Received: 13 April 2022 | Revised: 26 June 2022 | Accepted: 28 June 2022

DOI: 10.1002/oby.23550

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Epidemiology/Genetics

Prediagnostic BMI trajectories in relation to pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Margaret Hoyt[1] | Yiqing Song[1] | Sujuan Gao[2] | Jacquelynn O'Palka[3] | Jianjun Zhang[1,4]

[1]Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University–Purdue University, Indianapolis, Indiana, USA

[2]Department of Biostatistics and Health Data Science, Richard M. Fairbanks School of Public Health and School of Medicine, Indiana University–Purdue University, Indianapolis, Indiana, USA

[3]Department of Nutrition and Dietetics, School of Health and Human Sciences, Indiana University–Purdue University, Indianapolis, Indiana, USA

[4]Melvin and Bren Simon Comprehensive Cancer Center, Indiana University–Purdue University, Indianapolis, Indiana, USA

Correspondence
Jianjun Zhang, Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University–Purdue University, 1050 Wishard Blvd., RG6120, Indianapolis, IN 46202, USA.
Email: jz21@iu.edu

Abstract

Objective: It remains elusive whether prediagnostic BMI trajectory is associated with pancreatic cancer.

Methods: This study investigated this question among 145,489 participants who gave rise to 696 incident cases of pancreatic cancer over a median follow-up of 12 years in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. At baseline, participants were asked to recall their weight at ages 20, 50, and 55 to 74 years (at enrollment), as well as their height.

Results: At age 50 years, people with obesity had a significantly increased risk of pancreatic cancer compared with those with a normal weight after adjustment for confounders (hazard ratio [95% CI]: 1.27 [1.01-1.60]). Individuals who had overweight at age 20 years experienced a marginally significant elevated risk of pancreatic cancer (hazard ratio [95% CI]: 1.22 [0.99-1.50]). Compared with individuals who maintained a steady normal weight during follow-up, no significantly altered risk of pancreatic cancer was observed for those whose weight status changed from normal weight to overweight, from normal weight to obesity, and from overweight to obesity.

Conclusions: The present study revealed that prediagnostic adulthood BMI trajectory was not associated with pancreatic cancer risk, but overweight at young adulthood and obesity at middle adulthood may confer an elevated risk of this malignancy.

INTRODUCTION

Pancreatic cancer is one of the deadliest malignancies, with a 5-year relative survival rate of only 10% [1]. It currently has the third highest mortality rate of all types of cancer in both men and women and it is predicted to surpass colorectal cancer as the second leading cause of cancer-related death by 2030 in the United States [2]. Approximately 80% of patients with pancreatic cancer are diagnosed at an advanced stage because of the high aggressiveness of tumors and the lack of effective screening tests [3]. The etiology of pancreatic cancer remains largely elusive because cigarette smoking, type 2 diabetes, chronic pancreatitis, and family history are the only established risk

factors [4]. To prevent pancreatic cancer, it is necessary to identify its risk factors, especially modifiable ones such as body mass index (BMI).

Obesity prevalence has been increasing at an alarming pace during the past several decades worldwide. It was estimated that nearly 40% of adult American individuals had obesity in 2016 [5]. A growing body of biological mechanisms have linked overweight and obesity to the development of pancreatic cancer. Excess fat accumulation may promote the carcinogenesis of several organs (including the pancreas) by increasing the circulating levels of insulin and insulin like growth factor 1 and inducing subsequent insulin resistance [6, 7]. These metabolic perturbations enhance tumor initiation and growth by adversely regulating cell proliferation, apoptosis, and angiogenesis [6]. Other biological mechanisms underlying the promoting effect of obesity on carcinogenesis include low-grade chronic inflammation and altered cytokine production induced by accumulated adipose tissue [6–8].

The association between obesity and pancreatic cancer has been investigated in many epidemiological studies, yielding inconsistent results. One of the potential reasons for the discrepant results was the measurement of BMI as an indicator of obesity at a single time point in most previous studies [9–11]. Changes in body weight over time may be more relevant to the etiology of pancreatic cancer than a single assessment of this anthropometric metric. However, it remains largely unknown whether lifetime BMI trajectory is associated with pancreatic cancer. In the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health Study, having overweight or obesity at ages 18, 35, 50, or >50 years and having a longer duration of overweight were associated with a significantly increased risk of pancreatic cancer [12]. The impact of adulthood overweight and obesity durations on pancreatic cancer risk was examined in the Women's Health Initiative. No significant association was observed between overweight and obesity duration and pancreatic cancer risk [13]. A study evaluated the influence of body shape trajectory on the risk of obesity-related cancers. Both men and women in the heavy-stable/increase trajectory had a higher but insignificant risk of pancreatic cancer than those in the lean-stable trajectory [14].

The inconsistent association between lifetime weight change and pancreatic cancer risk across previous studies accentuates the need to further pursue this research question in more prospective cohort studies. The present study was thereby conducted to investigate the associations among BMI measured at ages 20, 50, and 55 to 74 years (baseline) and pancreatic cancer risk among participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Study Importance

What is already known?

- Epidemiological studies on the association between obesity and pancreatic cancer have yielded inconsistent results, which may be in part due to a single body mass index (BMI) measurement used in most previous studies.
- A growing body of biological mechanisms have linked overweight and obesity to the development of pancreatic cancer, but few studies have investigated the impact of lifetime BMI trajectory on the risk of this malignancy.

What does this study add?

- Having overweight at age 20 years or obesity at age 50 years was associated with an increased risk of pancreatic cancer compared with normal weight at the two respective time points, although risk estimates for the association with BMI at age 20 years were borderline statistically significant.
- Adult BMI trajectory was not significantly associated with pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

How might these results change the direction of research or the focus of clinical practice?

- Dietary and lifestyle modifications that lead to a healthy body weight in early and middle adulthood may help decrease the risk of developing pancreatic cancer.

