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A case–control study of reproductive factors, female hormone use, and risk of pancreatic cancer

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Abstract

Findings from several previous studies that have assessed the relation of reproductive factors and female hormone use to the risk of pancreatic cancer are inconclusive. The authors examined the association between reproductive factors and the use of oral contraceptives and postmenopausal hormone therapy to the risk of pancreatic cancer among 284 patients with pancreatic cancer and 1,096 controls using data from the hospital-based Case–Control Surveillance Study. Older age at first pregnancy and long-duration oral contraceptive use were associated with an increased risk of pancreatic cancer: the odds ratio was 2.0 (95% CI: 1.1–3.3) for first birth at age 30 or older compared with before age 20 (p for trend = 0.042) and 2.0 (95% CI: 1.0–4.0) for ten or more years of use of oral contraceptive use relative to no-use (p for trend < 0.01). Risk of pancreatic cancer risk was not associated with postmenopausal female hormone use. The findings suggest that increased exposure to estrogen during the reproductive years may play a role in the development of pancreatic cancer in women. Further studies are needed to confirm the findings.

Keywords

Pancreatic neoplasm; Oral contraceptive; Reproductive factors; Case–control studies

Introduction

Pancreatic cancer is the fifth leading cause of cancer death in the United States. Approximately 38,000 new cases of pancreatic cancer were diagnosed, and about 34,000 people died of the disease in 2007. Older age, being male or African American, cigarette smoking, family history

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of pancreatic cancer, diabetes, and chronic pancreatitis have been identified as risk factors [1]. The lower risk of pancreatic cancer in women has prompted investigators to hypothesize that reproductive factors and hormone use may contribute to the gender difference [2].

The findings from epidemiologic studies of the relation of reproductive factors and female hormone use to the risk of pancreatic cancer have been inconsistent [3–20]. In several studies, pancreatic cancer risk was associated with high parity [3,4,18], early age at menarche [7,14, 16,17], late age at menopause [4,9,11] or first birth [12], and use of oral contraceptives [18]. However, in others high parity [5,8,12], late age at menopause [19], late age at first birth [13, 17,18], and use of oral contraceptive [12] have been associated with reduced risk. Most studies have reported menopausal female hormone therapy was not associated with pancreatic cancer risk [8–11,19].

We examined the relation of reproductive factors and female hormone use to the risk of pancreatic cancer using data from the hospital-based Case–Control Surveillance Study.

Materials and methods

Beginning in 1976, the Case–Control Surveillance Study was conducted in hospitals located in four centers, Boston, New York, Philadelphia, and Baltimore. Subjects were interviewed in hospital by trained nurse-interviewers who used a structured questionnaire to collect information on demographic factors, reproductive and medical history, family history of cancer, and lifetime history of medication use. To reduce the risk of potential selection bias from referrals to the hospital, only patients who lived in areas that were within 50 miles of the hospital were enrolled; to ensure that this criterion was met, the nurse-interviewers were supplied with lists of acceptable zip codes.

Histories of drug use were elicited by questions about 42 indications, which included queries about use of female hormones, specifically, oral contraceptives and menopausal hormone therapy. For each episode of use, the medication name and the duration, timing, and frequency of use were recorded. After discharge, the patient's diagnosis that led to hospital admission was abstracted from the hospital record; discharge summaries were obtained for all patients and pathology reports for patients with cancer.

The participation rate of patients approached for an interview was 90% before 1998 and 82% in the subsequent years. Patients included in the present analyses were interviewed during 1976–2006.

Cases

Eligible patients were 284 women aged 23–78 years who met the following criteria: (1) a diagnosis of pancreatic cancer confirmed by pathology report and with the initial cancer diagnosis less than 12 months before the current admission and (2) no other primary cancer or history of cancer with the exception of non-melanoma skin cancer.

