Reproductive and Menstrual Risk Factors for Pancreatic Cancer: A Population-based Study of San Francisco Bay Area Women

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Study results regarding risks associated with reproductive characteristics and pancreatic cancer have been mixed. Using data from a population-based case-control study of pancreatic cancer, the authors assessed the role of menstrual factors, reproductive factors, and hormone use in the etiology of pancreatic cancer among women (241 cases, 818 controls). Rapid case ascertainment was used in six San Francisco Bay Area counties in California between 1995 and 1999. Controls were sampled by using random digit dialing. All statistical tests were two sided. Age at menopause (>45 years vs. <45 years) was associated with a 1.8-fold increased risk of pancreatic cancer (95% confidence interval: 1.2, 2.8). No association was found between age at menarche, parity, oral contraceptive use, estrogen replacement therapy (ERT), or history of oophorectomy and pancreatic cancer. The adjusted odds ratio for current smoking and pancreatic cancer was stronger for women who had never used oral contraceptives or ERT (odds ratio = 11.5, 95% confidence interval: 3.5, 38.1) than for those who reported using both (odds ratio = 1.7, 95% confidence interval: 0.56, 5.0). Other than a possible reduced risk estimate for smoking-related pancreatic cancer for users of exogenous hormones (oral contraceptives and ERT), results did not show a consistent pattern for reproductive factors, estrogen exposure, and risk of pancreatic cancer.

case-control studies; estrogens; hormones; menstruation; pancreatic neoplasms; reproduction; smoking; women

Abbreviations: BMI, body mass index; ERT, estrogen replacement therapy.

Carcinoma of the exocrine pancreas is the fourth leading cause of cancer deaths among women and among men in the United States (1). Cigarette smoking is one of the few known environmental risk factors. For many years, reproductive and menstrual factors have been suspected, but the results of epidemiologic studies to date have been mixed. Reports have linked age of less than 13 years at menarche to increased relative risk (hereafter called risk) estimates for pancreatic cancer (2–5), whereas later age at menopause has been associated with increased risk in one study (3) and decreased risk in others (2, 4–6). Multiple births have been reported as a risk factor in some studies (2, 6, 7) and a protective factor in others (3–5, 8). Likewise, reported associations between younger age at first birth and pancreatic cancer have been inconsistent, with some studies reporting reduced (2, 4, 5) and others reporting increased (6, 9, 10) risk.

Of the studies that have evaluated use of estrogen replacement therapy (ERT) and pancreatic cancer risk, two reported a reduced risk (2, 11), while two suggested a nonstatistically significant increased risk (5, 12). Regarding use of oral contraceptives, two studies reported risk estimates below the null (2, 4); two reported risks above the null (5, 6). Comparison of results across these studies has been hampered by several factors, including inconsistent referent groups, inadequate control for potential confounding factors, use of proxy data, and small sample size.

We investigated the role of menstrual, reproductive, and hormonal factors in the etiology of adenocarcinoma of the exocrine pancreas by using questionnaire data obtained by in-person interviews with San Francisco Bay Area women (241 cases and 818 controls) in a population-based case-control study of pancreatic cancer (532 cases and 1,701

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controls). Our analyses included multivariable adjustment for age, smoking, education, and potential reproductive risk factors. We also investigated modification of odds ratios by age, body mass index (BMI; weight in kilograms divided by height in meters squared), and oral contraceptive and/or ERT use.

MATERIALS AND METHODS

Study population

Patients with primary adenocarcinoma of the exocrine pancreas diagnosed between 1995 and 1999 were identified by using rapid case ascertainment in six San Francisco Bay Area counties in California (Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara) in an ongoing study of pancreatic cancer. Eligible participants resided in one of the six counties at the time of diagnosis, were 21–85 years of age, and were alive and able to complete an interview in English. A total of 532 eligible cases completed the interview, for a 67 percent response rate. Patient diagnoses were confirmed by participants' physicians and by Surveillance, Epidemiology, and End Results Program abstracts that included histologic confirmation of disease. Detailed methods have been published elsewhere (13–18).

