Parity, Reproductive Factors, and the Risk of Pancreatic Cancer in Women[1]

Halcyon G. Skinner,[2] Dominique S. Michaud, Graham A. Colditz, Edward L. Giovannucci, Meir J. Stampfer, Walter C. Willett, and Charles S. Fuchs

Department of Epidemiology [H. G. S., G. A. C., E. L. G., M. J. S., W. C. W.] and Department of Nutrition, Harvard School of Public Health [G. A. C., E. L. G., M. J. S., W. C. W.], Boston, Massachusetts 02115; The Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115 [H. G. S., G. A. C., E. L. G., M. J. S., W. C. W., C. S. F.]; Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115 [C. S. F.]; and Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland 20892 [D. S. M.]

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 assessed 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[2] 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

Received 8/30/02; revised 1/27/03; accepted 2/4/03.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] The work reported in this manuscript was supported by grants CA87969, CA55075, CA86102 and CA9001 from the National Cancer Institute.
[2] To whom requests for reprints should be addressed, at The Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115. Phone: (617) 525-2086; E-mail: hskinner@hsph.harvard.edu.

[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.

biennially thereafter. Most deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, searches of the National Death Index for nonrespondents were conducted, resulting in a sensitivity of ~98% in identifying decedents (12). After exclusions for prior cancer (except nonmelanoma skin cancer) and missing information on parity, 115,474 women were eligible for analysis in 1976. Participants representing 98% of the total potential person-time in the cohort either completed the 1998 questionnaire or have been verified as deceased.

Reproductive Factors and Exogenous Hormone Use. We inquired about pregnancy and number of live births in 1976 and subsequently 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 contraceptives. 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. Smoking status and history of smoking were obtained at baseline, and in all of the subsequent questionnaires. Current smokers reported the average number of cigarettes smoked per day on each questionnaire. We categorized participant cigarette-smoking 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 multiplying 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 m^2. In validation substudies the correlation between self-reported weight and weight measured 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 pathology 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 pancreatic cancer. We were able to obtain pathology reports confirming 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 including 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 between 1976 and 1998.

Statistical Analysis. We computed person-time of follow-up for each participant from the return date of the baseline questionnaire 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-varying 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 assessed 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 biennially. For these analyses height was categorized into quintiles. Cigarette smoking status was categorized as five groups; quartiles of pack-years smoked among ever-smokers were compared with the reference category never-smokers. We controlled 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 analyses 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 categorized into five groups of baseline BMI in 1976 using whole number cut points including widely used definitions of overweight and obesity (20, 21). Tests for linear trend were performed using continuous values for the independent variable. All of the statistical procedures were performed using SAS version 8. All of the *P*s 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

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

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

[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.

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 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 (*P*s for interaction with

