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Adiposity, history of diabetes, and risk of pancreatic cancer in postmenopausal women

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ABSTRACT

Purpose: The purpose of this study was to examine the association of type II diabetes and anthropometric variables with risk of pancreatic cancer among postmenopausal women.
Methods: Weight, height, waist circumference, and hip circumference were measured by trained personnel, whereas history of diabetes and weight earlier in life were self-reported. Pancreatic cancer was ascertained via central review of medical records by physician adjudicators. After exclusions, 1045 cases of pancreatic cancer were diagnosed among 156,218 women over a median follow-up of approximately 18 years. Cox proportional hazards models were used to estimate the associations of study factors with pancreatic cancer risk.
Results: Diabetes (hazards ratio (HR): 1.30; 95% confidence intervals (95% CI): 1.01–1.66), and in particular, waist circumference, waist-to-hip ratio, and waist-to-height ratio showed positive associations with pancreatic cancer risk (HRs for highest vs. lowest level 1.38; 95% CI: 1.14–1.66, 1.40; 1.17–1.68; and 1.36; 1.13–1.64, respectively). Body mass index at the baseline showed only a borderline positive association with risk (HR: 1.21; 95% CI: 0.97–1.51). Body mass index at age 50 years, but not at ages 18 and 35 years, was also associated with increased pancreatic cancer risk.
Conclusions: In this study of postmenopausal women, central adiposity and, to a lesser extent, general adiposity and a history of diabetes, were associated with increased pancreatic cancer risk.

Introduction

In the United States, pancreatic cancer is the eleventh most common cancer in men and the ninth most common cancer in women [1], with an estimated 27,970 cases in men and 25,700 cases in women in 2017. However, owing to its high lethality, pancreatic cancer ranks fourth among causes of cancer death in both men and women [1]. In view of its high fatality rate, the identification of modifiable risk factors for the disease is of urgent importance.

To date, aside from cigarette smoking [2,3], firmly established risk factors for pancreatic cancer are few. Obesity [4–7], a sedentary lifestyle [8–10], and diabetes [3,10,11] have been investigated as potential risk factors. However, of these hypothesized risk factors, only obesity shows consistent evidence of an association with the disease, and the association is weak [7]. Central adiposity in adulthood [12–14], as well as adiposity earlier in adulthood [12–14], may also be risk factors [6,13]; however, fewer studies have addressed these variables. It is challenging to determine whether diabetes is an independent risk factor for pancreatic cancer owing to the inter-related effects of obesity, sedentary

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behavior, and hyperglycemia and hyperlipidemia and the fact that diabetes can be an early symptom of pancreatic cancer [3]. In an umbrella review of meta-analyses of studies of type II diabetes and cancer [15], pancreatic cancer was not among the 5 cancers for which the association with diabetes was judged to be robust.

We used data from the Women's Health Initiative (WHI) cohort to examine the associations of diabetes, measured adiposity (overall and abdominal), and self-reported weight earlier in life with risk of incident pancreatic cancer.

Materials and methods

The WHI is a large, multicenter, multifaceted study designed to advance understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a clinical trial component (CT, $n = 68,132$) and an observational study component (OS, $n = 93,676$) [16]. 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 years and representing major racial 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 elsewhere [16,17]. Written informed consent was obtained from participants at all WHI centers in accordance with recognized ethical guidelines, and the study was approved by the institutional review board of each center, as well as by that of the Coordinating Center at the Fred Hutchinson Cancer Research Center.

Exposures and covariates ascertainment

At study entry, self-administered questionnaires were used to collect information on demographics, medical (including history of diabetes), reproductive, and family history, and on dietary and lifestyle factors, including smoking history, alcohol consumption and recreational physical activity. In relation to diabetes, women in the OS and CT groups were asked if they had ever been diagnosed with diabetes by a doctor while they were not pregnant [18,19]. Women were categorized as having diabetes, if they answered yes to this question.

All participants had their weight, height, and waist and hip circumferences measured by trained staff at the baseline. Weight was measured to the nearest 0.1 kg, whereas height and waist and hip circumferences were measured to the nearest 0.1 cm.

Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. We used the World Health Organization classification of BMI (18.5–<25.0, 25.0–<30, 30–<35, ≥35 kg/m^2). Participants in the OS were also asked about their weight at ages 18, 35, and 50 years, as well as about the number of times that they had experienced substantial weight loss. BMI at earlier ages was computed using self-reported weight at those ages and height measured at enrollment. Given the small number of women whose BMI fell in the overweight and obese categories (particularly those with measurements at ages 18 and 35 years), the self-reported BMI variables were categorized into quartiles based on the distribution among the noncases. For waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), we also created quartiles based on the distribution among the noncases.

Outcome ascertainment

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the CT and annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of pancreatic cancer were verified by centralized review of medical records and pathology reports by trained physician adjudicators [20]. As of September 20, 2016, a total of 1078 incident cases of pancreatic cancer (occurring as the first cancer) had been ascertained among the 161,808 participants in the OS and CT after a median of 17.9 years of follow-up (interquartile range: 9.0–19.4).

For the analyses of risk in relation to the anthropometric measures, we excluded women who were missing information on smoking status ($n = 2105$) and BMI ($n = 1405$). Information about a previous history of cancer of the breast, endometrium, ovary, cervix, colorectum, bladder, leukemia, lymphoma, thyroid, and liver was elicited in WHI; however, pancreatic cancer was not included in the list. There was a category for “other prevalent cancer.” We excluded 9 cases and 1598 noncases who responded positively to this category. We also excluded women who lacked information on follow-up time ($n = 5505$). After exclusions, a total of 1045 incident pancreatic cancer cases and 155,173 noncases were available for analysis.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the associations of diabetes and anthropometric variables with risk of pancreatic cancer. The time scale was days to event. Cases contributed person-time to the study from their date of enrollment until their date of diagnosis. Noncases 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 HR 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), alcohol intake (servings/wk–continuous), education (less than high school graduate, high school graduate/some college, college graduate, post-college); race (white, black, other); and enrollment in the OS or intervention versus placebo or control arm of the four clinical trials (estrogen alone; estrogen + progestin; calcium + vitamin D; and low-fat diet). When diabetes was included as the main exposure, we additionally adjusted for WC, WHR, or BMI in separate models, and for the anthropometric variables, we conducted analyses both with and without diabetes in the models. In analyses of self-reported BMI at earlier stages of life, we included a binary variable indicating whether participants had ever intentionally (i.e., not because of pregnancy or illness) lost more than 10 pounds in the preceding 20 years (this variable was only available in the OS) in the multivariable models. Women with a BMI of less than 18.5 kg/m^2 were excluded from the analyses because such low values might reflect anorexia or other illness (1353 noncases, 5 cases). For categorical variables, tests for trend were performed by assigning the median value to each category and modeling this variable as a continuous variable. The proportional hazards assumption was tested using Schoenfeld residuals. The proportional hazards assumption was not violated.

As smoking is an established risk factor for pancreatic cancer [2,3], in this study, we performed analyses stratified by smoking status to determine whether the associations between the exposures and the outcome were modified by smoking status. P for interaction was calculated by including interaction terms in Cox regression models and testing their coefficients using the Wald tests.

We conducted several sensitivity analyses excluding the first 3 years of follow-up to address reverse causation (remaining sample size: 907 cases, 151,670 noncases).

Table 1
Distribution of selected characteristics among pancreatic cancer cases and noncases in the Women's Health Initiative (n = 156,218)

Characteristics	Cases (n = 1045)	Noncases (n = 155,173)	P-value
Means (SD)			
Age (yrs)	65.4 (7.0)	63.2 (7.2)	<.001
Body mass index (kg/m^2)	28.1 (5.9)	28.0 (5.9)	.437
Waist circumference (cm)	87.5 (13.1)	86.4 (13.8)	.016
Waist-hip ratio	0.82 (0.08)	0.81 (0.08)	<.001
Waist-height ratio	0.54 (0.08)	0.53 (0.09)	.016
Physical activity (MET-h/week)	11.8 (13.3)	11.9 (13.7)	.899
Alcohol intake (servings/wk)	2.7 (5.5)	2.4 (4.9)	.015
Smoking (pack-years)	11.4 (20.6)	9.6 (18.0)	.002
Proportions			
Diabetes	6.8	5.9	.440
Smoking status (%)			
Never	49.9	51.1	.046
Former	41.2	42.0	
Current	9.0	7.0	
Education (% post-college)	30.5	28.6	.248
Race (%)			
White	85.1	82.7	.199
Black	8.0	9.0	
Other	6.7	8.1	
Missing	0.2	0.3	
Study component			
OS	55.0	57.4	.122
CT	45.0	42.6	

CT = clinical trials; MET = metabolic equivalent; OS = observational study; SD = standard deviation.

