGFBPs (25). Although pregnancy induces an array of changes in the IGF axis (36–41), the relationship between parity and circulating IGF concentration is not well established. However, a recent analysis of plasma levels of insulin-like growth hormones in this cohort has demonstrated that serum concentrations of IGF-I are significantly lower in women with ≥4 births when compared with nulliparous women (180 ng/ml versus 212 ng/ml; Ref. 42).

Table 3  RR for pancreatic cancer by hormone use among women in the NHS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases/person-years</th>
<th>Age-adjusted RR (CI)a</th>
<th>Multivariate A RR (CI)b</th>
<th>Multivariate B RR (CI)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal Hormone use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never user</td>
<td>62/575,953</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Current user</td>
<td>54/431,725</td>
<td>1.07 (0.80–1.71)</td>
<td>1.21 (0.83–1.76)</td>
<td>1.20 (0.83–1.75)</td>
</tr>
<tr>
<td>Former user</td>
<td>50/289,147</td>
<td>1.48 (1.03–2.11)</td>
<td>1.19 (0.82–1.74)</td>
<td>1.19 (0.82–1.75)</td>
</tr>
<tr>
<td>Missing data</td>
<td>63/404,835</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>159/1,329,267</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>83/1,135,134</td>
<td>1.17 (0.88–1.56)</td>
<td>1.18 (0.88–1.57)</td>
<td>1.21 (0.91–1.61)</td>
</tr>
<tr>
<td>Missing data</td>
<td>1/11,764</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>159/1,329,267</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>1–11 months</td>
<td>26/269,682</td>
<td>1.42 (0.93–2.18)</td>
<td>1.40 (0.92–2.15)</td>
<td>1.45 (0.94–2.21)</td>
</tr>
<tr>
<td>12–35 months</td>
<td>13/304,719</td>
<td>0.75 (0.42–1.34)</td>
<td>0.76 (0.42–1.35)</td>
<td>0.78 (0.44–1.39)</td>
</tr>
<tr>
<td>36–95 months</td>
<td>27/368,404</td>
<td>1.26 (0.82–1.93)</td>
<td>1.27 (0.83–1.94)</td>
<td>1.30 (0.85–1.99)</td>
</tr>
<tr>
<td>&gt;95 months</td>
<td>17/192,328</td>
<td>1.20 (0.72–1.99)</td>
<td>1.23 (0.74–2.04)</td>
<td>1.26 (0.76–2.10)</td>
</tr>
<tr>
<td>Missing data</td>
<td>1/11,764</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a CI denotes 95% CI.

b “Multivariate A” RRs adjusted for age (5-year categories), time period (calendar year), cigarette smoking (quartiles of pack-years), diabetes (yes/no), BMI (cut points: 23.0, 25.0, 27.0, 30.0), and height (quintiles). “Multivariate B” RR adjusted for “Multivariate A” factors and parity.

c Results for “postmenopausal hormone use” are restricted to postmenopausal women.

References


Prospective Study of Parity and Pancreatic Cancer

Parity, Reproductive Factors, and the Risk of Pancreatic Cancer in Women


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