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ORIGINAL ARTICLE

Pancreatic Cancer Incidence in Relation to Female Reproductive Factors: Iowa Women's Health Study

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ABSTRACT

Objective Motivated by inconsistent literature, we evaluated the association between incident pancreatic cancer and reproductive characteristics.

Design The Iowa Women's Health Study is a large prospective population-based cohort followed from 1986 to 2003. Reproductive information was self-reported.

Participants The study population comprised 37,459 women aged 55-69 years at baseline. Over 18 years, 228 incident pancreatic cancers were identified.

Results In a multivariate-adjusted model there were no associations between incident pancreatic cancer and age at first birth, number of births, age at menarche, or use of hormones. There was a statistically significant inverse association between age at menopause and pancreatic cancer incidence. Compared to menopause less than 45 years, the hazard ratio of pancreatic cancer was 0.61 (95% CI, 0.40-0.94) for menopause at 45-49 years, 0.75 (95% CI, 0.51-1.09) for 50-54 years, and 0.35 (95% CI, 0.18-0.68) for menopause at 55 years or more (P trend=0.005). This association held after restricting the cohort to never smokers. The associations between pancreatic cancer and ages at natural and surgical menopause followed similar patterns. In a parallel fashion, risk of pancreatic cancer was decreased for women with intact ovaries compared to those who had oophorectomy: hazard ratio was 0.70 (95% CI, 0.50-0.99).

Conclusions Our results indicate that older age at menopause is associated with reduced pancreatic cancer risk, but further research is warranted.

INTRODUCTION

Fatality rates for pancreatic cancer are extremely high - about 5% of cases survive 5 years [1]. Understanding the etiology of pancreatic cancer is an important step towards cancer prevention. The most well established risk factor for pancreatic cancer is cigarette smoking, but smoking may account for only 25% of the cases [2]. Other factors, including diabetes mellitus, well-done meat intake, and obesity, may also play a role in the etiology of pancreatic cancer [3]. Reproductive factors may be associated with pancreatic cancer based on the following rationale: pancreatic cancer is more common in men than in women in both human and animal models [4]; steroid hormone receptors exist in normal human pancreas and some pancreas carcinomas; and anti-estrogenic agents such as tamoxifen inhibit the growth of pancreatic cancer in animal and human models [5]. Of note, however, clinical trials in pancreatic

cancer cases failed to find any therapeutic benefits of tamoxifen [6].

Epidemiological data on the role of reproductive factors and menstrual history in the development of pancreatic cancer are limited and inconsistent. Eight case-control studies [7, 8, 9, 10, 11, 12, 13, 14] and three cohort investigations [15, 16, 17] have reported contradictory results on the association of pancreatic cancer with parity, age at first live birth, age at menarche, and age at menopause. The largest cohort published to date [18] observed an inverse association between pancreatic cancer mortality and high parity, but no other associations.

Given the inconsistent findings, it remains unclear whether or not reproductive factors are associated with the risk of pancreatic cancer. The distinguishing feature of the Iowa Women's Health Study (IWHS) is that it is a large population-based prospective cohort of postmenopausal women, which was designed to examine risk factors associated with breast, endometrial and other cancers, so detailed information on reproductive history was collected at baseline. Our aim here was to examine the role of reproductive factors in pancreatic cancer etiology in IWHS.

METHODS

The Iowa Women's Health Study Cohort

In 1986 a mailed questionnaire was sent to 98,030 randomly selected women between 55 and 69 years of age who had valid Iowa driver's licenses in 1985. There were 41,836 women who responded (42%) and these women constituted the IWHS cohort. Five follow-up questionnaires were mailed to update vital status, residence, and exposure information, and the percent response to each was high: 91% in 1987, 90% in 1989, 83% in 1992, 79% in 1997, and 69% in 2004. The vital status of women who did not respond to the follow-up surveys was determined through the National Death Index of the National Center for Health Statistics and the State Health Registry of Iowa.