Table 2
Association of diabetes and measured anthropometric variables with risk of pancreatic cancer in the Women's Health Initiative

Exposures	Cases/noncases (N)	HR[*]	95% CI	HR[†]	95% CI	HR[‡]	95% CI
Diabetes							
No	973/145,945	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	71/9130	1.44	1.13–1.83	1.30[§]	1.01–1.66	1.33[‖]	1.04–1.70
Missing	1/98						
BMI (kg/m^2)							
Per 5 kg increase		1.08	1.03–1.14	1.08	1.02–1.14	1.07	1.02–1.13
18.5–<25.0	345/53,185	1.00	Ref.	1.00	Ref.	1.00	Ref.
25.0–<30.0	374/53,900	1.08	0.94–1.25	1.08	0.93–1.26	1.08	0.93–1.25
30.0–<35.0	205/28,737	1.20	1.01–1.43	1.21	1.01–1.44	1.19	0.99–1.42
≥35.0	116/17,998	1.24	1.00–1.53	1.25	1.00–1.56	1.21	0.97–1.51
P for trend		*0.013*		*0.016*		*0.038*	
Waist circumference (cm)							
Per 10 cm increase		1.10	1.05–1.15	1.10	1.05–1.15	1.09	1.04–1.14
<76.0	229/39, 052	1.00	Ref.	1.00	Ref.	1.00	Ref.
76.0–<84.5	256/38,718	1.10	0.92–1.31	1.09	0.91–1.30	1.08	0.91–1.30
84.5–<95.0	281/39,813	1.21	1.01–1.44	1.19	0.99–1.42	1.18	0.99–1.41
≥95.0	277/37,164	1.42	1.19–1.70	1.41	1.18–1.70	1.38	1.14–1.66
Missing	2/426						
P for trend		*<0.001*		*<0.001*		*<0.001*	
Waist-hip-ratio							
Per 0.1 cm increase		1.14	1.08–1.21	1.13	1.07–1.20	1.12	1.05–1.19
<0.76	218/38,702	1.00	Ref	1.00	Ref.	1.00	Ref.
0.76–<0.80	263/38,622	1.18	0.98–1.41	1.15	0.96–1.38	1.15	0.96–1.38
0.80–<0.86	247/38,937	1.11	0.93–1.34	1.08	0.90–1.30	1.07	0.89–1.28
≥0.86	313/38,347	1.50	1.26–1.79	1.44	1.21–1.72	1.40	1.17–1.68
Missing	4/565						
P for trend		*<0.001*		*<0.001*		*0.001*	
Waist-height ratio							
Per 0.1 cm increase		1.15	1.07–1.23	1.14	1.06–1.23	1.13	1.05–1.21
<0.47	230/38,692	1.00	Ref	1.00	Ref.	1.00	Ref.
0.48–<0.52	247/38,686	1.03	0.86–1.24	1.02	0.86–1.23	1.02	0.85–1.22
0.53–<0.59	269/38,688	1.16	0.97–1.38	1.14	0.95–1.36	1.13	0.94–1.35
≥0.59	297/38,681	1.41	1.19–1.67	1.40	1.17–1.67	1.36	1.13–1.64
Missing	2/426						
P for trend		*<0.001*		*<0.001*		*<0.001*	

[*] Adjusted for age only.
[†] Adjusted for age (continuous), smoking status (never smoked, former smoker, current smoker), pack-years of smoking (continuous), alcohol intake (servings/day), metabolic equivalent task hrs/week (MET-hrs/week—continuous), educational level (less than high school grad, high school grad/some college, college grad, post-college), race (white, black, other), and allocation to the OS or treatment/placebo/control arm of clinical trials unless included as main exposure.
[‡] Adjusted for variables in "b" + previous history of diabetes (yes, no).
[§] Adjusted for variables in "b" + waist circumference.
[‖] Adjusted for variables in "b" + waist to hip ratio.