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

Factor	Cases/person-years	Age-adjusted RR (CI)[a]	Multivariate A[b] RR (CI)[c]	Multivariate B[b,c] RR (CI)[a]
Parity				
Nulliparous	24/174,303	1.00 (Reference)	1.00 (Reference)	N/A
1–2 Births	86/880,030	0.85 (0.54–1.33)	0.86 (0.55–1.36)	1.00 (Reference)
3–4 Births	101/1,071,530	0.73 (0.47–1.14)	0.75 (0.48–1.17)	0.97 (0.70–1.35)
5+ Births	32/350,302	0.57 (0.34–0.97)	0.58 (0.34–0.98)	0.64 (0.38–1.05)
P_{trend}=		0.007	0.008	0.02
Age at first birth[d]				
<23 years	42/577,976	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
23–25 years	81/976,853	0.91 (0.63–1.33)	0.94 (0.64–1.36)	0.72 (0.47–1.09)
26–30 years	69/591,980	1.10 (0.75–1.63)	1.14 (0.77–1.68)	1.05 (0.69–1.60)
>30 years	27/155,053	1.41 (0.86–2.30)	1.43 (0.87–2.35)	1.23 (0.71–2.14)
P_{trend} =		0.48	0.44	0.68
Breast feeding[c]				
Never	71/456,501	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<1 month	19/114,963	0.97 (0.58–1.63)	1.03 (0.61–1.73)	1.08 (0.64–1.84)
1–3 months	17/127,313	0.82 (0.48–1.41)	0.88 (0.51–1.53)	0.92 (0.53–1.59)
4–6 months	23/127,180	1.22 (0.75–1.97)	1.26 (0.78–2.05)	1.33 (0.82–2.15)
7–11 months	12/102,285	0.93 (0.51–1.69)	0.99 (0.54–1.80)	0.95 (0.51–1.78)
12–23 months	12/128,107	0.70 (0.38–1.31)	0.76 (0.41–1.41)	0.82 (0.44–1.53)
>23 months	6/70,967	0.66 (0.28–1.52)	0.72 (0.31–1.67)	0.86 (0.36–2.02)
P_{trend} =		0.27	0.47	0.66
Age at menarche				
<12 years	55/496,519	1.00 (Reference)	1.00 (Reference)	
12 years	70/753,615	0.94 (0.67–1.35)	0.94 (0.66–1.34)	
13 years	71/651,299	1.13 (0.79–1.60)	1.11 (0.78–1.58)	
>13 years	47/574,731	0.89 (0.60–1.31)	0.84 (0.56–1.25)	
P_{trend} =		1.00	0.82	
Menopause				
Pre	14/774,517	1.00 (Reference)	1.00 (Reference)	
Post	229/1,701,651	1.62 (0.85–3.08)	1.51 (0.71–2.88)	
Age at menopause[e]				
<44 years	59/524,281	1.00 (Reference)	1.00 (Reference)	
44–47 years	38/276,387	0.86 (0.57–1.29)	0.85 (0.56–1.28)	
48–51 years	65/461,721	0.76 (0.53–1.08)	0.77 (0.54–1.10)	
>51 years	67/439,262	0.90 (0.63–1.28)	0.95 (0.67–1.35)	
P_{trend} =		0.85	0.97	

[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 all other variables in column, and is limited to parous women with follow-up from 1986.
[c] Results for "breast feeding" among parous women with follow-up from 1986.
[d] Results for "age at first birth" among parous women.
[e] Results for "age at menopause" among postmenopausal women.

parity = 1.00 for smoking, 1.00 for BMI, and 0.97 for physical activity).

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 ≥5 births had a 42% lower risk than nulliparous women, and the analysis of linear trend suggests that each birth confers an ~10% 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 small and, with one exception (4), the results were not statistically significant. However, each reported a ≥50% reduction in pancreatic cancer risk among women with >4 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 >40 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 3 RRs for pancreatic cancer by hormone use among women in the NHS

Factor	Cases/person-years	Age-adjusted RR (CI)[a]	Multivariate A RR[b] (CI)[a]	Multivariate B RR[b] (CI)[a]
Postmenopausal Hormone use[c]				
Never user	62/575,953	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Current user	54/431,725	1.07 (0.80–1.71)	1.21 (0.83–1.76)	1.20 (0.83–1.75)
Former user	50/289,147	1.48 (1.03–2.11)	1.19 (0.82–1.74)	1.19 (0.82–1.75)
Missing data	63/404,835			
Oral contraceptive use				
Never	159/1,329,267	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Ever	83/1,135,134	1.17 (0.88–1.56)	1.18 (0.88–1.57)	1.21 (0.91–1.61)
Missing data	1/11,764			
Oral contraceptive use duration				
Zero	159/1,329,267	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1–11 months	26/269,682	1.42 (0.93–2.18)	1.40 (0.92–2.15)	1.45 (0.94–2.21)
12–35 months	13/304,719	0.75 (0.42–1.34)	0.76 (0.42–1.35)	0.78 (0.44–1.39)
36–95 months	27/368,404	1.26 (0.82–1.93)	1.27 (0.83–1.94)	1.30 (0.85–1.99)
>95 months	17/192,328	1.20 (0.72–1.99)	1.23 (0.74–2.04)	1.26 (0.76–2.10)
Missing data	1/11,764			
P_{trend} =		0.59	0.53	0.47

[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.