For our analyses, we excluded women who at baseline self-reported cancer other than skin cancer (n=3,830) and then women who were premenopausal (n=547). The remaining 37,459 women (90%) constituted the analytic cohort. Incident cases of pancreatic cancer were defined according to the International Classification of Diseases of Oncology, Third Edition (ICD-O), and were identified between 1986 and 2003 by linkage to the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology and End-Results program.

Only cancer cases coded as ICD-O 25 and having exocrine pancreatic cancer were considered as cases; those with non-exocrine pancreatic tumors (n=4) were treated as non-cases. After exclusion, 228 women developed exocrine pancreatic cancer during 18 years of follow-up.

Data Collection

The baseline questionnaire asked about body size, lifestyle and sociodemographic factors, diet, medical and reproductive history as previously described [19, 20]. BMI (kg/m^2) was calculated from self-reported height and weight. A paper tape measure and written instructions were enclosed with directions to have a friend measure circumferences of the waist (1 inch above the umbilicus) and hips (maximal protrusion) [21]. Waist/hip circumference ratio (WHR) was calculated. Women were asked the age of first menstruation, details on each pregnancy (up to 10), the age at which their periods stopped completely and the reason for it: natural, surgical, or medical. Participants were also queried whether or not they had had their uterus and/or one or both ovaries surgically removed. In addition, they were asked about use of birth control pills and hormone replacement therapy (never, past, and current).

Women with natural cessation of menstruation were defined as undergoing natural menopause. Those who reported surgical cessation of menstruation and bilateral oophorectomy were defined as

having surgical menopause. For women who reported surgical cessation of menstruation due to hysterectomy but no total oophorectomy, the age when ovaries stopped functioning was undetermined; these women were excluded from analysis of age of menopause and length of ovulation. Length of ovulation was defined as the difference between age at menopause and age at menarche minus duration of pregnancy.

ETHICS

The IWHS was conducted under a protocol approved for human subjects research by the University of Minnesota Institutional Review Board. The return of baseline and follow-up questionnaires was considered a consent form.

STATISTICS

Baseline characteristics were reported as means and standard errors (SEs) or proportions and compared between cases and non-cases using the general linear model or Pearson chi-square, respectively. Age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were computed by Cox proportional hazards regression using SAS statistical software, version 8 [22]. We tested the assumptions of proportional hazards regression and found they were not violated.

Person-years were calculated from baseline until one of the following: date of pancreatic cancer diagnosis, date of death (if death occurred in Iowa), date of emigration from Iowa (if known), the midpoint of the interval between the last follow-up contact and December 31st, 2003 (if date of emigration was unknown), or the midpoint of the interval between the date of last contact and the date of death (for deaths of women who moved out of Iowa). All other women were assumed to be living in Iowa, and they contributed follow-up time until December 31st, 2003.

Data on reproductive and menstrual history were stratified into three, four or five logical categories; length of ovulation was categorized into tertiles. In addition, age at menopause was analyzed as a continuous variable. In supplemental analyses, current use of hormone replacement therapy (yes/no) at follow-ups was modeled as a time-dependent variable.

To control for potential confounders, we used variables considered as risk factors in previous studies of reproductive factors and pancreatic cancer and earlier studies of this cancer in the IWHS cohort. These variables included age at baseline (continuous), smoking status (never, former, current), number of pack-years (calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person smoked; continuous), BMI (continuous), WHR (continuous), education (less than high school, high school, more than high school), self-reported history of diabetes mellitus (yes, no), use of multivitamins (yes, no), use of oral contraceptives (yes, no), and use of hormone replacement therapy (yes, no). Since BMI, WHR, and education did not materially change hazard ratios, they were not included into the final model. This is in agreement with an earlier IWHS study, which did not find any association between pancreatic cancer and any weight characteristics [23]. However, because some other studies showed associations between obesity and pancreatic cancer [24, 25] and between obesity and age at menopause [26], we conducted a subgroup analysis including only normal-weight women (BMI less than 25 kg/m^2). To minimize possible residual confounding by smoking, we repeated analyses after restricting the cohort to never smokers.