Analyses were performed using Stata 14.1 (StataCorp, College Station, TX). All *P*-values are two-sided.

Results

Compared with noncases, women subsequently diagnosed with pancreatic cancer were older at enrollment and had significantly greater mean WC, WHR, WHtR, alcohol intake, and pack-years of smoking (Table 1). The proportion of women with a history of diabetes was nonsignificantly higher in cases compared with noncases (6.8 vs. 5.9 percent, $P = 0.44$).

A history of diabetes was positively associated with risk of pancreatic cancer (multivariable-adjusted HR: 1.41; 95% CI: 1.10–1.79). The association was attenuated in models additionally adjusted for WC (HR: 1.30; 95% CI: 1.01, 1.66), WHR (1.33; 1.04–1.70) (Table 2), and BMI (1.35; 1.05–1.72).

In multivariable-adjusted analyses (excluding diabetes as a covariate), compared with the lowest quartile, the highest quartile of BMI was positively associated with risk of pancreatic cancer (HR 1.25, 95% CI 1.00–1.56, *P* for trend = 0.016) (Table 2). Women in the highest quartile of WC, WHR, and WHtR also had increased risk of pancreatic cancer (HR: 1.41; 95% CI: 1.18–1.70, *P* for trend: <0.001 1.44; 1.21–1.72, *P* for trend: <0.001 and 1.40; 1.17–1.67, *P* for trend: <0.001, respectively) (Table 2). When diabetes was included in the models, the corresponding HRs were slightly attenuated. When the exposures of interest were examined as continuous variables, the HR per 5 kg/m^2 increment in BMI was 1.07 (95% CI: 1.02–1.13); the HR per 10 cm increase in WC was 1.09 (95% CI: 1.04–1.14); the HR per 0.1 unit increase in WHR was 1.12 (95% CI: 1.05–1.19) and the HR per 0.1 unit increase in WHtR was 1.13; 1.05–1.21 (Table 2).

There was no evidence to suggest that smoking modifies the associations between the metabolic factors and risk of pancreatic cancer (Table 3).

BMI at ages 18 and 35 years showed no association with risk of pancreatic cancer; however, the uppermost quartile of BMI at age 50 years was positively associated with risk (HR: 1.42; 95% CI: 1.11–1.92, *P* for trend 0.007) (Table 4).

When the first 3 years of follow-up were excluded, all 3 anthropometric variables remained positively associated with risk of pancreatic cancer, but, the association with diabetes was no longer apparent (Table S1).

Table 3
Association of diabetes and measured anthropometric variables with risk of pancreatic cancer in the Women's Health Initiative by smoking status