Control selection also has been described in detail previously (13–18). Briefly, eligibility criteria were identical for cases and controls except for pancreatic cancer status. Controls were identified within the six San Francisco Bay Area counties by using random digit dialing and were frequency matched to cases by sex and age within 5-year categories. Random digit dialing for controls over the age of 65 years was supplemented by random selection from Health Care Financing Administration (now the Centers for Medicare & Medicaid Services) lists for the six Bay Area counties. A total of 1,701 eligible controls completed the study interview, for a 64 percent response rate. Out-of-area controls were identified by random digit dialing and were frequency matched to out-of-area cases by telephone area code and prefix of residence and by age and sex.

Detailed in-person interviews were conducted in the participants' homes or at a location of their choice in the Bay Area and by telephone for out-of-area participants. There were no proxy interviews. Written informed consent was obtained from each study participant before interview and collection of blood for genetic analyses. The University of California San Francisco institutional review board approved all study procedures. The analyses presented here are based on 241 women with pancreatic adenocarcinoma and 818 women who served as controls (13–19).

Questionnaire

Exposure and demographic information was obtained at interview by self-report using structured questionnaires. Menopausal status was also determined; 17 cases (7 percent) and 108 controls (15 percent) were classified as pre- or perimenopausal. One case and nine controls had experienced surgical menopause because of oophorectomy and were included in analyses of menopausal status and age at menopause. Sixty-six cases and 215 controls who had also had an oophorectomy reported a younger age at menopause than their age at oophorectomy and were considered to have undergone a natural menopause. Oral contraceptive use was assessed by asking, “Have you ever taken birth control pills for any reason?” ERT was assessed by asking, “Have you ever taken estrogen, such as Premarin [Wyeth Pharmaceuticals, Philadelphia, Pennsylvania], for any reason?” According to the above definitions, we defined postmenopausal ERT use as use of ERT by postmenopausal women.

Participants were defined as never smokers if they had never smoked more than 100 cigarettes in their lifetime and had not smoked cigars or pipes at least once per month for 6 months or more. Because a substantial number of women had never smoked and reported a history of passive smoke exposure at home as an adult (32 cases and 95 controls), these participants were removed from the referent group of never smokers. In analyses of smoking status, data on passive smokers were combined with those on former active smokers and pipe or cigar smokers. Smoking duration was defined as the total number of years of cigarette smoking. Smoking intensity (pack-years) was defined as the number of packs of cigarettes smoked per day multiplied by the number of years of smoking.

BMI was based on self-reported usual adult weight and height and on self-reported weight at age 25 years. Average alcohol consumption in grams per day was computed for each participant by summing the average daily number of drinks consumed during the 1 year prior to diagnosis and multiplying the result by the average alcohol content of each type of beverage (11 g of alcohol per 4-ounce (120-ml) glass of wine, 14 g of alcohol per standard serving of liquor, and 12.8 g of alcohol per 12-ounce (360-ml) beer) (19). Cutpoints for categorical variables were based on quartiles or quintiles of the continuous distribution among the controls.

Statistical methods

We used unconditional multiple logistic regression with the PROC LOGISTIC procedure in SAS software (version 8.2; SAS Institute, Inc., Cary, North Carolina) to compute odds ratios as estimates of relative risks (i.e., risk) and 95 percent confidence intervals for reproductive factors and pancreatic cancer risk. All statistical tests were two sided. Stratified models were used to explore potential interactions among variables. Variables hypothesized to modify odds ratios for reproductive factors or other pancreatic cancer risk factors (e.g., smoking) included age in years (<60 or ≥60), upper quartile of usual adult BMI (<25.75 kg/m²), median usual adult BMI (<23.4 kg/m²), median BMI at age 25 years (<21.0 kg/m²), and exogenous hormone use (ever/never use of ERT and/or oral contraceptives). Statistical significance of interaction was assessed by using a likelihood ratio test comparing a model with an interaction term with a model without an interaction term.

term. Because age was used to determine sampling probabilities, it remained in multivariate models. Covariates, including known pancreatic cancer risk factors and potential confounders, remained in multivariate models if they changed parameter estimates for reproductive factors by more than 10 percent.