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 risk.

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 activity of high-affinity IGFBPs, which can either suppress or enhance the activity of IGF, and IGFBP proteases that affect 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).

Among the other physiological changes that underlie pregnancy is a marked reduction in total body iron stores. In two case-control studies, increased serum iron concentrations (43) and increased dietary iron consumption in women (44) have been reported to be associated with an increased risk for pancreatic cancer. Underlying this risk is a model of carcinogenesis induced by free iron causing oxidative stress and subsequent DNA damage (45). It is plausible, therefore, that pregnancy-related reductions in concentrations through pregnancy lead to a decrease in iron-related oxidative stress. Therefore, our observation that increased parity is associated with a decrease in the risk of pancreatic cancer may plausibly be related to a decrease in circulating IGF levels or decreases in total body iron stores after multiple childbirths. Nonetheless, we cannot exclude other physiological consequences of pregnancy as an explanation for our findings.

In conclusion, we observed a decreased risk of pancreatic cancer among women with greater numbers of births in this large prospective cohort. With each birth we observed a 10% lower risk of pancreatic cancer. Our results confirm those of others investigators who have reported a decrease in the risk of pancreatic cancer with increased parity and indicate a promising path for additional research on this fatal disease. Additional studies should examine the physiological or hormonal changes underlying pregnancy and/or childbirth that may explain this finding.

References

1. Greenlee, R. T., Hill-Harmon, M. B., Murray, T., and Thun, M. Cancer statistics, 2001. CA Cancer J. Clin., *51:* 15–36, 2001.

2. American Cancer Society. Cancer Facts and Figures. Atlanta, GA: American Cancer Society, 2002.

3. Fuchs, C., Colditz, G., Stampfer, M., Giovannucci, E., Hunter, D., Rimm, E., Willett, W., and Speizer, F. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch. Int. Med., *156:* 2255–2260, 1996.

4. Kreiger, N., Lacroix, J., and Sloan, M. Hormonal factors and pancreatic cancer in women. Ann. Epidemiol., *11:* 563–567, 2001.

5. Fernandez, E., La Vecchia, C., D'Avanzo, B., and Negri, E. Menstrual and reproductive factors and pancreatic cancer risk in women. Int. J. Cancer, *62:* 11–14, 1995.

6. Bueno de Mesquita, H. B., Maisonneuve, P., Moerman, C. J., and Walker, A. M. Anthropometric and reproductive variables and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. Int. J. Cancer, *52:* 24–29, 1992.

7. Hanley, A. J., Johnson, K. C., Villeneuve, P. J., and Mao, Y. Physical activity, anthropometric factors and risk of pancreatic cancer: results from the Canadian enhanced cancer surveillance system. Int. J. Cancer, *94:* 140–147, 2001.

8. Karlson, B. M., Wuu, J., Hsieh, C. C., Lambe, M., and Ekbom, A. Parity and the risk of pancreatic cancer: a nested case-control study. Int. J. Cancer, *77:* 224–227, 1998.

9. Persson, I., Yuen, J., Bergkvist, L., and Schairer, C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy–long-term follow-up of a Swedish cohort. Int. J. Cancer, *67:* 327–332, 1996.

10. Ji, B. T., Hatch, M. C., Chow, W. H., McLaughlin, J. K., Dai, Q., Howe, G. R., Gao, Y. T., and Fraumeni, J. F., Jr. Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. Int. J. Cancer, *66:* 432–437, 1996.

11. Adami, H. O., Persson, I., Hoover, R., Schairer, C., and Bergkvist, L. Risk of cancer in women receiving hormone replacement therapy. Int. J. Cancer, *44:* 833–839, 1989.