Exposures	Smoking					
	No			Yes		
	Cases/noncases	HR	95% CI	Cases/noncases	HR	95% CI
Diabetes						
No	482/74,407	1.00	Ref	491/71,538	1.00	Ref
Yes	38/4738	1.41	1.00–1.98	33/4392	1.17	0.82–1.69
Missing	1/57			0/41		
P for heterogeneity				0.706		
BMI (kg/m^2)						
Per 5 kg increase		1.06	0.98–1.15		1.06	0.99–1.15
18.5–<25.0	167/27,338	1.00	Ref.	178/25,847	1.00	Ref.
25.0–<30.0	202/27,325	1.19	0.97–1.47	172/26,575	0.94	0.76–1.17
30.0–<35.0	95/14,823	1.09	0.84–1.42	110/13,914	1.22	0.96–1.57
≥35.0	55/9007	1.18	0.86–1.63	61/8991	1.16	0.85–1.58
P for trend		*0.341*			*0.127*	
P for heterogeneity				0.564		
Waist circumference (cm)						
Per 10 cm increase		1.05	0.98–1.12		1.11	1.05–1.19
<76.0	116/21,042	1.00	Ref.	113/18,010	1.00	Ref.
76.0–<84.5	137/19,969	1.18	0.92–1.51	119/18,749	0.98	0.76–1.27
84.5–<95.0	151/20,057	1.31	1.02–1.68	130/19,756	1.04	0.80–1.34
≥95.0	115/17,928	1.20	0.91–1.58	162/19,236	1.47	1.14–1.90
Missing	2/206			0/220		
P for trend		*0.197*			*0.001*	
P for heterogeneity				0.313		
Waist-hip ratio						
Per 0.1 unit increase		1.04	0.94–1.16		1.19	1.10–1.29
<0.76	122/21,383	1.00	Ref.	96/17,319	1.00	Ref.
0.76–<0.80	140/19,939	1.17	0.91–1.49	123/18,683	1.15	0.88–1.50
0.80–<0.86	118/19,489	0.99	0.77–1.28	129/19,448	1.16	0.89–1.52
≥0.86	138/18,118	1.25	0.97–1.61	175/20,229	1.59	1.23–2.06
Missing	3/273			1/292		
P for trend		*0.182*			*<0.001*	
P for heterogeneity				*0.430*		
Waist-height ratio						
Per 0.1 unit increase		1.07	0.96–1.19		1.18	1.07–1.31
<0.47	120/20,327	1.00	Ref	110/18,365	1.00	Ref
0.48–<0.52	121/19,823	0.96	0.75–1.24	126/18,863	1.08	0.83–1.39
0.53–<0.59	145/19,739	1.17	0.91–1.50	124/18,949	1.08	0.83–1.41
≥0.59	133/19,107	1.18	0.91–1.53	164/19,574	1.55	1.20–2.01
Missing	2/206			0/220		
P for trend		*0.113*			*<0.001*	
				0.303		

Adjusted for age (continuous), alcohol intake (servings/day), previous history of diabetes (yes, no), metabolic equivalent task hrs/week (MET-hrs/week–continuous), educational level (less than high school grad, high school grad/some college, college grad, post-college), race (white, black, other), and allocation to the OS or treatment/placebo/control arm of clinical trials unless included as the main exposure.

Table 4
Association of self-reported BMI at ages 18, 35, and 50 years with risk of pancreatic cancer in the Women's Health Initiative observational study

Exposures	Cases/noncases	HR*	95% CI	HR†	95% CI	HR‡	95% CI
BMI at age 18 y							
Per 5 kg increase		1.06	0.91–1.23	1.05	0.91–1.22	1.05	0.90–1.22
Quartiles							
<19.70	105/17,882	1.00	Ref.	1.00	Ref.	1.00	Ref.
19.70–20.80	123/18,754	1.12	0.86–1.45	1.10	0.85–1.43	1.10	0.85–1.43
20.81–22.30	115/17,058	1.15	0.88–1.49	1.13	0.87–1.48	1.13	0.87–1.48
>22.30	118/17,700	1.21	0.93–1.58	1.17	0.90–1.53	1.17	0.90–1.53
		0.166		*0.267*		*0.271*	
BMI at age 35 y							
Per 5 kg increase		1.04	0.91–1.18	1.03	0.90–1.17	1.02	0.90–1.17
Quartiles							
<20.61	144/22,058	1.00	Ref.	1.00	Ref.	1.00	Ref.
20.61–21.93	142/20,208	1.07	0.85–1.35	1.07	0.85–1.35	1.07	0.85–1.35
21.94–23.74	124/20,510	0.94	0.74–1.20	0.93	0.73–1.19	1.03	0.74–1.19
>23.74	134/20,884	1.15	0.91–1.45	1.09	0.84–1.40	1.08	0.84–1.39
P for trend		*0.350*		*0.663*		*0.692*	
BMI at age 50 y							
Per 5 kg increase		1.10	1.01–1.20	1.10	1.00–1.20	1.10	1.00–1.20
Quartiles							
<21.64	132/22,010	1.00	Ref.	1.00	Ref.	1.00	Ref.
21.64–23.52	143/21,090	1.14	0.90–1.45	1.17	0.92–1.48	1.17	0.92–1.48
23.52–26.52	148/22,016	1.21	0.96–1.54	1.22	0.95–1.57	1.22	0.95–1.57
>26.52	135/21,016	1.44	1.13–1.83	1.46	1.11–1.91	1.46	1.11–1.91
P for trend		*0.003*		*0.007*		*0.007*	

Models examining BMI at earlier ages were limited to the observational study (377 participants were missing information on BMI at earlier times.).
* Adjusted for age only.
† Adjusted for age (continuous), smoking status (never smoked, former smoker, current smoker), alcohol intake (servings/day), previous history of diabetes (yes, no), metabolic equivalent task hrs/week (MET-hrs/week—continuous), lost more than 10 lbs. (yes, no), educational level (less than high school grad, high school grad/some college, college grad, post-college), race (white, black, other).
‡ Adjusted for variables in "b" + previous history of diabetes (yes, no).