To address a concern that excluding premenopausal women could have biased our results, we reanalyzed data for age at menopause by including premenopausal women into the category of age at menopause greater than, or equal to, 55 years (among 547 premenopausal women, 546 women were above 55). Since age at menopause was self-reported during 1986 for all women in the study, we were concerned that there could be some recall bias in reporting age at

Table 1. Baseline characteristics of women who developed incident pancreatic cancer and who did not (Iowa Women's Health Study, IWHS 1986-2003). Mean values±SE or relative frequencies are reported.

Characteristics	Pancreatic cancer cases (n=228)	Non-cases (n=37,231)	P value
Age (years)	62.4±0.29	61.7±0.02	0.006 [a]
BMI (kg/m^2)	27.0±0.35	27.0±0.03	0.983 [a]
WHR	0.844±0.006	0.838±0.0004	0.372 [a]
Hormone replacement therapy use	40%	38%	0.563 [b]
Oral contraceptive use	15%	19%	0.179 [b]
Diabetes mellitus	12%	6%	<0.001 [b]
Current or former smoker	38%	34%	0.363 [b]
Pack-years of smoking	11.5±1.20	9.3±0.09	0.072 [a]
Multivitamin users	26%	33%	0.016 [b]
Education			0.565 [b]
- Less than high school	18%	20%	
- High school	56%	52%	
- More than high school	26%	29%	
Age at menarche (years)	12.9±0.10	12.9±0.01	0.432 [a]
Age at menopause[c] (years)	47.1±0.42	48.7±0.03	<0.001 [a]
Age at first live birth (years)	23.1±0.30	22.8±0.02	0.228 [a]
Number of live births	3.0±0.13	3.1±0.01	0.831 [a]
Hysterectomy status	40%	33%	0.033 [b]

[a] General linear model
[b] Pearson chi-square
[c] Women with surgical cessation of menstruation due to hysterectomy but without total oophorectomy were excluded from analysis of age at menopause.

menopause. To test for systematic error, we conducted a sensitivity analysis. We assumed that error in the recall of age at menopause could increase with recall time and reach maximum of ±3 years.

RESULTS

The mean baseline age of the 37,459 women at risk was 62 years; 228 women (0.6%) developed incident pancreatic cancer with a mean age at diagnosis of 73 years (range: 59-87 years). Distinctive features of our cohort are that 99% of the women were white, 60% of them were overweight or obese, only 9% reported no live births, while 59% reported three or more live births.

Baseline characteristics of women who developed incident pancreatic cancer and those who did not are shown in Table 1. Women developing pancreatic cancer were older (P=0.006), more likely to have a history of diabetes (P<0.001) and less likely to be taking daily multivitamins (P=0.016) than non-cases. The percentage of ever smokers and mean pack-years of smoking were higher for cases. In comparison to non-cases, the proportion of hormone replacement therapy users was slightly higher and oral contraceptive users was lower for cases, but these differences were not statistically significant. There were no important differences between cases and non-cases in BMI, WHR, age at menarche, number of live births, age at first live birth, or education. Women who developed pancreatic cancer were more likely to have reported hysterectomy (P=0.033) and were characterized by a significantly lower mean age at menopause (P<0.001).

Table 2. Prevalence of baseline characteristics and age of pancreatic cancer diagnosis according to reported age at menopause (Iowa Women's Health Study, IWHS 1986-2003). Mean values±SE or relative frequencies are reported.

