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Reproductive factors, exogenous hormone use, and risk of pancreatic cancer in postmenopausal women

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ABSTRACT

Introduction: The epidemiologic literature on menstrual and reproductive factors associated with pancreatic cancer has yielded weak and inconsistent evidence of an association. Furthermore, few cohort studies have examined the association of exogenous hormone use, including type and duration, with this disease. The aim of this study was to assess the association of these exposures with risk of pancreatic cancer in a large cohort of postmenopausal women.

Methods: We used data from the Women's Health Initiative on 1003 cases of pancreatic cancer diagnosed among 158,298 participants over 14.3 years of follow-up. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations of interest.

Results: Being parous vs. nulliparous was associated with reduced risk (HR = 0.84, 95% CI 0.70–1.00), and women who had 1–2 and 3–4 births were at decreased risk compared to nulliparous women, whereas women who had >5 births showed no decrease in risk. Compared to women who gave birth between the ages of 20–29, women who gave birth at age 30 or above were at increased risk (HR 1.23, 95% CI 1.00–1.53, p for trend 0.003). Other reproductive factors and exogenous hormone use were not associated with risk.

Conclusions: Together with the existing literature on this topic, our results suggest that reproductive and hormonal exposures are unlikely to play an important role in the etiology of pancreatic cancer.

1. Introduction

Although pancreatic cancer is the eleventh most common cancer in males and the ninth most common cancer in females in the United States, it is the fourth leading cause of cancer death in both sexes [1]. Cancer of the pancreas has the lowest 5-year survival rate (7%) among the 24 leading cancer sites [2]. A number of risk factors or protective factors for pancreatic cancer have been identified, including smoking, obesity, diabetes, chronic pancreatitis, infection with Helicobacter pylori, ABO blood type, allergies, and fruit or folate intake [3,4]. Because pancreatic cancer occurs more commonly in males compared to females [5] and because there is some evidence that steroid hormones, including estrogen, may inhibit pancreatic cancer development [6–8], a number of epidemiologic studies have examined the association of menstrual and reproductive factors, as well as exogenous hormone use, with risk of the disease [9–22].

The epidemiologic literature indicates that any association of reproductive factors or hormone use with pancreatic cancer is weak and inconsistent. A number of studies have reported one or two of the factors investigated to be associated with risk, but different factors have been associated with risk in different studies, and in most cases the associations and trends reported have been weak. In the main, there is little reproducible evidence indicating that menstrual and reproductive factors are associated with risk. Few studies have examined exogenous hormone use in relation to pancreatic cancer [10,18,20–22], particularly the type of hormone therapy (estrogen alone or estrogen plus progestin) and duration of use.

Given the paucity of cohort studies that had information about the type of hormone therapy and duration of use, and the inconsistent findings for menstrual and reproductive factors, we used data from the Women's Health Initiative cohort to examine the association of hormonal, menstrual, and reproductive factors with risk of pancreatic cancer.

2. Methods

The Women's Health Initiative (WHI) is a large, multi-center, multi-faceted study designed to advance understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a Clinical Trial component (CT,

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N = 68,132) and an Observational Study component (OS, N = 93,676) [23]. The clinical trial component included three randomized controlled interventions: hormone therapy, low fat diet modification, and calcium-vitamin D supplementation. Women between the ages of 50 and 79 and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. Details of the design and reliability of the baseline measures have been published [23,24].

2.1. Data collection and variable definition

At study entry, self-administered questionnaires were used to collect information on demographics, medical, reproductive and family history, and on dietary and lifestyle factors, including smoking history, alcohol consumption, and recreational physical activity. In the reproductive history questionnaire, women were asked about age at first menstrual period, whether periods were regular "for most of [their] life," age at last regular menstrual period, whether ever pregnant, number of pregnancies, number of pregnancies lasting at least 6 months, and number of births, stillbirths, and spontaneous miscarriages. Participants were also asked whether they had ever taken oral contraceptives (OC) and, if so, the age at which they started and the age of stopping, how many years and months they had used OCs, whether they had used OCs before a first full-term pregnancy, and, if so, for how many years and months. Information on lifetime use of menopausal hormones was obtained using structured questionnaires and charts displaying colored photographs of various hormone preparations. Detailed information was collected on the type of preparation, estrogen and progestin doses, schedule, and route of administration. Ages of starting and stopping the use of each preparation were recorded. Diabetes at enrollment was defined as an affirmative response to the question "did a doctor ever say that you have sugar diabetes or high blood sugar when you were not pregnant?" Incident diabetes was ascertained during follow-up based on reported prescribed diabetes treatment with pills or insulin injections on a follow-up questionnaire. A validation study indicated that reporting of diabetes had high reliability: 92% for prevalent diabetes and 82% for incident diabetes, and evidence of diabetes was found in only 5% of women who did not report it [25].