Fully adjusted odds ratios included terms for age (continuous), education (high school or less, college, graduate study), and smoking status (never active or passive smoker as referent, passive or former active smoker, current active smoker). The results of models that included a term for pack-years of smoking were similar to those that included a term for smoking status, so only those results adjusted for smoking status are reported here. Variables that we evaluated as potential confounders but did not include in final models included race (Caucasian, African American, Asian American, other); adult BMI (kg/m²); alcohol consumption (g/day); saturated fat consumption (g/day); coffee consumption (cups/day); income level; and medical history, including pancreatitis, non-insulin-dependent diabetes, vitamin B₁₂ deficiency, gallbladder disease, stomach or duodenal ulcer, allergy, and family history of pancreatic cancer.

RESULTS

Distributions by BMI were similar for cases and controls ($\chi^2$ p = 0.92) but somewhat different by age ($\chi^2$ p = 0.053) and race/ethnicity ($\chi^2$ p = 0.15) (table 1). Cases were more likely than controls to have less education ($\chi^2$ p < 0.0001) and more likely to have been classified as current active smokers ($\chi^2$ p = 0.0002) and to have a history of diabetes ($\chi^2$ p = 0.020) (table 1).

Age at menarche and parity and age at first birth

Age at menarche of 13 years or less was associated with a somewhat decreased risk of pancreatic cancer, but this result was not statistically significant (table 2). There was little evidence for an association between pancreatic cancer risk and parity or age at first birth (table 2).

Age at menopause

Mean and median ages at menopause were higher for cases (mean = 47.6, median = 49.0) than for controls (mean = 46.6, median = 48.0; Wilcoxon rank-sum test p = 0.04). Smoking status was associated with age at menopause ($\chi^2$ p = 0.04), with younger age at menopause (<45 years) associated with current, former, or passive smoking. Older age at menopause was associated with being less likely to have ever used ERT ($\chi^2$ p = 0.02). Age at menopause was not related to oral contraceptive use or alcohol consumption ($\chi^2$ p > 0.5). Women who reached menopause at age 45 years or older had a nearly twofold increased risk of pancreatic cancer compared with women whose age at menopause was less than 45 years (table 2). Age at menopause (≥45 years vs. <45 years) was associated with a 1.8-fold increased risk of pancreatic cancer (95 percent confidence interval: 1.2, 2.8). Further statistical adjustment for parity and age at menarche (in addition to age, smoking status, and education) did not materially alter the odds ratios for age at menopause (data not shown). There were too few premenopausal and perimenopausal participants to analyze reproductive factors stratified by menopausal status.

Oophorectomy and hysterectomy

Odds ratios for having had a partial or full oophorectomy and for age at oophorectomy provided no consistent patterns of association with risk of pancreatic cancer (table 3). Having had a hysterectomy, relative to not having had one, was inversely associated with pancreatic cancer risk, but confidence limits overlapped unity. Odds ratios for age at hysterectomy provided no consistent pattern of association with risk of pancreatic cancer (table 3). Odds ratios for having had an oophorectomy did not differ substantially by oral contraceptive use (ever/never), ERT use (ever/never), or combined oral contraceptive and ERT use (data not shown).