METHODS

Study population

The design of the PLCO Cancer Screening Trial has been described in detail elsewhere [15]. Briefly, 154,897 individuals aged 55 to 74 years were recruited from 10 medical centers throughout the US from 1993 to 2001. Participants were randomized to receive either the screening tests in the intervention arm (38,340 men and 39,104 women) or the standard of care in the control arm (38,342 men and 39,111 women). The PLCO Cancer Screening Trial ended in 2009. After that time, participants who provided reconsent were continuously followed, and additional data were collected through 2015. For the present analysis, extended follow-up data were not considered in order to avoid potential biases introduced by the reconsent process. We excluded 9408 individuals, including 4920 for failure to complete a sex-specific baseline questionnaire, 3629 for missing data on BMI at any time point considered, 40 for implausible BMI values (defined as BMI < 15 or >60 kg/m^2) [16], 93 for personal history of pancreatic cancer, and 726 for loss of follow-up (Supporting Information Figure S1). After the aforementioned exclusions, a total of 145,489 individuals remained in the cohort (n = 73,664 for the screening arm and n = 71,825 for the control arm), which gave rise to 696 cases of pancreatic cancer (including 311 cases of early-stage disease, defined as stages I and II) documented over a median follow-up period of 12 years. The cases of pancreatic cancer were ascertained through self-report upon annual study follow-up and reviews of medical

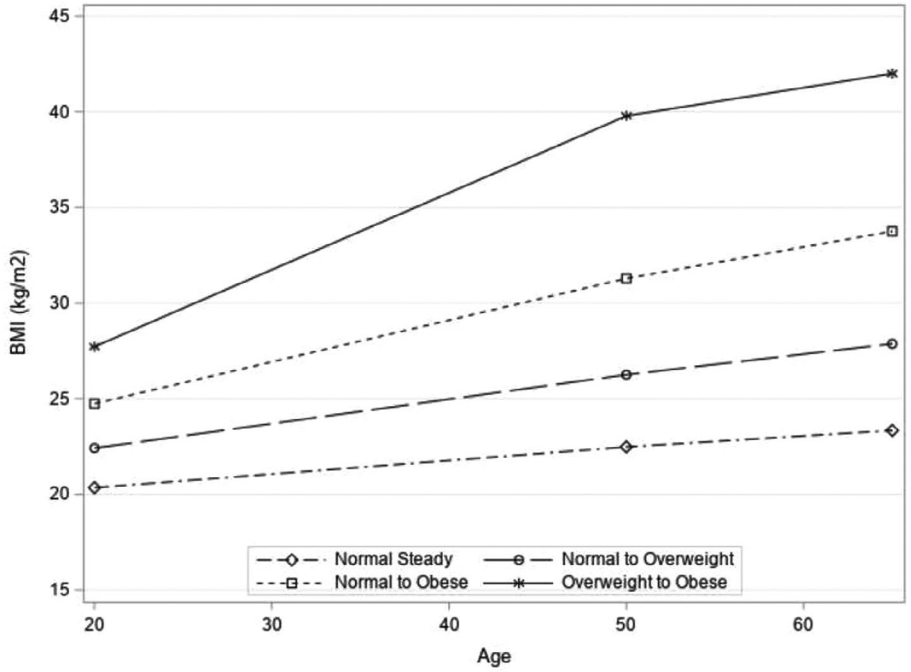

FIGURE 1 Adult life course BMI trajectories (steady normal weight [37.9%], normal weight to overweight [45.4%], normal weight to obesity [14.2%], and overweight to obesity [2.5%]) among participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, 1993 to 2009

records and death certificates. Pathology reports were retrieved to obtain the staging information of the cases.

Data collection

Study participants were asked to respond to the baseline questionnaire [17] that solicited information on age, sex, race, education, marital status, family history of pancreatic cancer, cigarette smoking, and diabetes. Self-reported weight (at ages 20, 50, and 55 to 74 years [baseline]) and height were also collected in the interview. The PLCO Cancer Screening Trial was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all participants [17].

Statistical analysis

BMI at the three time points was calculated by dividing weight in kilograms by height in meters squared. Age, sex (male, female), race (White non-Hispanic, Black non-Hispanic, Hispanic, Asian, other), marital status (married or cohabitating, single), education level (less than high school, high school graduate, some college, college graduate, postgraduate), cigarette smoking (never, former, current), and family history of pancreatic cancer (yes, no, possible) were compared among individuals who were free from pancreatic cancer, those who developed the disease, or those who were diagnosed with early-stage disease.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model for pancreatic cancer risk in relation to height (divided into quartiles, with quartile 1 as reference) and BMI variables. Specifically, the BMI variables included in our analysis were BMI at each of the three time points (ages 20, 50, and 55 to 74 years [baseline]), mean BMI of ages 20 and 50 years, mean BMI of the three time points, higher BMI at ages 20 and 50 years, maximum BMI at the three time points, and the time when BMI first exceeded 25 (never, at age 20 years, at age 50 years, or at baseline, with never as reference). In the analysis of all BMI variables (except the time when BMI first exceeded 25), the normal weight group (BMI: 18.5-24.9) was treated as reference to estimate HRs and 95% CIs for the underweight (BMI: <18.5), overweight (BMI: 25-29.9), and obesity (BMI: ≥30) groups. Individuals were divided into the four weight status groups according to the definition of the World Health Organization (WHO) [18]. Linear trends across categories of height and BMI variables were tested by modeling median value for each category as a continuous variable in Cox regression. All BMI variables were also analyzed as continuous variables to calculate HRs and 95% CIs for pancreatic cancer per 5-kg/m^2 increase in BMI. Time to event was calculated from the date of randomization to date of diagnosis with pancreatic cancer, death, diagnosis of another cancer (except nonmelanoma skin cancer), study dropout, or the censor date (December 31, 2009), whichever came earlier.

Trajectory groups were determined from the latent class growth models obtained by executing SAS PROC TRAJ (SAS Institute Inc,

TABLE 1 Baseline characteristics of study participants by diagnosis and stage of PC in the PLCO Cancer Screening Trial, 1993 to 2009[a]