Characteristics	Age at menopause[a] (years)				
	Less than 45 (n=5,253)	45-49 (n=8,214)	50-54 (n=13,372)	55 or more (n=3,728)	P value
Age at baseline (years)	62±0.06	62±0.05	62±0.04	63±0.06	<0.001 [b]
Age at diagnosis of pancreatic cancer (years)	73±0.02	72±0.02	74±0.01	75±0.02	<0.001 [b]
Body mass index (BMI)					<0.001 [c]
- Less than, or equal to, 24.9 kg/m^2	40%	42%	41%	35%	
- 25-29.9 kg/m^2	36%	36%	37%	38%	
- More than, or equal to, 30 kg/m^2	24%	22%	22%	27%	
Diabetes	7%	6%	6%	7%	<0.001 [c]
Education					<0.001 [c]
- Less than high school	23%	19%	17%	18%	
- High school	53%	53%	52%	50%	
- More than high school	24%	28%	31%	33%	
Smoking					<0.001 [c]
- Never	58%	63%	68%	73%	
- Former	21%	20%	19%	18%	
- Current	22%	18%	13%	9%	
Smoking (more than, or equal to, 40 pack-years)	13%	10%	8%	6%	<0.001 [c]
Alcohol intake (ever)	42%	44%	45%	43%	0.004 [c]
Regular physical activity	39%	41%	42%	45%	<0.001 [c]
Physical activity					<0.001 [c]
- Low	50%	48%	46%	44%	
- Moderate	27%	27%	28%	28%	
- High	24%	24%	25%	28%	
Use of multivitamins	33%	32%	33%	36%	0.003 [c]
Age at menarche (years)	13±0.02	13±0.02	13±0.01	13±0.02	0.249 [b]
Age at first live birth (years)	22±0.06	23±0.05	23±0.04	23±0.07	<0.001 [b]
Three or more live births	50%	57%	61%	63%	<0.001 [c]
Hysterectomy	49%	24%	13%	8%	<0.001 [c]
Oral contraceptive use	14%	19%	21%	19%	<0.001 [c]
Hormone replacement therapy use	50%	38%	31%	30%	<0.001 [c]
Length of ovulation (tertiles)					<0.001 [c]
- Less than, or equal to, 32.0 years	99%	52%	5%	0%	
- 32.1-36.4 years	1%	46%	46%	5%	
- More than, or equal to, 36.5 years	0%	2%	49%	95%	

[a] Women with surgical cessation of menstruation due to hysterectomy but without total oophorectomy were excluded from analysis
[b] General linear model
[c] Pearson chi-square

We also analyzed baseline characteristics and age at diagnosis of pancreatic cancer according to age at menopause (Table 2). Mean age at baseline and mean age of diagnosis were slightly higher for women with age at menopause above 55 years. Women with older age of menopause were more likely to be overweight and/or obese and have 3 or more live births. The percent of current smokers and of those who smoked more than 40 pack-years decreased with increasing age at menopause across

Table 3. Age-adjusted hazard ratios for incident pancreatic cancer in relation to reproductive and menstrual history factors at baseline (Iowa Women's Health Study, IWHS 1986-2003).

Baseline variable	Number of cases	Person-years	Age-adjusted hazard ratio (95% CI)
Age at menarche			
- Less than, or equal to, 11 years	32	89,690	1 (reference)
- 12 years	52	157,608	0.90 (0.58-1.39)
- 13 years	71	173,763	1.11 (0.73-1.68)
- More than, or equal to, 14 years	70	162,198	1.16 (0.76-1.76)
P trend			0.325
Number of live births			
- 0	19	51,836	1 (reference)
- 1-2	77	187,407	1.14 (0.69-1.88)
- 3-4	89	233,544	1.10 (0.67-1.81)
- More than 4	42	113,567	1.09 (0.63-1.87)
P trend			0.800
Age at first live birth			
- Less than 20 years	60	170,673	1 (reference)
- 20-25 years	94	248,115	1.03 (0.75-1.43)
- 26-30 years	38	79,075	1.23 (0.82-1.86)
- More than 30 years	10	25,077	1.00 (0.51-1.96)
- Nulliparous	19	51,836	0.96 (0.57-1.06)
P trend			0.841
Oral contraceptive use			
- Never	193	477,876	1 (reference)
- Ever	35	111,309	0.90 (0.62-1.30)
P value			0.566
Hormone replacement therapy			
- Never	135	362,265	1 (reference)
- Ever	91	225,758	1.07 (0.82-1.40)
P value			0.606

CI: confidence interval

categories. Furthermore, compared to other menopausal categories, a greater proportion of women with menopause at 55 years or more had education beyond high school and was involved in regular and high-level physical activity. Age of menarche was distributed similarly across categories. Women with earlier menopause (less than 45) had lower mean age at first live birth, were less likely to have a history of oral contraceptive use and more likely to have undergone hysterectomy and use hormone replacement therapy.