12. Rich-Edwards, J., Corsano, K., and Stampfer, M. Test of the National Death Index and Equifax Nationwide Death Search. Am. J. Epidemiol., *140:* 1016–1019, 1994.

13. Rimm, E. B., Stampfer, M. J., Colditz, G. A., Chute, C. G., Litin, L. B., and Willett, W. C. Validity of self-reported waist and hip circumferences in men and women. Epidemiology, *1:* 466–473, 1990.

14. Cox, D., and Oakes, D. Analysis of Survival Data. London: Chapman and Hall, 1984.

15. Therneau, T. Extending the Cox model. *In:* D. Y. Lin and T. R. Fleming (eds.), First Seattle Symposium in Biostatistics: Survival Analysis, pp. 51–84. Seattle, WA: Springer Verlag, 1997.

16. Everhart, J., and Wright, D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA, *273:* 1605–1609, 1995.

17. Silverman, D. T., Schiffman, M., Everhart, J., Goldstein, A., Lillemoe, K. D., Swanson, G. M., Schwartz, A. G., Brown, L. M., Greenberg, R. S., Schoenberg, J. B., Pottern, L. M., Hoover, R. N., and Fraumeni, J. F., Jr. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br. J. Cancer, *80:* 1830–1837, 1999.

18. Michels, K. B., Willett, W. C., Rosner, B. A., Manson, J. E., Hunter, D. J., Colditz, G. A., Hankinson, S. E., and Speizer, F. E. Prospective assessment of breastfeeding and breast cancer incidence among 89, 887 women. Lancet, *347:* 431–436, 1996.

19. Michaud, D. S., Giovannucci, E., Willett, W. C., Colditz, G. A., Stampfer, M. J., and Fuchs, C. S. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA, *286:* 921–929, 2001.

20. Baik, I., Ascherio, A., Rimm, E. B., Giovannucci, E., Spiegelman, D., Stampfer, M. J., and Willett, W. C. Adiposity and mortality in men. Am. J. Epidemiol., *152:* 264–271, 2000.

21. Manson, J. E., Stampfer, M. J., Hennekens, C. H., and Willett, W. C. Body weight and longevity. A reassessment. JAMA, *257:* 353–358, 1987.

22. Kvale, G., Heuch, I., and Nilssen, S. Parity in relation to mortality and cancer incidence: a prospective study of Norwegian women. Int. J. Epidemiol., *23:* 691–699, 1994.

23. Stampfer, M., Willett, W., Speizer, F., and *et al.* Test of the National Death Index. Am. J. Epidemiol., *119:* 837–839, 1984.

24. Sumi, C., Longnecker, D. S., Roebuck, B. D., and Brinck-Johnsen, T. Inhibitory effects of estrogen and castration on the early stage of pancreatic carcinogenesis in Fischer rats treated with azaserine. Cancer Res., *49:* 2332–2336, 1989.

25. Yu, H., and Rohan, T. Role of the insulin-like growth factor family in cancer development and progression. J. Natl. Cancer Inst., *92:* 1472–1489, 2000.

26. Jones, J., and Clemmons, D. Insulin-like growth factors and their binding proteins: biological actions. Endocrine Rev., *16:* 3–34, 1995.

27. Hankinson, S. E., Willett, W. C., Colditz, G. A., Hunter, D. J., Michaud, D. S., Deroo, B., Rosner, B., Speizer, F. E., and Pollak, M. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet, *351:* 1393–1396, 1998.

28. Chan, J. M., Stampfer, M. J., Giovannucci, E., Gann, P. H., Ma, J., Wilkinson, P., Hennekens, C. H., and Pollak, M. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science (Wash. DC), *279:* 563–566, 1998.

29. Chan, J. M., Stampfer, M. J., Giovannucci, E., Ma, J., and Pollak, M. Insulin-like growth factor I (IGF-I), IGF-binding protein-3 and prostate cancer risk: epidemiological studies. Growth Horm. IGF Res., *10 (*Suppl. A*):* S32–S33, 2000.