	All participants ($n = 145,489$)	Total PC (1) ($n = 696$)	Early-stage PC (2) ($n = 311$)	Cancer free (3) ($n = 144,793$)	*p* value[b], (1) vs. (3)	*p* value[b], (2) vs. (3)
Age (y)	62.6 (5.4)	64.4 (5.2)	64.8 (5.0)	62.6 (5.4)	<0.0001	<0.001
Sex, *n* (%)					<0.0001	0.007
Male	71,673 (49.3)	400 (57.5)	177 (56.9)	71, 273 (49.2)		
Female	73,816 (50.7)	296 (42.5)	134 (43.1)	73,520 (50.8)		
Race/ethnicity, *n* (%)					0.66	0.46
White, Non-Hispanic	129,112 (88.8)	612 (87.9)	274 (88.1)	128,500 (88.8)		
Black, Non-Hispanic	7221 (5.0)	34 (4.9)	14 (4.5)	7187 (5.0)		
Hispanic	2658 (1.8)	14 (2.0)	4 (1.3)	2644 (1.8)		
Asian	5280 (3.6)	32 (4.6)	17 (5.5)	5248 (3.6)		
Other	1153 (0.8)	4 (0.6)	2 (0.6)	1149 (0.8)		
Education, *n* (%)					0.08	0.54
Less than high school	10,490 (7.2)	62 (8.9)	24 (7.7)	10,428 (7.2)		
High school graduate	51,616 (35.6)	237 (34.1)	112 (36.0)	51,379 (35.6)		
Some college	31,794 (21.9)	165 (23.7)	77 (24.8)	31,629 (21.9)		
College graduate	24,737 (17.0)	126 (18.1)	51 (16.4)	24,611 (17.0)		
Postgraduate	26,569 (18.3)	106 (15.2)	47 (15.1)	26,463 (18.3)		
Marital status, *n* (%)					0.63	0.71
Married or cohabiting	110,314 (76.0)	534 (76.7)	239 (76.9)	109,780 (75.9)		
Single	34,938 (24.1)	162 (23.3)	72 (23.1)	34,776 (24.1)		
Family history of PC, *n* (%)					0.05	0.18
Yes	3713 (2.6)	28 (4.1)	13 (4.2)	3685 (2.6)		
No	136,699 (94.6)	644 (93.2)	287 (93.2)	136,055 (94.6)		
Possible	4069 (2.8)	19 (2.7)	8 (2.6)	4050 (2.8)		
Cigarette smoking status, *n* (%)					<0.0001	0.004
Never smokers	67,157 (46.2)	274 (39.4)	130 (41.8)	66,883 (46.2)		
Former smokers	62,829 (43.2)	306 (44.0)	130 (41.8)	62,523 (43.2)		
Current smokers	15,487 (10.7)	116 (16.7)	51 (16.4)	15,371 (10.6)		
Cumulative amount (pack-year)	19.2 (27.9)	19.2 (27.9)	26.3 (35.0)	19.1 (27.9)	<0.0001	0.0004
BMI (kg/m^2)						
Age 20 years	22.1 (3.0)	22.3 (3.0)	22.2 (2.9)	22.1 (3.1)	0.030	0.66
Age 50 years	25.9 (4.3)	26.0 (4.3)	25.8 (4.0)	25.9 (4.3)	0.59	0.65
Age 55-74 years (baseline)	27.3 (4.9)	27.2 (4.5)	27.2 (4.2)	27.3 (4.9)	0.59	0.59
Comorbidity, *n* (%)						
Diabetes					<0.0001	0.016
Yes	11,083 (7.7)	84 (12.1)	20 (15.1)	10,999 (7.6)		
No	133,641 (92.3)	609 (87.9)	112 (84.9)	133,032 (92.4)		
Heart attack					0.0014	0.0064
Yes	13,130 (9.1)	87 (12.5)	22 (16.7)	13,043 (9.1)		
No	131,549 (90.9)	606 (87.5)	110 (83.3)	130,943 (90.9)		
Hypertension					0.0045	0.012
Yes	49,351 (34.1)	272 (39.2)	54 (40.9)	49,079 (34.1)		
No	95,416 (65.9)	422 (60.8)	78 (59.1)	94,994 (65.9)		
Stroke					0.73	0.84
Yes	3477 (2.4)	18 (2.6)	6 (4.5)	3459 (2.4)		
No	141,247 (97.6)	673 (97.4)	126 (95.5)	140,574 (97.6)		

(Continues)

TABLE 1 (Continued)

	All participants ($n = 145,489$)	Total PC (1) ($n = 696$)	Early-stage PC (2) ($n = 311$)	Cancer free (3) ($n = 144,793$)	p value[b], (1) vs. (3)	p value[b], (2) vs. (3)
Colon disease					0.54	0.46
Yes	2075 (1.4)	8 (1.2)	4 (3.1)	2067 (1.4)		
No	142,078 (98.6)	682 (98.8)	126 (96.9)	14,1396 (98.6)		
Gallbladder disease					0.031	0.98
Yes	16,677 (11.5)	98 (14.1)	11 (8.3)	16,579 (11.5)		
No	127,904 (88.5)	595 (85.9)	121 (91.7)	127,309 (88.5)		
Arthritis					0.19	0.81
Yes	54,936 (38.0)	280 (40.4)	48 (36.4)	54,656 (38.0)		
No	89,713 (62.0)	413 (59.6)	84 (63.6)	89,300 (62.0)		
Osteoporosis					0.26	0.26
Yes	76,44 (5.3)	30 (4.3)	6 (4.5)	7614 (5.3)		
No	136,846 (94.7)	661 (95.7)	126 (95.5)	136,185 (94.7)		
NSAID					0.31	0.43
Yes	86,129 (59.2)	399 (57.3)	82 (62.1)	85,730 (59.2)		
No	59,327 (40.8)	297 (42.7)	50 (37.8)	59,030 (40.8)		

Abbreviations: NSAID, nonsteroidal anti-inflammatory drugs; PC, pancreatic cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian.
[a]Values shown are means (SD) for continuous variables and percentages for categorical variables.
[b]p values are calculated using Student t test for continuous variables and χ^2 test for categorical variables.

Cary, North Carolina) [19]. The best-fitting model was established based on the Bayesian information criterion and using the guidelines proposed by Jones, Nagin, and Roeder [20] and group membership of at least 1%. Our analysis generated four BMI trajectory groups: steady normal weight (37.9%); normal weight to overweight (45.4%); normal weight to obesity (14.2%); and overweight to obesity (2.5%) (Figure 1). HRs (95% CIs) for pancreatic cancer risk in relation to BMI trajectory groups were also estimated by performing Cox proportional hazards regression analysis, with steady normal weight as reference.

Age, sex, race, cigarette smoking (pack-years), and family history of pancreatic cancer were adjusted for as confounders in the multivariate Cox regression models because of their established or suspected associations with BMI and pancreatic cancer. Randomization arm was also adjusted for to account for potential assignment bias. Diabetes was not considered as a confounder because it may lie on the causal pathway between obesity and pancreatic cancer. The interactions among considered covariates and BMI on pancreatic cancer risk were evaluated using the likelihood ratio test. No apparent interactions were detected in our data analysis. In all analyses, separate analysis was performed for early-stage pancreatic cancer because risk factors may be different for the initiation and progression of this malignancy.