Controls

Controls were selected from a pool of 10,593 women aged 23–78 years with no history of cancer with the exception of non-melanoma skin cancer who had been admitted to the hospital for non-malignant diseases that we considered unrelated to reproductive factors, hormone use, or risk of pancreatic cancer: infections, traumatic injury, calculus of kidney or ureter, gallbladder disease, musculoskeletal diseases, and diseases of the respiratory system. The potential controls were frequency matched to the cases in a ratio of up to 4:1 on 5-year age group, study center, year of interview (5-year categories), and race (white, black). The final control series comprised 1,096 women.

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Data analysis

We divided the factors of interest into the following categories: parity (nulliparous, 1–2, 3–4, ≥5 births); age at menarche (<12, 12, 13–14, ≥15); age at menopause (<45, 45–49, 50–54, ≥55); age at first birth (<20, 20–24, 25–29, ≥30); duration of oral contraceptive use (never used,<1, 1–4, 5–9, ≥10 years); and duration of menopausal hormone therapy (never used,<1, 1–4, ≥5 years). A woman was considered to be postmenopausal if she had a natural menopause (her periods had ceased at least a year previously) or bilateral oophorectomy. For the 205 women whose menstrual periods had stopped because they had undergone hysterectomy without bilateral oophorectomy, we used the median age at natural menopause among the controls (50 years) as the age at menopause of women aged 50 or older. Younger women were considered to be premenopausal.

We assessed the relation of each reproductive factor and the duration of hormone use to the risk of pancreatic cancer using multivariable logistic regression models adjusted for age, study center, race, interview year, years of education, body mass index 10 years prior to the current hospitalization, cigarette smoking (never, ex-smoker, and current smoker), alcohol consumption (never, ex-drinker, and current drinker), history of diabetes before the pancreatic cancer for patients and before current admission for controls (no/yes), and all other reproductive factors or hormone use. We tested for a dose–response relationship between pancreatic cancer risk and each reproductive factor and duration of hormone use by including the original value of that variable in a term in the multivariable logistic regression model. All analyses were performed using SAS 9.1 software (SAS Institute, Inc., Cary, North Carolina).

Results

Characteristics of patients and controls are presented in Table 1. Compared with the controls, patients were thinner, had less frequently completed college, and were more likely to be current smokers, and to report a history of diabetes. There was little difference in alcohol consumption.

The prevalence of oral contraceptive use standardized by age was similar across various diagnostic categories among the controls. Age at menarche and age at first birth were also similar across the groups. The prevalence of oral contraceptive use for 5 years or more was 7.9% among controls admitted for infections, 7.9% for traumatic injuries, 7.9% for calculus of the kidney or ureter, 7.8% for musculoskeletal diseases, and 8.2% for other genitor-urinary diseases. The mean age at menarche was 12.6 among controls admitted for infections, 12.8 for traumatic injuries, 12.6 for calculus of the kidney or ureter, 12.6 for musculoskeletal diseases, and 13.1 for other genitor-urinary diseases. The corresponding mean age at first birth was 23.5, 24.2, 22.9, 23.9, and 22.6, respectively.

The relation of reproductive factors and female hormone use to the risk of pancreatic cancer is listed in Table 2. The odds ratio (OR) for age at menarche at 15 years and older compared with age at menarche less than 12 was 0.6 (95% confidence interval (CI) 0.4–1.1) (p for trend = 0.105). The OR increased as age at first birth increased (p for trend = 0.042), to 2.0 (95% CI: 1.1–3.1) for age at first birth 30 and older relative to 20 or younger. There was a significant association between duration of oral contraceptive use and risk of pancreatic cancer. Compared with those who never used oral contraceptives, women who used oral contraceptives were at an increased risk of pancreatic cancer, with ORs of 1.0, 1.3, 1.8, and 2.0, respectively, for oral contraceptive use of less than 1, 1–4, 5–9, and 10 years or more (p for trend < 0.01). While postmenopausal women appeared to have a slightly increased risk of pancreatic cancer relative to premenopausal women (OR = 1.2, 95% CI: 0.8–1.7), there was no trend in the odds ratio across categories of age at menopause (p = 0.259). The OR for 5 or more years of menopausal hormone therapy relative to no-use was 0.7 (95% CI: 0.4–1.2); there was no trend in the odds ratio across increasing duration (p = 0.56).