Age at menarche, age at first live birth, number of live births, use of hormone replacement therapy and history of oral contraceptive use showed no association with incident pancreatic cancer after adjustment for baseline age or for other potential risk factors (Table 3). When hormone replacement therapy was treated as a time-dependent covariate, there were no associations between pancreatic cancer risk and current use of hormone replacement therapy *versus* nonuse at any time during follow up.

Older age at menopause was inversely associated with a risk of pancreatic cancer (Table 4). Compared to age of menopause under 45 years, the age-adjusted hazard ratio (HR) of pancreatic cancer for menopause at 45-49 years was 0.66, for 50-54 years it was 0.74, and for menopause above 55, it was 0.32 (P trend=0.002). The age-adjusted HR was 0.65 for ages of 45 or more *versus* less than 45 years (95% CI, 0.46-0.92). After adjustment for smoking, age at menopause remained inversely associated with the risk of pancreatic cancer (HR=0.65, 95% CI: 0.46-0.92 for ages of 45 or more *versus* less than 45 years). After further adjustment for age,

Table 4. Multivariate-adjusted hazard ratios for incident pancreatic cancer in relation to age at menopause (natural or surgical), oophorectomy status, hysterectomy, and length of ovulation (Iowa Women's Health Study, IWHS 1986-2003).

Baseline variable	Number of cases	Person-years	Hazard ratio (95% CI)		
			Age-adjusted	Adjusted for age and smoking[a]	Multivariate adjusted[b]
Age at menopause[c]					
- Less than 45 years	43	80,638	1 (reference)	1 (reference)	1 (reference)
- 45-49 years	45	128,901	0.66 (0.44-1.00)	0.63 (0.41-0.96)	0.61 (0.40-0.94)
- 50-54 years	84	213,263	0.74 (0.52-1.07)	0.75 (0.52-1.09)	0.75 (0.51-1.09)
- 55 years or more	11	59,132	0.32 (0.17-0.63)	0.34 (0.18-0.67)	0.35 (0.18-0.68)
P trend			0.002	0.003	0.005
Age at menopause[c]					
- Less than 45 years	43	80,638	1 (reference)	1 (reference)	1 (reference)
- 45 years or more	140	401,296	0.65 (0.46-0.92)	0.65 (0.46-0.92)	0.64 (0.45-0.91)
P value			0.014	0.015	0.014
Age at menopause[c] (continuous[d])	183	481,935	0.80 (0.71-0.89)	0.81 (0.76-0.85)	0.81 (0.72-0.91)
P value			<0.001	<0.001	<0.001
Age at natural menopause[e]					
- Less than 45 years	16	35,096	1 (reference)	1 (reference)	1 (reference)
- 45-49 years	31	98,116	0.73 (0.40-1.33)	0.69 (0.37-1.27)	0.65 (0.35-1.21)
- 50-54 years	77	189,499	0.95 (0.56-1.64)	0.98 (0.57-1.69)	0.97 (0.57-1.68)
- 55 years or more	11	53,987	0.41 (0.20-0.93)	0.46 (0.21-0.98)	0.48 (0.22-1.03)
P trend			0.058	0.094	0.129
Age at surgical menopause[f]					
- Less than 45 years	23	41,495	1 (reference)	1 (reference)	1 (reference)
- 45-49 years	12	27,054	0.79 (0.39-1.59)	0.76 (0.37-1.56)	0.74 (0.36-1.55)
- 50 years or more	6	21,603	0.49 (0.20-1.20)	0.42 (0.16-1.11)	0.40 (0.15-1.08)
P trend			0.119	0.079	0.070
Oophorectomy					
- Bilateral	50	104,019	1 (reference)	1 (reference)	1 (reference)
- Unilateral or partial	24	49,134	0.99 (0.61-1.61)	1.02 (0.62-1.66)	1.02 (0.62-1.68)
P value			0.964	0.954	0.929
- No surgery	151	427,026	0.72 (0.53-1.00)	0.73 (0.53-1.01)	0.70 (0.50-0.99)
P value			0.047	0.057	0.049
Hysterectomy					
-Yes	90	193,814	1 (reference)	1 (reference)	1 (reference)
- No	136	390,332	0.74 (0.57-0.97)	0.75 (0.57-0.99)	0.73 (0.55-0.98)
P value			0.029	0.039	0.038
Length of ovulation[c](tertiles)					
- Less than, or equal to, 32.0 years	74	156,480	1 (reference)	1 (reference)	1 (reference)
- 32.1-36.4 years	58	157,864	0.78 (0.55-1.10)	0.81 (0.57-1.15)	0.83 (0.58-1.18)
- More than, or equal to, 36.5 years	49	160,283	0.63 (0.44-0.90)	0.68 (0.47-0.97)	0.69 (0.48-1.00)
P trend			0.012	0.035	0.049