The proportional hazards assumption was graphically tested for all of the models constructed, and none of them violated the assumption. SAS version 9.4 (SAS Institute) was used for statistical analysis, and a p value of <0.05 (two-sided) was considered statistically significant.

RESULTS

Table 1 shows that individuals who were diagnosed with pancreatic cancer during follow-up were slightly older and were more likely to be male, to be current or heavy smokers, to have diabetes, and to have a family history of pancreatic cancer than those who remained free from cancer. Similar differences in these characteristics were observed for individuals diagnosed with early-stage pancreatic cancer. Mean (SD) BMI values for all persons analyzed were 22.3 (3.0) at age 20 years, 26.0 (4.3) at age 50 years, and 27.2 (4.5) at baseline.

HRs (95% CIs) for height, BMI at the three time points examined, and time at which BMI first exceeded 25 in relation to total and early-stage pancreatic cancer are presented in Table 2. At age 50 years, individuals with obesity had a significantly increased risk of pancreatic cancer compared with those who had normal weight after adjustment for confounders (HR [95% CI]: 1.27 [1.01-1.60]). Individuals who had overweight at age 20 years experienced a marginally significantly elevated risk of pancreatic cancer (HR [95% CI]: 1.22 [0.99-1.50]). An approximately threefold increased risk of early-stage pancreatic cancer was observed for individuals with underweight compared with those with normal weight (HR [95% CI]: 2.97 [1.20-7.32]). After adjustment for confounders, height and time at which BMI first exceeded 25 were not significantly associated with total and early-stage pancreatic cancer, except for an increased risk of early-stage pancreatic cancer for individuals in the second quartile of height in comparison with those in the first (lowest) quartile (HR [95% CI]: 1.48 [1.01-2.18]).

TABLE 2 HRs and 95% CIs for height- and age-specific BMI in relation to risk of total and early-stage pancreatic cancer in the PLCO Cancer Screening Trial

	Total pancreatic cancer					Early-stage pancreatic cancer				
	Person-years	Cases	IR[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)	Person-years	Cases	IR[a]	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Height at baseline (cm)										
Q1: <163	330,015	122	37.0	Reference	Reference	329,449	42	12.7	Reference	Reference
Q2: 163-170	429,087	165	38.5	1.04 (0.82-1.32)	1.03 (0.81-1.31)	428,488	77	18.0	1.41 (0.97-2.05)	1.48 (1.01-2.18)
Q3: 171-177	371,266	166	44.7	1.21 (0.96-1.53)	1.01 (0.76-1.46)	370,522	65	17.5	1.38 (0.93-2.03)	1.30 (0.81-2.08)
Q4: >177	484,124	243	50.2	1.35 (1.09-1.68)	1.06 (0.77-1.46)	483,194	104	21.5	1.69 (1.18-2.41)	1.54 (0.92-2.58)
p value for trend				0.002	0.75				0.008	0.15
Continuous, per 5 cm				1.05 (1.01-1.09)	0.99 (0.93,1.04)				1.07 (1.01-1.13)	1.04 (0.95-1.13)
BMI (kg/m^2) at age 20 years										
<18.5	129,649	46	35.5	0.84 (0.62-1.13)	0.84 (0.62-1.14)	129,445	21	16.2	0.81 (0.51-1.30)	0.79 (0.49-1.28)
18.5--24.9	1,240,598	527	42.5	Reference	Reference	1,238,537	244	19.7	Reference	Reference
25-29.9	215,436	112	52.0	1.23 (1.00-1.51)	1.22 (0.99-1.50)	214,900	42	19.5	1.06 (0.76-1.48)	1.08 (0.77-1.52)
≥30	28,809	11	38.2	0.91 (0.50-1.66)	0.99 (0.55-1.81)	28,771	4	13.9	0.78 (0.29-2.09)	0.86 (0.32-2.30)
p value for trend				0.071	0.19				0.68	0.73
Continuous, per 5 kg/m^2				1.16 (1.03-1.30)	1.12 (0.98-1.27)				1.09 (0.91-1.31)	1.07 (0.87-1.30)
BMI (kg/m^2) at age 50 years										
<18.5	11,837	7	59.1	1.45 (0.69-3.07)	1.43 (0.68-3.03)	11,824	4	33.8	1.91 (0.71-5.17)	1.89 (0.70-5.11)
18.5-24.9	747,891	307	41.0	Reference	Reference	746,681	143	19.2	Reference	Reference
25-29.9	635,620	278	43.7	1.07 (0.91-1.26)	1.09 (0.93-1.29)	634,409	118	18.6	0.95 (0.74-1.22)	0.98 (0.76-1.27)
≥30	219,145	104	47.5	1.15 (0.94-1.47)	1.27 (1.01-1.60)	218,739	46	21.0	1.15 (0.81-1.61)	1.25 (0.88-1.79)
p value for trend				0.21	0.18				0.75	0.65
Continuous, per 5 kg/m^2				1.05 (0.96-1.14)	1.06 (0.97-1.17)				1.00 (0.87-1.15)	1.01 (0.87-1.18)
BMI (kg/m^2) at baseline										
<18.5	10,310	6	58.2	1.43 (0.64-3.22)	1.33 (0.59-2.99)	10,306	5	48.5	3.21 (1.30-7.91)	2.97 (1.20-7.32)
18.5-24.9	534,937	221	41.3	Reference	Reference	533,957	91	17.0	Reference	Reference
25-29.9	688,299	304	44.2	1.07 (0.90-1.27)	1.06 (0.89-1.27)	687,086	138	20.1	1.22 (0.93-1.61)	1.21 (0.91-1.60)
≥30	380,946	165	43.3	1.06 (0.87-1.30)	1.08 (0.88-1.33)	380,303	77	20.2	1.25 (0.91-1.71)	1.29 (0.93-1.77)
p value for trend				0.68	0.66				0.41	0.36
Continuous, per 5 kg/m^2				0.99 (0.92-1.08)	1.00 (0.92-1.09)				1.00 (0.88-1.12)	1.01 (0.89-1.14)
Time when BMI (kg/m^2) first exceeds 25										
Never	479,544	196	40.9	Reference	Reference	478,710	83	17.3	Reference	Reference
At baseline age	260,554	110	42.2	1.04 (0.82-1.31)	0.96 (0.76-1.22)	260,207	61	23.4	1.45 (1.03-2.04)	1.33 (0.95-1.88)
At age 50 years	630,148	267	42.4	1.04 (0.87-1.26)	1.06 (0.88-1.27)	629,064	121	19.2	1.11 (0.83-1.49)	1.12 (0.83-1.51)
At age 20 years	244,245	123	50.4	1.24 (0.99-1.56)	1.23 (0.98-1.55)	243,671	46	18.9	1.19 (0.82-1.72)	1.21 (0.83-1.76)

Abbreviations: HR, hazard ratio; IR, incidence rate; PLCO, Prostate, Lung, Colorectal, and Ovarian.