TABLE 1. Characteristics of women study participants, pancreatic adenocarcinoma cases and controls, San Francisco Bay Area, California, 1995–1999

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>44 18.3</td>
<td>198 24.2</td>
<td></td>
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<tr>
<td>55–66</td>
<td>65 27.0</td>
<td>210 25.7</td>
<td></td>
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<tr>
<td>67–73</td>
<td>61 25.2</td>
<td>210 25.7</td>
<td></td>
</tr>
<tr>
<td>≥74</td>
<td>71 29.5</td>
<td>200 24.4</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>195 80.9</td>
<td>713 87.2</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>23  9.5</td>
<td>41  5.0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>20  8.3</td>
<td>45  5.5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3  1.2</td>
<td>19  2.3</td>
<td></td>
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<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High school or less</td>
<td>121 50.2</td>
<td>282 34.5</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>93 38.6</td>
<td>394 48.2</td>
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<tr>
<td>Graduate study</td>
<td>27 11.2</td>
<td>142 17.4</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
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<tr>
<td>&lt;21.46</td>
<td>69 28.6</td>
<td>208 25.6</td>
<td></td>
</tr>
<tr>
<td>21.46–23.40</td>
<td>51 21.2</td>
<td>206 25.4</td>
<td></td>
</tr>
<tr>
<td>23.41–25.74</td>
<td>60 24.9</td>
<td>199 24.5</td>
<td></td>
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<tr>
<td>≥25.75</td>
<td>61 25.3</td>
<td>198 24.4</td>
<td></td>
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<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never active or passive</td>
<td>46 19.1</td>
<td>225 27.5</td>
<td></td>
</tr>
<tr>
<td>Former, passive, pipes/cigars</td>
<td>150 62.2</td>
<td>506 61.9</td>
<td></td>
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<tr>
<td>Current active</td>
<td>45 18.7</td>
<td>87 10.6</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>210 87.1</td>
<td>753 92.0</td>
<td></td>
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<tr>
<td>Yes</td>
<td>31 12.9</td>
<td>65  8.0</td>
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</table>
Overall, we found no association between ever/never oral contraceptive use and pancreatic cancer risk (table 3). However, mean and median duration of oral contraceptive use in months was higher for cases (mean = 576.5, median = 560.0) than for controls (mean = 560.1, median = 548.0; Wilcoxon rank-sum test \( p = 0.03 \)), and this difference was reflected in the odds ratio for women who had used oral contraceptives for 8 or more years having a somewhat increased risk estimate (table 3). In addition to oral contraceptive use and duration of use, we estimated adjusted odds ratios for pancreatic cancer and age at first use of oral contraceptives and years since first and last use of oral contraceptives.

**Oral contraceptives**

Overall, we found no association between ever/never oral contraceptive use and pancreatic cancer risk (table 3). However, mean and median duration of oral contraceptive use in months was higher for cases (mean = 76.5, median = 60.0) than for controls (mean = 60.1, median = 48.0; Wilcoxon rank-sum test \( p = 0.03 \)), and this difference was reflected in the odds ratio for women who had used oral contraceptives for 8 or more years having a somewhat increased risk estimate (table 3). In addition to oral contraceptive use and duration of use, we estimated adjusted odds ratios for pancreatic cancer and age at first use of oral contraceptives and years since first and last use of oral contraceptives.
contraceptives. We found no evidence for associations in either direction (data not shown).

Postmenopausal ERT use

Adjusted odds ratios for ERT use were associated with a non-statistically significant decreased risk of pancreatic cancer (table 3). We examined duration of ERT use in years in relation to pancreatic cancer risk and found some evidence for decreased estimates with longer duration of ERT use (≥18 years), but this result was not statistically significant and there was no trend. We also examined age at first and last use of ERT and years since first and last use of ERT, and we found no evidence for an association with pancreatic cancer (data not shown).

We estimated odds ratios for women who reported using either oral contraceptives and/or ERT compared with women who reported using neither. The odds ratio for oral contraceptive ever use alone was 1.2 (95 percent confidence interval: 0.70, 2.0); the odds ratio for ERT ever use alone was 0.96 (95 percent confidence interval: 0.64, 1.4); and the odds ratio for ever use of both ERT and oral contraceptives was 0.82 (95 percent confidence interval: 0.51, 1.3). We also estimated adjusted odds ratios for interaction between duration of oral contraceptive use (never used oral contraceptives, ≤4 years, >4 years) and duration of ERT use (never used ERT, ≤7 years, >7 years) and found no evidence for interaction among any combinations of duration of oral contraceptive/ERT use (relative to never users of both oral contraceptives and ERT) in relation to pancreatic cancer risk (data not shown).