Age at menopause was defined as the youngest age at which the participant experienced any of the following: last menstrual bleeding (all participants were >12 months after the last menstrual period at baseline), removal of both ovaries, or initiation of menopausal hormone therapy. Age at first birth was defined as the age at first pregnancy lasting 6 months or longer.

Clinical outcomes (including new cancer diagnoses) were updated semi-annually in the CT and annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of pancreatic cancer were verified by trained physician adjudicators who examined records of hospitalizations, surgeries, pathology reports, and procedures [26]. As of September 20, 2015 a total of 1027 incident cases of pancreatic cancer (occurring as the first cancer) had been diagnosed among the 161,808 participants in the OS and CT after a median of 16.9 years of follow-up (mean, 14.3 years).

For the analyses reported here, we excluded women who were missing information on smoking status (N = 2105) or body mass index (N = 1427). After exclusions, 1003 cases and 157,295 non-cases were available for analysis. Four hundred and forty-five cases were from the CT and 558 from the OS. Among 1003 pancreatic cancers, 762 had an ICD morphology code. However, 140 cases were coded only as "neoplasm malignant," "tumor cells malignant," "carcinoma NOS,"or "carcinoma anaplastic NOS." Of the 622 cases with a specific morphology code, 584 (94.0%) were adenocarcinomas.

2.2. Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the associations of reproductive and hormonal exposures with the risk of pancreatic cancer, with days to event as the time scale. Cases contributed person-time to the study from their date of enrollment until their date of diagnosis. Non-cases contributed person-time from enrollment and were censored as of the end of follow-up, date of death, or date of withdrawal from the study, whichever occurred earliest. We computed both age-adjusted and multivariable-adjusted HRs and 95% CI. We examined the association of each variable of interest with risk by adjusting for a common set of covariates in the final multivariable model: age (continuous), smoking status (never smoked, former smoker, current smoker), pack-years of smoking (continuous); history of diabetes (yes, no); body mass index (weight (kg)/height $(m)^2$); education (less than high school graduate, high school graduate/some college, college graduate, post-college); ethnicity (white, black, other); and enrollment in the Observational Study or intervention vs. placebo or control arm of the four clinical trials (estrogen alone; estrogen + progestin; calcium + vitamin D; and low-fat diet). Because diabetes is a risk factor for pancreatic cancer, a diagnosis of diabetes (self-reported at enrollment or taking anti-diabetes medication at a subsequent clinic visit) was treated as a time-dependent covariate. For categorical variables, tests for trend were performed by assigning the median value to each category and modeling this variable as a continuous variable. In further analyses, we repeated the main analyses restricted to: (1) women with no history of a cancer diagnosis (other than non-melanoma skin cancer) prior to enrollment; (2) women who were not in the treatment arms of the hormone therapy clinical trials; and (3) cases of adenocarcinoma of the pancreas.

3. Results

Compared to non-cases, women subsequently diagnosed with pancreatic cancer were somewhat older at enrollment, and had more pack-years of smoking (Table 1). Age at first birth, breastfeeding (ever, never), hysterectomy, bilateral oophorectomy, oral contraceptive use (ever, never), hormone therapy use (ever, never), and ethnicity differed between cases and non-cases; however, most differences were modest. Age at menarche, age at menopause, and history of miscarriage and stillbirth did not differ between cases and non-cases.

In age-adjusted and multivariable adjusted analyses, being parous vs. nulliparous was associated with reduced risk (HR = 0.84, 95% CI 0.70–1.00), and women who had 1–2 and 3–4 births were at decreased risk compared to nulliparous women, whereas women who had 5+ births showed no decrease in risk (Table 2). Compared to women who gave birth between the ages of 20–29, women who gave birth at age 30 or older were at increased risk, and the trend of increasing risk with increasing age at first birth was significant (0.003). When the associations of parity and age at first birth were mutually adjusted among parous women, the inverse association with parity (for fewer than 5 births) and the positive association with age at first birth were still evident (HR for 1–2 births 0.68, 95% CI 0.52–0.89; HR for 3–4 births 0.68, 95% CI 0.52–0.87; HR for >5 births 0.83, 95% CI 0.63–1.10; p for linear trend 0.35; HR for age at first birth <20 years 0.74, 95% CI 0.60–0.92; HR for >30 years 1.27, 95% CI 1.01–1.58; p for trend 0.001). Other reproductive factors (age at menarche, age at menopause, total years of menstruation,