CI: confidence interval

[a] Adjusted for smoking status and pack-years

[b] Adjusted for age, smoking status, pack-years, diabetes, multivitamin, estrogen and oral contraceptive use

[c] Women with surgical cessation of menstruation due to hysterectomy but without total oophorectomy were excluded from analysis of age at menopause and length of ovulation

[d] HRs were estimated for a 5-year increase in age at menopause considered as continuous variable

[e] Only women with natural menopause were included

[f] Only women with surgical menopause due to total oophorectomy were included

smoking, diabetes, use of multivitamins, estrogen, and oral contraceptives, the HR was 0.64 (95% CI: 0.45-0.91) for menopause after 45 *versus* before 45 years. The associations between pancreatic cancer and natural and surgical menopause followed similar patterns

Table 5. Multivariate-adjusted hazard ratios for incident pancreatic cancer in relation to age at menopause for never smokers and for women with BMI less than 25 kg/m^2 (Iowa Women's Health Study, IWHS 1986-2003).

Age at menopause[a]	Number of cases	Person-years	Hazard ratio (95% CI)	
			Age-adjusted	Multivariate adjusted[b]
Never smokers:				
- Less than 45 years	26	48,026	1 (reference)	1 (reference)
- 45-49 years	26	81,745	0.60 (0.35-1.03)	0.59 (0.34-1.02)
- 50-54 years	54	146,079	0.70 (0.44-1.13)	0.68 (0.42-1.10)
- 55 years or more	8	43,262	0.32 (0.15-0.71)	0.33 (0.15-0.73)
P trend			0.009	0.010
Women with BMI less than 25 kg/m^2:				
- Less than 45 years	14	32,370	1 (reference)	1 (reference)
- 45-49 years	20	53,779	0.87 (0.44-1.72)	0.74 (0.36-1.51)
- 50-54 years	32	86,953	0.86 (0.46-1.61)	0.81 (0.42-1.54)
- 55 years or more	4	20,779	0.42 (0.14-1.27)	0.43 (0.14-1.31)
P trend			0.127	0.152

CI: confidence interval

[a] Women with surgical stop of menstruation due to hysterectomy but without total oophorectomy were excluded from analysis

[b] Adjusted for age, diabetes, use of multivitamins, estrogen and oral contraceptives for never-smokers. In addition, hazard ratios were adjusted for smoking in the analysis of women with BMI less than 25 kg/m^2

(Table 4). In a multivariate-adjusted model, women who had natural menopause at ages 55 years or more were half as likely to have pancreatic cancer as those who were younger than 45 years (P trend=0.129). For ages at surgical menopause less than 45, 45-49, and 50 years or more, HRs were 1.00, 0.74, and 0.40, respectively (P trend=0.070).