[a]Crude IR per 100,000 person-years.

[b]Adjusted for age, sex, race, family history of pancreatic cancer, smoking status, and randomization arm.

TABLE 3 HRs and 95% CIs for mean and maximum BMI at three time points in relation to risk of total and early-stage pancreatic cancer in the PLCO Cancer Screening Trial

	Total pancreatic cancer					Early-stage pancreatic cancer				
	Person-years	Cases	IR[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[2]	Person-years	Cases	IR[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
Mean BMI (kg/m^2) at age 20 years and age 50 years										
<18.5	19,787	7	35.4	0.85 (0.40-1.80)	0.92 (0.43-1.94)	19,778	5	25.3	1.43 (0.59-3.47)	1.53 (0.63-3.74)
18.5-24.9	1,093,869	458	41.9	Reference	Reference	1,092,052	213	19.5	Reference	Reference
25-29.9	424,035	194	45.8	1.10 (0.93-1.30)	1.09 (0.91-1.30)	423,156	77	18.2	0.96 (0.73-1.25)	0.94 (0.71-1.25)
≥30	76,802	37	48.2	1.17 (0.84-1.64)	1.23 (0.87-1.74)	76,667	16	20.9	1.19 (0.71-1.98)	1.28 (0.75-2.17)
p value for trend				0.16	0.16				0.95	0.89
Continuous, per 5 kg/m^2				1.11 (0.99-1.24)	1.11 (0.98-1.25)				1.04 (0.87-1.24)	1.04 (0.86-1.25)
Mean BMI (kg/m^2) at age 20 years, age 50 years, and baseline										
<18.5	9132	4	43.0	1.06 (0.40-2.84)	1.15 (0.43-3.08)	9129	3	32.9	1.88 (0.60-5.90)	2.04 (0.65-6.42)
18.5-24.9	888,620	370	41.6	Reference	Reference	887,142	169	19.0	Reference	Reference
25-29.9	581,978	262	45.0	1.09 (0.93-1.27)	1.05 (0.89-1.24)	580,870	116	20.0	1.04 (0.81-1.33)	1.00 (0.78-1.30)
≥30	134,763	60	44.5	1.09 (0.83-1.43)	1.12 (0.84-1.50)	134,513	23	17.1	0.99 (0.64-1.53)	1.07 (0.68-1.69)
p value for trend				0.35	0.39				0.92	0.98
Continuous, per 5 kg/m^2				1.06 (0.96-1.18)	1.06 (0.95-1.19)				1.02 (0.87-1.20)	1.03 (0.86-1.23)
Higher BMI (kg/m^2) at age 20 years and age 50 years										
<18.5	7150	4	55.9	1.37 (0.51-3.67)	1.42 (0.53-3.80)	7147	3	42.0	2.36 (0.75-7.41)	2.45 (0.78-7.71)
18.5-24.9	732,948	302	41.2	Reference	Reference	731,771	141	19.3	Reference	Reference
25-29.9	648,313	285	44.0	1.07 (0.91-1.26)	1.03 (0.87-1.22)	647,066	121	18.7	0.95 (0.74-1.23)	0.93 (0.71-1.20)
≥30	226,081	105	46.4	1.15 (0.92-1.43)	1.19 (0.94-1.50)	225,669	46	20.4	1.10 (0.78-1.55)	1.15 (0.81-1.61)
p value for trend				0.24	0.22				0.87	0.77
Continuous, per 5 kg/m^2				1.04 (0.96-1.14)	1.06 (0.96-1.16)				0.99 (0.86-1.13)	1.00 (0.86-1.16)
Maximum BMI (kg/m^2) at age 20 years, age 50 years, and baseline										
<18.5	2972	2	67.3	1.68 (0.42-6.74)	1.69 (0.42-6.80)	2969	1	33.7	2.19 (0.30-15.74)	2.21 (0.31-15.89)
18.5-24.9	476,572	194	40.7	Reference	Reference	475,742	82	17.2	Reference	Reference
25-29.9	714,089	309	43.3	1.07 (0.89-1.27)	1.00 (0.83-1.20)	712,854	143	20.1	1.20 (0.90-1.60)	1.14 (0.85-1.53)
≥30	420,859	191	45.4	1.13 (0.93-1.38)	1.09 (0.89-1.34)	420,089	85	20.2	1.24 (0.90-1.70)	1.20 (0.87-1.66)
p value for trend				0.26	0.43				0.24	0.33
Continuous, per 5 kg/m^2				1.03 (0.95-1.11)	1.02 (0.94-1.11)				1.01 (0.89-1.13)	1.00 (0.88-1.14)

Abbreviations: HR, hazard ratio; IR, incidence rate; PLCO, Prostate, Lung, Colorectal, and Ovarian.

[a]Crude IR per 100,00 person-years.

[b]Adjusted for age, sex, race, family history of pancreatic cancer, smoking status, and randomization arm.

TABLE 4 Adult BMI trajectory in relation to risk of total and early-stage pancreatic cancer in the PLCO Cancer Screening Trial

BMI trajectory	Total pancreatic cancer					Early-stage pancreatic cancer				
	Person-years	Cases	IR[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[b]	Person-years	Cases	IR[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
Steady normal weight	613,574	249	40.6	Reference	Reference	612,561	113	18.4	Reference	Reference
Normal weight to overweight	746,244	336	45.0	1.11 (0.94-1.31)	1.06 (0.90-1.26)	744,823	146	19.6	1.05 (0.82-1.36)	1.01 (0.77-1.31)
Normal weight to obesity	216,992	94	43.3	1.08 (0.85-1.37)	1.04 (0.81-1.34)	216,655	47	21.7	1.20 (0.84-1.70)	1.18 (0.82-1.71)
Overweight to obesity	37,681	17	45.1	1.14 (0.70-1.87)	1.43 (0.87-2.34)	37,614	5	13.3	0.79 (0.32-1.94)	1.01 (0.41-2.48)

Abbreviations: HR, hazard ratio; IR, incidence rate; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer.