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Discussion

In this hospital-based case control study, we found that late age at first birth and long-term oral contraceptive use were associated with an increased risk of pancreatic cancer. These findings are contrary to the proposed hypothesis that estrogen may reduce the risk of pancreatic cancer in women.

Various studies have shown that pancreatic cancer is more common in younger men than in younger women [21], with the sex difference decreasing with age. This observation suggests that female hormones may contribute to the lower risk of pancreatic cancer among women. However, the totality of epidemiologic evidence on this issue is not consistent [2,6–9,11,12, 14–19,22,23].

To date, five studies have reported that parous women were at a lower risk than nulliparous women [5,8,11,12,14], but others have shown the opposite effect [3,15,18] or no effect [7,9, 10,13,19,20]. Likewise, age at first birth has been reported to reduce [13,17,18], increase [10,12], and not affect [4,7–9] the risk of pancreatic cancer. While five studies showed no association between age at menarche and risk of pancreatic cancer [7,9–12], three found that early age at menarche increased the risk [14,16,17]. Three studies reported no association between age at menopause and risk of pancreatic cancer [8,14,17], three found that late age at menopause decreased the risk [7,12,19], and four studies suggested that late age at menopause increased the risk [4,9–11].

Three cohort studies reported that oral contraceptive use was not associated with an increased risk of pancreatic cancer [8,9,11], although one study [8] found that long-term users had an increased risk, 20% for 6–10 years of use and 30% for use of 11 years or more, compared with non-users. Results from three case–control studies were inconsistent: one reported no association between oral contraceptive use and pancreatic cancer risk [10], one suggested use of oral contraceptive 6 months or more had 60% decreased risk of pancreatic cancer compared with use of less than 6 months [12], and one found that ever use of oral contraceptive was associated with an increased risk of pancreatic cancer [18].

Biological mechanisms linking estrogen exposure to the risk of pancreatic cancer are not established. In a rodent study, estradiol decreased the risk of experimentally induced pancreatic cancer [24]. High levels of estrogen receptor proteins [25] and several sex-steroid biosynthetic enzymes (e.g., pancreatic homogenates and aromatase) have been detected in pancreatic cancer tissue [26], suggesting that estrogen may play a role in the development of pancreatic cancer. The results from two small case–control studies showed that serum estrogen levels were higher in pancreatic cancer cases compared with age-matched controls [27,28]. However, tamoxifen, a competitive inhibitor of estrogens on estrogen receptors, has no significant beneficial effect on survival from pancreatic cancer [29].

Several characteristics of this study were noteworthy. Important pancreatic cancer risk factors, such as race, smoking, and history of diabetes, were controlled simultaneously in multivariable analysis. The data on reproductive factors and female hormone use were collected in the context of questions about many details of reproductive, medical, and medication history, and the participants and interviewers were unaware of the hypotheses at issue. Thus, it is unlikely that biased reporting of reproductive factors or oral contraceptive use accounts for the present results. Furthermore, consistent with the findings of previous studies, being African American, cigarette smoking and diabetes were associated with increased risk of pancreatic cancer [1].

Selection of appropriate hospital controls in a Case–Control Study is a challenge, especially for the evaluation of lifestyle factors like oral contraceptive or menopausal hormone use. If hospitalized controls were less likely to use oral contraceptives or menopausal hormone therapy

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than the general population, an adverse effect of female hormone use, if any, on risk of pancreatic cancer would be exaggerated. The distribution of exposures of interest among subgroups of the controls was similar, suggesting the selection of the controls was appropriate.

In summary, our study found that late age of first birth and use of oral contraceptives were associated with an increased risk of pancreatic cancer. Given the conflicting results in the literature, further studies are needed to clarify the associations of reproductive factors and female hormones use with risk of pancreatic cancer.