To further study the association of menopause with pancreatic cancer, we examined age at menopause as a continuous variable (Table 4). Each five-year increase in the age at menopause was associated with lower risk of pancreatic cancer: (HR=0.80, 95% CI: 0.71-0.89, in the age-adjusted model; HR=0.81, 95% CI: 0.72-0.91, in the multivariate-adjusted model). To check for departure from linearity, we fitted a model with a quadratic term for age at menopause, but it was not statistically significant.

There was an indication that length of ovulation was inversely associated with pancreatic cancer risk. In a multivariate-adjusted model, compared to the first tertile, HR=0.83 (95% CI, 0.58-1.18) and HR=0.69 (95% CI, 0.48-1.00) were found for the second and the third tertile, respectively (P trend=0.049). Oophorectomy and hysterectomy also showed associations with pancreatic cancer, consistent with the finding that later menopause may reduce pancreatic cancer risk. Compared to those with total oophorectomy, the HR was 0.70 (95% CI: 0.50-0.99) for those with no ovarian surgery. For women without hysterectomy *versus* those with hysterectomy, the HR was 0.73 (95% CI: 0.55-0.98) (Table 4).

Since smoking is an established risk factor for pancreatic cancer, and it reduces age at menopause [27, 28, 29], we restricted the cohort to never smokers and reexamined the association between pancreatic cancer and age at menopause. Compared to menopause at age under 45, the multivariate-adjusted hazard ratio of pancreatic cancer was 0.59 for menopause at 45-49 year, 0.68 for menopause at 50-54 year, and 0.33 for menopause at age 55 year or more (P trend=0.010) (Table 5). We also conducted a subgroup analysis for normal-weight women and found that HRs were 1.00, 0.74, 0.81, and 0.43 for ages at menopause less than 45, 45-49, 50-54 and more than 54 years, respectively (P trend=0.152) (Table 5).

From a sensitivity analysis we conducted to test for possible recall bias, we found that relative changes in regression coefficients were less than 10% for positive or negative error, and point estimates accounting for potential bias were within the 95% confidence

limits for the point estimate of age at menopause in the main analysis. Finally, inclusion of premenopausal women into the analysis of age at menopause did not materially change our results.

DISCUSSION

In this large cohort of elderly women, no associations were found between pancreatic cancer and number of live births, age at menarche, age at first live birth, or use of sex hormones. We found that the incidence of pancreatic cancer was reduced for those who had later *versus* earlier age at menopause. In a parallel fashion, risk of pancreatic cancer was decreased for women who had ovulation for longer period of life, and for women who did not report having a total oophorectomy or hysterectomy compared to those who had such surgeries.

Data from previous studies on this topic are contradictory. Shortcomings in several of these studies may explain, in part, this inconsistency: three studies [9, 12, 15] did not control for smoking and three case-control studies [7, 8, 13] had less than one hundred cases. However, even among studies without such limitations, inconsistencies remain. One large cohort study [16] found a linear inverse association between parity and pancreatic cancer incidence. The largest prospective cohort published to date [18] reported that women who had five or more births had lower death rates from pancreatic cancer, but there was not a linear association. In contrast, a case-control study [11] reported a positive association with a number of births. Another case-control study [10] found no significant association with parity, but an inverse relation with early age (less than 25 years) at first and last births compared to nulliparous women and an increased risk for women with early menarche.

Our findings differ from case-control data reported by Duell and Holly [14]. They found an increased risk associated with later onset of menopause. Our results are also at odds with findings of Skinner *et al*. [16], Teras *et al*. [18], and Ji *et al*. [11] who reported no associations with age at menopause. In two case-control studies [10, 13] there were indications of an inverse relation between pancreatic cancer and age at menopause, but these were not statistically significant. Our results are consistent with those from a Canadian prospective study [17]. The authors did not present results for age at menopause, but they reported an increased risk of pancreatic cancer HR=2.44 (95% CI: 1.45-4.09) for post-menopausal *versus* premenopausal women in a multivariate-adjusted analysis that included age, smoking, BMI, and height as covariates.