[a]Crude IR per 100,00 person-years.

[b]Adjusted for age, race, sex, family history of pancreatic cancer, smoking status, and randomization arm.

Risk estimates for total and early-stage pancreatic cancer in relation to mean, higher, or maximum BMI measured at two or three time points are presented in Table 3. There were no statistically significant associations of mean BMI at age 20 and age 50 years; mean BMI at age 20 years, age 50 years, and baseline; higher BMI at age 20 and age 50 years; and maximum BMI at age 20 years, age 50 years, and baseline with the risk of total and early-stage pancreatic cancer in multivariable Cox regression analysis. Four BMI trajectory groups were identified in our statistical analysis: steady normal weight, normal weight to overweight, normal weight to obesity, and overweight to obesity (Figure 1). Compared with individuals who maintained a steady normal weight during follow-up, no significantly altered risk of total and early-stage pancreatic cancer was observed for those whose weight status was changed from normal weight to overweight, from normal weight to obesity, and from overweight to obesity (Table 4).

DISCUSSION

In the present study, we found that overweight at age 20 years or obesity at age 50 years was associated with an increased risk of pancreatic cancer compared with normal weight at the two respective time points, although risk estimates for the association with BMI at age 20 years were borderline statistically significant. An elevated risk of early-stage pancreatic cancer was identified for individuals who had underweight at baseline (mean age: 62.6 years). Furthermore, prediagnostic adulthood BMI trajectory was not associated with pancreatic cancer risk.

The biological mechanisms for the effect of overweight and obesity on pancreatic carcinogenesis have been discussed earlier. Despite the biological plausibility for the associations of overweight and obesity with pancreatic cancer risk, the results of epidemiological studies have been inconsistent. Specifically, an increased risk of pancreatic cancer associated with overweight and obesity have been observed in some, but not all, epidemiological studies [9–11]. One of the potential reasons for the discrepant results is that most previous studies have evaluated BMI measured at a single time point (at baseline for cohort studies and at the time of study for case–control studies) in relation to the risk of pancreatic cancer [21–23]. Although it is biologically reasonable that changes in body weight over an extended period of time are more relevant to the etiology of pancreatic cancer than weight assessed at one time point, relatively fewer epidemiological studies have explored the influence of life-span BMI on the development of this malignancy [12, 13]. The present analysis was thus performed to fill in this gap in the research of pancreatic cancer etiology.

In the PLCO Cancer Screening Trial, we revealed that having overweight at early adulthood and having obesity at middle adulthood were likely to confer an elevated risk for pancreatic cancer later in life. Our findings are in agreement with those of studies conducted in Canadian, Chinese, and European populations [24–26] but are not confirmed in Japanese women [27]. Multiple factors may account for the inconsistent results of the association between life-span BMI and pancreatic cancer risk across previous studies, including

differences in the validity of weight and height data, time points at which BMI was assessed, the number of cases analyzed, and confounding control. We also observed an approximately threefold increased risk of pancreatic cancer among individuals who had underweight at baseline compared with those who had normal weight. This risk elevation might have occurred because of potential underlying chronic diseases in individuals with underweight or imprecise risk estimates resulting from a small number of the individuals who had underweight and were diagnosed with pancreatic cancer during follow-up ($n = 5$).

Our analysis did not show significant associations among mean, higher, and maximum BMI from the three time points (age 20 years, age 50 years, and baseline [mean age: 62.6 years]) and total or early-stage pancreatic cancer risk, regardless of whether BMI was treated as both a categorical (4 groups) or continuous (per 5-unit increase) variable in the regression models. This observation was contrary to the results of a case–control study in which a per five-unit increase in mean BMI from ages 14 to 59 years was associated with a significant 55% elevated risk of pancreatic cancer [28]. These divergent findings might have arisen from differences in study design, confounding adjustment, and accuracy of BMI data. In that case–control study, participants were asked to recall their usual and current height and weight starting from ages 14 to 19 years and continuing over 10-year intervals until the year prior to enrollment [28]. However, information was not provided on whether the participants were able to accurately recall their weights every 10 years. The present study did not find a significant association among maximum lifetime BMI and pancreatic cancer risk, which was consistent with the findings of some [12, 24], but not all [13, 14], studies.

In the PLCO Cancer Screening Trial, we did not find a significant association between lifetime BMI trajectory and pancreatic cancer risk. The results of the present study were similar to those of several previous studies [14, 29, 30]. Song et al. evaluated body shape trajectory in early and middle life in relation to the risk of pancreatic cancer and other cancers in the Nurses' Health Study and Health Professionals Follow-Up Study. Participants were asked to recall their body shape from ages 5 up to 60 years by choosing one of nine pictorial body diagrams. Compared with individuals in the lean-stable trajectory, no significantly altered risk of pancreatic cancer was detected for those in lean-moderate, lean-marked increase, medium-stable/increase, and heavy-stable/increase trajectories [14]. In addition, there was not a significantly elevated risk of pancreatic cancer associated with overweight and obesity duration (per 10 years) in the observational study of the Women's Health Initiative [13] nor weight changes (per 5 kg increase) since age 20 years in the Shanghai Women's Health Study [29]. As a main determinant of body weight, physical activity levels have been associated with a reduced risk of pancreatic cancer in previous studies [31, 32]. However, little is known about the impact of lifetime physical activity trajectory on pancreatic cancer risk. A population-based case–control study conducted in Ontario, Canada did not provide evidence that changes in moderate and vigorous physical activity across young adulthood, mid-adulthood, and old-adulthood were associated with pancreatic cancer risk [30]. A common weakness in most previous studies was that trajectories of weight, body shape, and physical activity were characterized by using self-reported data collected at a small number of time points. To further estimate the influence of BMI trajectory on pancreatic cancer risk, it is necessary to conduct more prospective cohort studies in which weight and height are accurately measured at multiple time points across the adult life course.