Discussion

The results of this study suggest that a history of diabetes, overall obesity, and, in particular, central adiposity measured at enrollment have modest positive associations with risk of pancreatic cancer. The associations with measured anthropometric factors persisted in sensitivity analyses, whereas the association with diabetes was somewhat attenuated when the early years of follow-up were excluded. Except for a positive association between self-reported BMI at age 50 years and risk of pancreatic cancer, self-reported BMI at earlier points in life showed no association with risk.

In the present study, the association between diabetes and pancreatic cancer appeared to be explained partly by level of central adiposity, as adjusting for WC significantly attenuated the HR for the association between diabetes and pancreatic cancer. Nevertheless, as in several previous studies, diabetes was observed to have a modest positive association with risk of pancreatic cancer independent of level of adiposity and other confounders [21–29]. Pooled results from a recent meta-analyses also showed that diabetes was associated with an almost two-fold increased risk of pancreatic cancer (RR: 1.97, 95% CI: 1.78–2.18) [30]. A recent umbrella review of meta-analyses of diabetes and cancer [15] judged the evidence regarding pancreatic cancer to be uncertain because of heterogeneity between studies and raised the possibility of biases, including publication bias and selective reporting of positive results.

Our findings regarding the associations of the baseline BMI, WC, and WHR with pancreatic cancer risk are also in agreement with the results of previous cohort studies [4–7]. However, we found little evidence of an association with BMI earlier in life, in contrast to the results of several previous analyses, including 2 pooled analyses [12–14]. This may be because of the reduced sample size with information on weight earlier in life in our study, and to the fact that weight in earlier life was self-reported, which might have attenuated associations because of misclassification of the exposure.

Recently, a Mendelian randomization study [31] was carried out in a large series of pancreatic cancer cases and controls to examine the association between genetic instruments for obesity, body shape, dyslipidemia, insulin resistance, and type II diabetes to evaluate their role in pancreatic cancer etiology. The results indicated causal associations with pancreatic cancer risk of increasing BMI in both sexes and of fasting insulin in males but not in females. No association was seen for variants associated with diabetes, fasting glucose, waist-to-hip ratio, or dyslipidemia. The inconsistency regarding results for serum insulin by sex, as well as the lack of an association with diabetes or fasting glucose, underscore the need for further study of the inter-relationships between these factors in relation to pancreatic cancer risk.

Adiposity could contribute to the development of pancreatic cancer via hyperinsulinemia and hyperglycemia. Insulin promotes cell proliferation and inhibits apoptosis, both by direct action and through increased bioavailability of IGF-1 [32,33], and elevated glucose concentrations can also promote cell proliferation [34,35] and enhance the invasive potential of pancreatic cancer cells [36]. However, while the literature implicates excess adiposity and insulin resistance in the etiology of pancreatic cancer, the associations of anthropometric measures, insulin resistance, and diabetes are modest in magnitude, and there are inconsistencies in the results of different studies. A clearer understanding of the role of these factors in pancreatic carcinogenesis will require large studies with repeated measurements of risk factors to improve the precision of the estimates of these inter-related factors, as well as to clarify the temporal relationships among them. The possibility that adiposity and insulin resistance play a role in the development

of pancreatic cancer holds out the prospect of prevention by reversing insulin resistance through lifestyle changes, including improving energy balance through increased physical activity [37].