To further investigate potential modification of pancreatic cancer risk due to oral contraceptive and ERT use, we examined modification of odds ratios for pancreatic cancer and smoking (a known risk factor) by reported use of oral contraceptives and/or ERT (table 4). The adjusted odds ratio for current active smoking was of similar magnitude for women who reported use of both oral contraceptives and ERT (odds ratio = 1.7) and for women who reported use of ERT but not oral contraceptives (odds ratio = 1.7), but it was stronger for women who reported use of oral contraceptives but not ERT (odds ratio = 2.4). For women who had never used oral contraceptives and had never used ERT, the adjusted odds ratio for current smoking and pancreatic cancer (relative to never active or passive smokers) was increased 11.5-fold, and the adjusted odds ratio for former active or passive smoking was raised 2.5-fold (table 4). A likelihood ratio test comparing a model with and without an interaction term between smoking status (never/former vs. current) and oral contraceptive/ERT use (never use of either vs. use of one or both) was statistically significant (p = 0.02).

Alcohol

Consuming small or moderate amounts of alcohol daily (≥10 g) was not related to pancreatic cancer in this study population. In general, there was a lack of heavy drinkers. We observed no association between alcohol consumption and age at menopause (data not shown).

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<tr>
<td>Smoking status</td>
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<td>----------------</td>
</tr>
<tr>
<td>Cases (no.)</td>
</tr>
<tr>
<td>Never active or passive</td>
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<tr>
<td>Former active, passive</td>
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<tr>
<td>Current active</td>
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</table>

* Odds ratios were adjusted for age, education, and age at menopause. Participants were defined as never smokers if they had never smoked >100 cigarettes in their lifetime and had not smoked pipes or cigars at least once per month for >6 months. Data on never smokers with a history of passive smoke exposure at home as an adult or as a child were combined with those for former active smokers and pipe or cigar smokers.

† ERT, estrogen replacement therapy; OR, odds ratio; CI, confidence interval.
BMI

We found no consistent modifying effect of adult BMI ($\geq 23.4$ vs. $<23.4$ kg/m$^2$) or BMI at age 25 years ($\geq 21.0$ vs. $<21.0$ kg/m$^2$) on the odds ratios for age at menarche, age at menopause, parity, age at first birth, ERT use, duration of ERT use, oral contraceptive use, and duration of use of oral contraceptives (data not shown).

Age

There was no statistically significant modification of odds ratios for reproductive factors by age at diagnosis ($<$60 vs. $\geq$60 years) with pancreatic cancer (data not shown).

DISCUSSION

We studied reproductive and menstrual risk factors for pancreatic cancer in women from a population-based, case-control study conducted in the San Francisco Bay Area of California. Our results do not support the hypothesis that endogenous or exogenous estrogens reduce or promote development of pancreatic cancer in a largely postmenopausal group of women. We did not find evidence for main effects of oral contraceptive or ERT use in relation to pancreatic cancer risk, but relative risks for smoking and pancreatic cancer were substantially stronger for never users of oral contraceptives and ERT than for women who reported past use of oral contraceptives and/or ERT. This result suggests that oral contraceptive and ERT use might lower the risk of smoking-related pancreatic cancer in women, although this association will require replication in other study populations.