30. Wu, X., Yu, H., Amos, C. I., Hong, W. K., and Spitz, M. R. Joint effect of insulin-like growth factors and mutagen sensitivity in lung cancer risk. J. Natl. Cancer Inst., *92:* 737–743, 2000.

31. Yu, H., Spitz, M. R., Mistry, J., Gu, J., Hong, W. K., and Wu, X. Plasma levels of insulin-like growth factor-I and lung cancer risk: a case-control analysis. J. Natl. Cancer Inst., *91:* 151–156, 1999.

32. Giovannucci, E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. J. Nutr., *131:* 3109S–3120S, 2001.

33. Giovannucci, E., Pollak, M. N., Platz, E. A., Willett, W. C., Stampfer, M. J., Majeed, N., Colditz, G. A., Speizer, F. E., and Hankinson, S. E. A prospective study of plasma insulin-like growth factor-I and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol. Biomark. Prev., *9:* 345–349, 2000.

34. Ma, J., Giovannucci, E., Pollak, M., Chan, J. M., Gaziano, J. M., Willett, W., and Stampfer, M. J. Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. J. Natl. Cancer Inst., *93:* 1330–1336, 2001.

35. Ma, J., Pollak, M. N., Giovannucci, E., Chan, J. M., Tao, T., Hennekens, C. H., and Stampfer, M. J. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3. J. Natl. Cancer Inst., *91:* 620–625, 1999.

36. Lassarre, C., and Binoux, M. Insulin-like growth factor binding protein-3 is functionally altered in pregnancy plasma. Endocrinology, *134:* 1254–1262, 1994.

37. Bang, P., and Fielder, P. J. Human pregnancy serum contains at least two distinct proteolytic activities with the ability to degrade insulin-like growth factor binding protein-3. Endocrinology, *138:* 3912–3917, 1997.

38. Hills, F. A., English, J., and Chard, T. Circulating levels of IGF-I and IGF-binding protein-1 throughout pregnancy: relation to birthweight and maternal weight. J. Endocrinol., *148:* 303–309, 1996.

39. Kubler, B., Cowell, S., Zapf, J., and Braulke, T. Proteolysis of insulin-like growth factor binding proteins by a novel 50-kilodalton metalloproteinase in human pregnancy serum. Endocrinology, *139:* 1556–1563, 1998.

40. Langford, K. S., Nicolaides, K. H., Jones, J., Abbas, A., McGregor, A. M., and Miell, J. P. Serum insulin-like growth factor-binding protein-3 (IGFBP-3) levels and IGFBP-3 protease activity in normal, abnormal, and multiple human pregnancy. J. Clin. Endocrinol. Metab., *80:* 21–27, 1995.

41. Langford, K., Nicolaides, K., and Miell, J. P. Maternal and fetal insulin-like growth factors and their binding proteins in the second and third trimesters of human pregnancy. Hum. Reprod., *13:* 1389–1393, 1998.

42. Holmes, M. D., Pollak, M. N., and Hankinson, S. E. Lifestyle correlates of plasma insulin-like growth factor I and insulin- like growth factor binding protein 3 concentrations. Cancer Epidemiol. Biomark. Prev., *11:* 862–867, 2002.

43. Friedman, G., and Van Den Eeden. S. Risk factors for pancreatic cancer: an exploratory study. Int. J. Epidemiol., *22:* 30–37, 1993.

44. Silverman, D. T., Swanson, C. A., Gridley, G., Wacholder, S., Greenberg, R. S., Brown, L. M., Hayes, R. B., Swanson, G. M., Schoenberg, J. B., Pottern, L. M., Schwartz, A. G., Fraumeni, J. F., Jr., and Hoover. R. N. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. J. Natl. Cancer Inst., *90:* 1710–1719, 1998.

45. Toyokuni, S. Iron-induced carcinogenesis: the role of redox regulation. Free Radic. Biol. Med., *20:* 553–566, 1996.