Strengths of the present study include the large number of pancreatic cancer cases, the availability of anthropometric factors measured at enrollment, low loss to follow-up (~1%), long-term follow-up, as well as self-reported weight (used to compute BMI) at earlier points in life, and detailed information on potential confounding factors. Associations with measured anthropometric factors were unchanged in sensitivity analyses. Limitations include the fact that fasting serum glucose and insulin levels were not available to assess current glycemic control status. Furthermore, by design, the WHI includes only postmenopausal women. The WHI is also not representative of the general population; thus, the results of this study may not be generalizable, although they should be internally valid. Finally, in the present study, we observed that after exclusion of the first 3 years of follow-up the association between diabetes and pancreatic cancer disappeared. This finding may be because of reduced power resulting from reduced sample size. However, it also suggests that cases diagnosed soon after enrollment may have contributed to the observed association, and therefore, reverse causality may have contributed to the observed associations.

In conclusion, our results suggest that both a history of diabetes and adiposity (overall and central) are associated with increased risk of pancreatic cancer.

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Appendix

Table S1
Association of diabetes and measured anthropometric variables with risk of pancreatic cancer in the Women's Health Initiative excluding the first 3 years of follow-up

Exposures	HR[*]	95% CI	HR[†]	95% CI	HR[‡]	95% CI
Diabetes						
No	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	1.34	1.02–1.76	1.19[§]	0.90–1.58	1.24[‖]	0.94–1.63
BMI (kg/m^2)						
Per 5 kg increase	1.10	1.04–1.16	1.10	1.04–1.16	1.09	1.03–1.16
18.5–<25.0	1.00	Ref.	1.00	Ref.	1.00	Ref.
25.0–<30.0	1.07	0.92–1.25	1.08	0.92–1.26	1.07	0.91–1.26
30.0–<35.0	1.18	0.98–1.42	1.19	0.98–1.45	1.18	0.97–1.43
≥35.0	1.32	1.06–1.65	1.33	1.06–1.68	1.31	1.03–1.65
P for trend	*0.008*		*0.008*		*0.015*	
Waist circumference (cm)						
Per 10 cm increase	1.10	1.05–1.15	1.10	1.05–1.15	1.10	1.04–1.15
<76.0	1.00	Ref.	1.00	Ref.	1.00	Ref.
76.0–<84.5	1.09	0.91–1.32	1.09	0.90–1.32	1.09	0.90–1.32
84.5–<95.0	1.14	0.95–1.38	1.14	0.94–1.38	1.13	0.93–1.37
≥95.0	1.43	1.19–1.73	1.43	1.18–1.74	1.41	1.16–1.72
P for trend	*<0.001*		*<0.001*		*<0.001*	
Waist-hip ratio						
Per 0.1 unit increase	1.12	1.05–1.20	1.11	1.04–1.19	1.10	1.03–1.18
<0.76	1.00	Ref	1.00	Ref.	1.00	Ref.
0.76–<0.80	1.15	0.95–1.39	1.13	0.93–1.36	1.13	0.93–1.36
0.80–<0.86	1.10	0.91–1.33	1.07	0.88–1.30	1.06	0.87–1.29
≥0.86	1.43	1.19–1.72	1.38	1.14–1.67	1.35	1.12–1.64
P for trend	*<0.001*		*0.002*		*0.004*	
Waist-height ratio						
Per 0.1 unit increase	1.15	1.06–1.23	1.15	1.06–1.24	1.14	1.05–1.23
<0.76	1.00	Ref	1.00	Ref.	1.00	Ref.
0.76–<0.80	1.04	0.85–1.25	1.03	0.85–1.25	1.03	0.85–1.25
0.80–<0.86	1.14	0.94–1.38	1.13	0.93–1.37	1.12	0.93–1.36
≥0.86	1.40	1.17–1.69	1.40	1.16–1.70	1.38	1.14–1.68
P for trend	*<0.001*		*<0.001*		*<0.001*	

[*] Adjusted for age only.
[†] Adjusted for age (continuous), smoking status (never smoked, former smoker, current smoker), pack-years of smoking (continuous), alcohol intake (servings/day), metabolic equivalent task hrs/week (MET-hrs/week—continuous), educational level (less than high school grad, high school grad/some college, college grad, post-college), race (white, black, other), and allocation to the OS or treatment/placebo/control arm of clinical trials unless included as main exposure.
[‡] Adjusted for variables in "b" + previous history of diabetes (yes, no).
[§] Adjusted for variables in "b" + waist circumference.
[‖] Adjusted for variables in "b" + waist to hip ratio.