Our results on the association of later age at menopause with increased risk of pancreatic cancer are not consistent with the hypothesis that endogenous estrogens are protective for pancreatic cancer, because women experiencing a later age at menopause are assumed to have had a longer duration of circulating estrogens. In addition to age, education, and smoking, we also adjusted odds ratios for age at menopause for other reproductive factors (such as parity and age at menarche) and found no material differences in the odds ratio estimates. Our findings of increased risk with later age at menopause are in agreement with one previous report (3), whereas other reports for this association found no effect (2, 6, 8) or an inverse association (4, 5) with pancreatic cancer. Regarding oral contraceptives, two of the five previous reports that evaluated oral contraceptive use and pancreatic cancer risk found a nonstatistically significant reduced risk (2, 4), two reported increased risk (5, 6), and one reported no association (8). In terms of hormone replacement therapy, two of six previous reports that evaluated its use and pancreatic cancer reported a nonstatistically significant reduced risk (2, 11), two found increased risk (4, 5), and two reported mixed results or no association (8, 12). Reasons for these discrepant findings might include differences across studies by dose and formulation of oral contraceptives and hormone replacement therapy, population differences in reproductive patterns and other risk factors such as smoking, incomplete control for confounding, small sample size, and use of proxy data, but they most likely indicate no association.

Circulating estrogen levels increase dramatically during pregnancy (20). Thus, if endogenous estrogens are associated with a reduced risk of pancreatic cancer, we would expect pregnancy to offer some protection from pancreatic cancer. Overall, our data on number of births did not support this conclusion.

Our results regarding risk of pancreatic cancer after oophorectomy or hysterectomy showed no increase or decrease. If endogenous hormones were associated with reduced risk, we would have expected to have found an increased risk of pancreatic cancer subsequent to ovary removal. We observed no such associations in our data, and use of oral contraceptives or ERT did not substantially alter the odds ratios for oophorectomy or hysterectomy.

In general, the mechanistic effects of endogenous and exogenous sex hormones on the pancreas are unknown. Sex steroid receptors are found in the normal pancreas, and while testosterone has been shown to stimulate growth of human pancreatic tumor cell lines, estrogen has been shown to inhibit their growth (21). Two small case-control studies reported higher levels of total circulating estradiol in men and women with pancreatic cancer than in otherwise-healthy controls (22, 23). Definitive conclusions from this type of retrospective study design are not possible since the presence of cancer may have influenced circulating levels of steroid hormones.

The idea that exogenous estrogens might lower the risk of pancreatic cancer is supported by our observation of lower odds ratios of smoking and pancreatic cancer for oral contraceptive and ERT users compared with nonusers, although this association will require further evaluation in other study populations. This result suggests a possible hormonal mechanism for some smoking-related pancreatic cancer in women. One explanation is that exogenous estrogens may affect the metabolism of tobacco-related carcinogens via the cytochrome P-450 enzyme system and result in lower levels of tobacco-carcinogen intermediates and lower risk (24). Furthermore, the use of exogenous hormones may improve insulin profiles (25), and the effect of estrogens could possibly be mediated through insulin and insulin-like growth factors in ways that currently are poorly characterized. Hypotheses that estrogens may prevent colon tumor growth by inhibiting the action of insulin and insulin-like growth factors at the receptor level (26) may be relevant in pancreatic cancer. Two recent prospective cohort studies concluded that impaired glucose metabolism and insulin resistance may play a role in exocrine pancreatic carcinogenesis (27, 28).

As in all case-control study designs, our analyses and conclusions must be tempered by the quality of our data. Because our study used only in-person and no proxy data, we believe that our data generally are reliable and accurate. Moreover, our results agree with those from previous published epidemiologic studies that evaluated similar risk factors (smoking, alcohol consumption, medical history, BMI, etc.). We cannot rule out the possibility that women who used oral contraceptives or hormone replacement therapy were healthier overall than women who did not,
thus making these compounds appear protective. Recall bias is possible, but less likely than for other common cancers since few risk factors are known. It is possible that variables for oral contraceptive use and duration may be less reliable than variables for ERT use in this population of older women because, in general, many years have passed since these women used oral contraceptives. However, controls were age matched to cases, and differential bias between cases and controls is less likely. Our data may have suffered from the rapid fatality associated with pancreatic cancer. However, our rates of participant refusal were quite low at 8 percent in spite of the severity of the disease. Overall, our results do not show a consistent pattern for reproductive factors, estrogen exposure, and risk of development of pancreatic cancer.

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