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Table 1

Characteristics of women with pancreatic cancer and controls, the Case–Control Surveillance Study, 1976–2006

Characteristics	Patients (*n* = 284)	Controls (*n* = 1,096)
Age (years, mean, and range)	57.5 (23–78)	57.0 (22–78)
Race (%)		
White	84.5	84.2
Black	15.5	15.8
Area (%)		
Boston	7.0	7.3
New York	28.2	29.1
Philadelphia	55.6	54.1
Baltimore	9.2	9.5
Year at interview		
1976–1979	6.0	6.2
1980–1989	47.5	49.2
1990–1999	32.0	33.0
2000–2006	14.4	11.6
Years of education		
≤12	58.5	54.2
13–15	20.8	18.6
≥16	20.8	27.2
BMI 10 years prior to hospital admission (kg/m^2)		
<25	35.9	39.8
25–29.9	25.4	21.6
≥30	15.5	18.0
Missing	23.2	20.6
Smoking status (%)		
Never	33.6	42.8
Ex-smoker	24.2	27.6
Current smoker	42.2	29.6
Alcohol consumption (%)		
Never	33.3	36.3
Ex-drinker	8.6	7.9
Current drinker	58.1	55.8
History of diabetes (%)		
No	84.2	90.6
Yes	15.9	9.4

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Table 2

Reproductive factors and female hormone use in relation to risk of pancreatic cancer

Reproductive factors	Controls	Patients	OR (95% CI)[a]	Multivariable-adjusted OR[b] (95% CI)
Age at menarche (years)				
<12	249	75	1.0 (ref)	1.0 (ref)
12	272	70	0.8 (0.6–1.2)	0.9 (0.6–1.3)
13–14	425	108	0.8 (0.6–1.2)	0.8 (0.6–1.2)
≥15	132	27	0.7 (0.4–1.1)	0.6 (0.4–1.1)
p for trend				0.105
Age at first birth (years)				
Nulliparous	182	36	1.0 (0.6–1.6)	1.2 (0.7–2.1)
<20	194	41	1.0 (ref)	1.0 (ref)
20–24	392	102	1.3 (0.8–1.9)	1.5 (0.9–2.3)
25–29	215	70	1.6 (1.0–2.5)	2.1 (1.3–3.4)
≥30	113	35	1.5 (0.9–2.5)	2.0 (1.1–3.3)
p for trend				0.042
Number of years of oral contraceptive use (years)				
No-use	816	200	1.0 (ref)	1.0 (ref)
>0 to <1	81	20	1.1 (0.6–1.9)	1.0 (0.6–1.9)
1 to <5	113	30	1.2 (0.8–1.9)	1.3 (0.8–2.2)
5 to <10	46	17	1.7 (0.9–3.2)	1.8 (1.0–3.5)
10+	40	17	2.0 (1.1–3.8)	2.0 (1.0–4.0)
p for trend				<0.01
Age at menopause[c]				
<45	164	41	1.0 (ref)	1.0 (ref)
45–49	188	52	1.0 (0.6–1.6)	1.0 (0.6–1.7)
≥50	453	120	1.0 (0.7–1.5)	1.1 (0.7–1.8)
p for trend				0.259
Number of years of hormone use (years)				
No-use	880	235	1.0 (ref)	1.0 (ref)
>0 to <1	68	19	1.0 (0.6–1.8)	1.0 (0.6–1.8)
1 to <5	66	14	0.8 (0.4–1.4)	0.8 (0.4–1.5)
≥5	82	16	0.7 (0.4–1.2)	0.7 (0.4–1.2)
p for trend				0.599
Parity				
Nulliparous	182	36	1.0 (ref)	1.0 (ref)
1–2	418	120	1.5 (1.0–2.2)	1.5 (1.0–2.3)
3–4	327	87	1.4 (0.9–2.2)	1.4 (0.9–2.2)
≥4	143	37	1.3 (0.8–2.2)	1.5 (0.8–2.6)
p for trend				0.411

[a] Adjusted for age group (5-year age interval), study center, year of interview (5-year categories), and race (white, black)

[b] Adjusted for age, study center, race, interview year, years of education, body mass index, cigarette (never, ex-smoker, current smoker), alcohol consumption (never, ex-drinker, current drinker), history of diabetes (no/yes), and other reproductive factors or female hormone use

[c] Among postmenopausal women only

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