The present study has several advantages. Our results were obtained after an analysis of BMI data collected from a large prospective cohort study of men and women at their young, middle, and old adulthoods who were recruited from 10 medical centers across the US. Almost all suspected and established confounders for the associations of interest were considered and adjusted for in the regression models. Recall bias is unlikely to substantially distort our risk estimates because individuals were free from pancreatic cancer and were unaware of our study hypothesis when they were asked to recall their weight and/or height at age 20 years, age 50 years, and enrollment. Selection bias is uncommon in prospective cohort studies. In the PLCO Cancer Screening Trial, only 3.5% of participants withdrew from the screening trial, were lost to follow-up, or were unable to remain in the cohort owing to the development of medical conditions [33]. This extremely low rate of dropout suggests that the influence of selection bias (if any) on our obtained results should be small. We have also evaluated the associations of BMI trajectory with both total pancreatic cancer and early-stage pancreatic cancer, a subset of the tumor that is potentially curable by surgery, and thus have a remarkably better prognosis.

We also performed competing risk analysis and investigated the influence of diabetes on our risk estimates. After additionally censoring other types of cancer in the competing risk models, a marginally significantly increased risk of pancreatic cancer among individuals with overweight at age 20 years and a significantly increased risk among those with obesity at age 50 years no longer existed. Although reasons for these changes of results are unclear, it is reasonable to speculate that the individuals who were diagnosed with other types of cancer during follow-up and were thereby censored were more likely to have overweight or obesity and have a higher risk of developing pancreatic cancer than those who were not. There was a significant threefold elevated risk of early-stage pancreatic cancer among individuals with underweight at baseline. However, HRs could not be estimated for that group of people, as there were not any cases in that category after those diagnosed with other cancers were censored in the competing risk models. An analysis of individuals without diabetes at baseline yielded results that were overall similar to those obtained from the competing risk analysis. These findings are not surprising because overweight and obesity are risk factors for diabetes that have been associated with an elevated risk of pancreatic cancer [4, 34].

Some limitations of the present study should be taken into account. In the PLCO Cancer Screening Trial, weight and height at the three time points examined were self-reported by participants. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) indicated that men tended to overestimate their past weight, but the opposite results were observed for women [35].

A validation study conducted among 1931 NHANES participants demonstrated a strong correlation between weight measured in 1971 to 1975 and weight recalled for the same time period during the follow-up interview in 1982 to 1984 ($r = 0.73$ for men and $r = 0.74$ for women) [35]. The findings of this validation study suggest that the influence of potential recall bias for weight among PLCO Cancer Screening Trial participants on those of the present study should not be consequential. The numbers of cases were small for the separate analysis of early-stage pancreatic cancer, especially for those who were in the categories of underweight, obesity, or overweight to obesity trajectory, which could have somewhat reduced the precision of our risk estimates obtained. In addition, the small number of cases may account, at least in part, for our observed null association of interest among individuals with obesity at age 20 years. An Israeli national cohort study found that adolescents (ages 16-19 years) with obesity experienced a more than threefold significantly increased risk of pancreatic cancer [36]. It is etiologically important to investigate BMI trajectory across the life-span, from childhood to late adulthood. However, a lack of BMI data in childhood and adolescence for PLCO Cancer Screening Trial participants precluded us from performing such an analysis. Central obesity may play a more critical role in the development of pancreatic cancer than overall obesity [37], but data on indicators of central obesity (e.g., waist circumference) were not available from the PLCO Cancer Screening Trial. Residual confounding due to inadequately measured or uncontrolled factors should always be considered in any observational studies. Comorbidities and medication use might have influenced the weight status of PLCO Cancer Screening Trial participants and thereby may have possibly resulted in a reverse causality for our observed associations between BMI and pancreatic cancer. However, the reverse causality is unlikely to occur because additional adjustment for diseases (i.e., heart attack, hypertension, stroke, colon polyps, gallbladder disease, arthritis, and osteoporosis) associated with overweight and obesity in epidemiological studies [38, 39] and nonsteroidal anti-inflammatory drugs (the only medications with data available from the PLCO Cancer Screening Trial) did not materially alter our obtained risk estimates.

Although the participants were recruited from 10 locations across the US, potential sampling bias might have compromised the extrapolation of our obtained results to the overall population. A recent study reported increasing trends in pancreatic cancer incidence in both sexes during the period from 2000 to 2018 [40]. This increase was more remarkable among women aged 55 years or younger, especially among those aged 15 to 34 years. Despite unknown reasons, the changing epidemiology of pancreatic cancer observed in that study suggests that our findings derived from PLCO Cancer Screening Trial participants who were recruited at the age of 55 74 years in 1993 to 2001 might not be generalized to individuals who were diagnosed with this tumor at the age of 55 years or younger after 2000. Finally, a number of HRs have been calculated for the associations evaluated in the present analysis. Therefore, chance findings arising from multiple comparisons could not be entirely ruled out for our obtained results and should be cautiously considered in data interpretation.

In summary, the present study has shown a marginally significant positive association of overweight in young adulthood and a significant positive association of obesity in middle adulthood with pancreatic cancer risk in a US national prospective cohort study. A significantly increased risk of pancreatic cancer was also observed for the individuals who had underweight at baseline, although this association was based on a small number of cases. These associations became nonstatistically significant when the diagnosis of other cancers was censored and when patients with diabetes identified at baseline were excluded from the analysis. However, it should be pointed out that these additional analyses tended to underestimate the true magnitude of the associations examined. We did not find a significant association between BMI trajectory and pancreatic cancer risk in the PLCO Cancer Screening Trial. The influence of BMI trajectory on pancreatic cancer merits further investigation in large prospective cohort studies with longitudinal and objective measurements of BMI across the life course. Such research has tremendous public health impact, as it may reduce incidence and mortality of pancreatic cancer through maintenance of a lifelong healthy weight through modifications of diet and other lifestyle factors.O

AUTHOR CONTRIBUTIONS

Margaret Hoyt, Jianjun Zhang, Yiqing Song, Sujuan Gao, and Jacquelynn O'Palka designed research and were involved in the critical revision of the manuscript; Margaret Hoyt and Jianjun Zhang conducted research; Margaret Hoyt analyzed data; and Margaret Hoyt and Jianjun Zhang wrote the paper. Jianjun Zhang had primary responsibility for final content. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We thank the National Cancer Institute for access to data collected by the PLCO Cancer Screening Trial. The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the National Cancer Institute.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

ORCID

Margaret Hoyt https://orcid.org/0000-0002-9486-2095
Jianjun Zhang https://orcid.org/0000-0003-2179-2388

REFERENCES

1. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet*. 2020;395:200-2020.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74:2913-2921.
3. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. *Am Fam Physician*. 2006;73:485-492.
4. Krejs GJ. Pancreatic cancer: epidemiology and risk factors. *Dig Dis*. 2010;28:355-358.

5. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA*. 2018;319:1723-1725.
6. Bracci PM. Obesity and pancreatic cancer: overview of epidemiologic evidence and biologic mechanisms. *Mol Carcinog*. 2012;51:53-63.
7. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med*. 2010; 61:301-316.
8. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. *NCHS Data Brief*, no. 288. National Institute of Health Statistics; 2017.
9. de Gonzalez AB, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer*. 2003;89:519-523.
10. Dobbins M, Decorby K, BJIpm C. The association between obesity and cancer risk: a meta-analysis of observational studies from 1985 to 2011. *Int Sch Res Notices*. 2013;2013:680536. doi:10.5402/2013/680536.
11. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. *Int J Cancer*. 2007; 120:1993-1998.
12. Stolzenberg-Solomon RZ, Schairer C, Moore S, Hollenbeck A, Silverman DT. Lifetime adiposity and risk of pancreatic cancer in the NIH-AARP diet and health study cohort. *Am J Clin Nutr*. 2013;98: 1057-1065.
13. Arnold M, Jiang L, Stefanick ML, et al. Duration of adulthood overweight, obesity, and cancer risk in the Women's Health Initiative: a longitudinal study from the United States. *PLoS Med*. 2016;13: e1002081. doi:10.1371/journal.pmed.1002081.
14. Song M, Willett WC, Hu FB, et al. Trajectory of body shape across the lifespan and cancer risk. *Int J Cancer*. 2016;138:2383-2395.
15. Zhu CS, Pinsky PF, Kramer BS, et al. The prostate, lung, colorectal, and ovarian cancer screening trial and its associated research resource. *J Natl Cancer Inst*. 2013;105:1684-1693.
16. Petrick JL, Kelly SP, Liao LM, Freedman ND, Graubard BI, Cook MB. Body weight trajectories and risk of oesophageal and gastric cardia adenocarcinomas: a pooled analysis of NIH-AARP and PLCO studies. *Br J Cancer*. 2017;116:951-959.
17. United States Department of Health and Human Services. PLCO-404: Interaction of Calcium Intake and Obesity on Pancreatic Cancer in the PLCO Trial: Data Dictionary. United States Department of Health and Human Services; 2018. https://cdas.cancer.gov/approved-projects/1945/
18. Weir CB, Jan A. BMI Classification Percentile and Cut off Points. StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK541070/
19. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. *Sociol Methods Res*. 2007; 35:542-571.
20. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociol Methods Res*. 2001;29:374-393.
21. Arslan AA, Helzlsouer KJ, Kooperberg C, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). *Arch Intern Med*. 2010;170:791-802.
22. Luo J, Iwasaki M, Inoue M, et al. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan–the JPHC study. *Cancer Causes Control*. 2007;18:603-612.
23. Rawla P, Thandra KC, Sunkara T. Pancreatic cancer and obesity: epidemiology, mechanism, and preventive strategies. *Clin J Gastroenterol*. 2019;12:285-291.
24. De Rubeis V, Cotterchio M, Smith BT, et al. Trajectories of body mass index, from adolescence to older adulthood, and pancreatic cancer risk; a population-based case–control study in Ontario, Canada. *Cancer Causes Control*. 2019;30:955-966.
25. Pang Y, Holmes MV, Kartsonaki C, et al. Young adulthood and adulthood adiposity in relation to incidence of pancreatic cancer: a prospective study of 0.5 million Chinese adults and a meta-analysis. *J Epidemiol Community Health*. 2017;71:1059-1067.
26. Urayama KY, Holcatova I, Janout V, et al. Body mass index and body size in early adulthood and risk of pancreatic cancer in a central European multicenter case–control study. *Int J Cancer*. 2011;129:2875-2884.
27. Koyanagi YN, Matsuo K, Ito H, et al. Body-mass index and pancreatic cancer incidence: a pooled analysis of nine population-based cohort studies with more than 340,000 Japanese subjects. *J Epidemiol*. 2018;28:245-252.
28. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA*. 2009;301:2553-2562.
29. Liu Y, Warren Andersen S, Wen W, et al. Prospective cohort study of general and central obesity, weight change trajectory and risk of major cancers among Chinese women. *Int J Cancer*. 2016;139:1461-1470.
30. Sandhu J, De Rubeis V, Cotterchio M, et al. Trajectories of physical activity, from young adulthood to older adulthood, and pancreatic cancer risk; a population-based case-control study in Ontario, Canada. *BMC Cancer*. 2020;20:139. doi:10.1186/s12885-020-6627-8
31. Behrens G, Jochem C, Schmid D, Keimling M, Ricci C, Leitzmann MF. Physical activity and risk of pancreatic cancer: a systematic review and meta-analysis. *Eur J Epidemiol*. 2015;30:279-298.
32. Farris MS, Mosli MH, McFadden AA, Friedenreich CM, Brenner DR. The association between leisure time physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2015;24:1462-1473.
33. Pretzel SM, Andrews TS, Broski K, et al. Participants' views of retention materials used in the PLCO cancer screening trial. *Clin Med Res*. 2015;13:139-148.
34. Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. *Endocrinol Metab Clin*. 2003;32:805-822.
35. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of self-reports of past body weights by US adults. *Epidemiology*. 1995;6:61-66.
36. Furer A, Afek A, Sommer A, et al. Adolescent obesity and midlife cancer risk: a population-based cohort study of 2· 3 million adolescents in Israel. *Lancet Diabetes Endocrinol*. 2020;8:216-225.
37. Genkinger JM, Kitahara CM, Bernstein L, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. *Ann Oncol*. 2015;26:2257-2266.
38. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med*. 1995;122:327-334.
39. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA*. 1999;282:1523-1529.
40. Gaddam S, Abboud Y, Oh J, et al. Incidence of pancreatic cancer by age and sex in the US, 2000-2018. *JAMA*. 2021;326:2075-2077.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hoyt M, Song Y, Gao S, O'Palka J, Zhang J. Prediagnostic BMI trajectories in relation to pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Obesity (Silver Spring)*. 2022; 30(11):2275-2285. doi:10.1002/oby.23550