In the IWHS cohort, we showed that the inverse association of age at menopause with pancreatic cancer was not the result of residual confounding by cigarette smoking, as this association held for never smokers in a stratified analysis. Moreover, though not significant, there were inverse relationships between pancreatic cancer and age at menopause for normal-weight women, women with natural and women with surgical menopause.

The strengths of our study are that it is a large population-based prospective cohort with 18 years of nearly complete follow-up. We asked detailed information on reproductive and other possible risk factors for pancreatic cancer at baseline and during follow-up and we could adjust our analyses for important potential confounders including BMI, smoking, and diabetes. However, the number of cases available for stratified analyses, i.e., analysis of age at menopause for normal-weight women (n=70) and analyses of age at natural (n=135) and age at surgical menopause (n=41), reduced our power to detect significant associations in these subgroups.

Generalizability of our results may be limited since almost all IWHS participants are white postmenopausal women who live in one state in the United States. A 42% response rate to the invitation to join the cohort may also limit generalizability. However, the very high response rate to each follow-up survey argues for high internal validity. An annual migration rate from Iowa of less than 1% also argues for high validity.

Data on risk factors were obtained by self-report in this study. This is a potential limitation; however, if random error in reporting age at menopause existed, it should have attenuated our association. In addition, we conducted a sensitivity analysis and showed that our results were unlikely to be explained by systematic bias. Further, the association between pancreatic cancer and age at menopause was not biased by exclusion at baseline of premenopausal women. Of note, data on all reproductive factors have been investigated in several studies in the IWHS cohort [19, 30, 31, 32] and the findings were consistent with established associations for breast, endometrial, and ovarian cancers.

If in fact, late onset of menopause decreases the risk of pancreatic cancer, one possible mechanism is that women having menopause at an older age have circulating estrogen for a longer period of time. This would be consistent with laboratory findings that estrogen treatment inhibits the growth of preneoplastic lesions in rats and carcinoma of human pancreas *in vitro* [33, 34]. Longnecker and Sumi [35] also reported that pancreatic tumors grow faster in female rats after oophorectomy. It has also been argued that estrogen could have anticarcinogenic effects by inhibiting the action of insulin and insulin-like growth factors at the receptor level [14]. Not all animal studies support the hypothesis that estrogen inhibits pancreatic carcinogenesis. Chester *et al*. [36] found no effect of oophorectomy on pancreatic cancer incidence in hamsters.

An alternative mechanism to explain an inverse association between age at menopause and pancreatic cancer is related to iron. Menopause leads to a marked increase of body iron stores in women, especially during the first years after menopause [37, 38, 39, 40]. Plasma ferritin concentration - a commonly accepted marker for body iron stores - increases from a median of 40 μg/L in 40-year-old women to 95 μg/L for those above 60-70 years [38]. When iron storage is overloaded, or an external trigger is present, free iron is produced. Several studies report free iron to be carcinogenic [41, 42, 43]; it catalyzes the formation of hydroxyl radicals, suppresses the activity of host defense cells, and promotes cancer cell multiplication. Friedman and Van Den Eeden [44] demonstrated a positive association between risk of pancreatic cancer and higher levels of serum iron (estimated RR=1.14, 95% CI: 1.02-1.28) and higher percentage of iron saturation. A case-control study by Silverman *et al*. [45] also reported an association between iron and pancreatic cancer risk. It is plausible that women who have early menopause have higher concentrations of iron for a longer time than women with late menopause, thus increasing the risk of pancreatic cancer. This mechanism is consistent with our findings that only reproductive variables related to menopause (age at menopause, length of ovulation, oophorectomy, and hysterectomy) are associated with pancreatic cancer.

In summary, our results suggest that older age at menopause may be associated with reduced pancreatic cancer risk. Future studies using biomarkers such as markers for estrogens, iron, and genetic polymorphism affecting hormone metabolism may provide the best approach to test specific hypotheses.

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Abbreviations HR: hazard ratio; ICD-O: International Classification of Diseases of Oncology; IWHS: Iowa Women's Health Study; RR: relative risk; WHR: waist-to-hip ratio

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