Annals of Oncology 26: 2257–2266, 2015
doi:10.1093/annonc/mdv355
Published online 7 September 2015

Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies

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Received 15 April 2015; revised 7 August 2015; accepted 16 August 2015

Background: Body mass index (BMI), a measure of obesity typically assessed in middle age or later, is known to be positively associated with pancreatic cancer. However, little evidence exists regarding the influence of central adiposity, a high BMI during early adulthood, and weight gain after early adulthood on pancreatic cancer risk.

Design: We conducted a pooled analysis of individual-level data from 20 prospective cohort studies in the National Cancer Institute BMI and Mortality Cohort Consortium to examine the association of pancreatic cancer mortality with measures of central adiposity (e.g. waist circumference; $n = 647\,478$; 1947 pancreatic cancer deaths), BMI during early adulthood (ages 18–21 years) and BMI change between early adulthood and cohort enrollment, mostly in middle age or later ($n = 1\,096\,492$; 3223 pancreatic cancer deaths). Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models.

Results: Higher waist-to-hip ratio (HR = 1.09, 95% CI 1.02–1.17 per 0.1 increment) and waist circumference (HR = 1.07, 95% CI 1.00–1.14 per 10 cm) were associated with increased risk of pancreatic cancer mortality, even when adjusted for BMI at baseline. BMI during early adulthood was associated with increased pancreatic cancer mortality (HR = 1.18, 95% CI 1.11–1.25 per 5 kg/m^2), with increased risk observed in both overweight and obese individuals (compared with BMI of

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21.0 to <23 kg/m^2, HR = 1.36, 95% CI 1.20–1.55 for BMI 25.0 < 27.5 kg/m^2, HR = 1.48, 95% CI 1.20–1.84 for BMI 27.5 to <30 kg/m^2, HR = 1.43, 95% CI 1.11–1.85 for BMI ≥30 kg/m^2). BMI gain after early adulthood, adjusted for early adult BMI, was less strongly associated with pancreatic cancer mortality (HR = 1.05, 95% CI 1.01–1.10 per 5 kg/m^2).

Conclusions: Our results support an association between pancreatic cancer mortality and central obesity, independent of BMI, and also suggest that being overweight or obese during early adulthood may be important in influencing pancreatic cancer mortality risk later in life.

Key words: central adiposity, BMI, pancreatic cancer, pooled analysis

introduction

Pancreatic cancer is the sixth most common cause of cancer death in the world [1] and has the highest case fatality of any major cancer [2, 3]; only 6% of individuals diagnosed with pancreatic cancer survive past 5 years [2]. Despite declines in cigarette smoking, an important pancreatic cancer risk factor, pancreatic cancer mortality rates are increasing both in the United States [4] and in Western Europe [5]. Identifying modifiable risk factors is crucial for reducing morbidity and mortality from this cancer.

Body mass index (BMI), usually measured in middle or late adulthood, has been positively associated with pancreatic cancer incidence and mortality in most studies [6–11], and an expert panel convened by the World Cancer Research Fund (WCRF) stated the evidence linking increasing BMI to pancreatic cancer risk is convincing [6, 10]. Recently, a meta-analysis including 9504 pancreatic cancer cases and a pooled analysis including 2135 pancreatic cancer cases, reported a 10% and 14% increase in risk for each 5 kg/m^2 incremental increase in BMI, respectively [12, 13]. Much less is known about the associations of other measures of obesity, including central adiposity and the influence of obesity earlier in life, with pancreatic cancer.

Central obesity, as measured by waist circumference or waist-to-hip ratio, could plausibly contribute to pancreatic cancer risk beyond its contribution to overall obesity, as measured by BMI. Prior studies report a larger waist circumference and waist-to-hip ratio to be positively associated, independently of BMI, with insulin resistance and diabetes [14–19], which are both risk factors for pancreatic cancer [6, 20–25]. Only a few studies have reported on measures of central obesity and pancreatic cancer and results have been somewhat inconsistent. Since 2010, two pooled analyses [7, 13] and one meta-analysis [12], each including ~500–1000 cases of pancreatic cancer, have each reported that higher waist-to-hip ratio was associated with statistically significant higher risk, whereas waist circumference was positively and statistically significantly associated with higher pancreatic cancer risk only in one analysis [12]. In only one of these analyses [13] were associations with measures of central obesity adjusted for BMI. Owing to the relatively small size of those prior analyses, important uncertainties remain about the magnitude of these associations, and whether central obesity measures predict risk independent of BMI.

Two large analyses of prospective data have carefully examined timing of obesity [9, 13] and changes in obesity in relation to pancreatic cancer risk. BMI during early adulthood (ages 18–21 years) was positively associated with pancreatic cancer risk in both analyses, but results were not consistent for BMI gain [9, 13] after early adulthood. Owing to limited case numbers, neither analysis was able to examine obesity at early adulthood (BMI ≥30 kg/m^2).

In the National Cancer Institute's BMI and Mortality Cohort Consortium, the largest study to date, we examined the associations between pancreatic cancer mortality and two measures of central obesity (waist circumference and waist-to-hip ratio) and two measures related to timing of obesity (BMI during early adulthood and change in BMI after early adulthood) [26]. Inclusion of six additional cohort studies that were not included in the two prior pooled analyses [7, 13] provided greater statistical power to examine more extreme categories of these anthropometric exposures (e.g. a BMI ≥30 kg/m^2 during early adulthood), timing of obesity and to examine whether associations differed by a priori effect measure modifiers.

methods

study population

We conducted a pooled analysis using individual-level data from the following 20 cohorts: NIH-AARP Diet and Health Study (AARP) [27], Adventist Health Study (AHS-1) [28], Agricultural Health Study (AHS) [29], Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP) [30], California Teachers Study (CTS) [31], Cancer Prevention Study-II Nutrition Cohort (CPS) [32], CLUE II (CLUE) [33], Cohort of Swedish Men (COSM) [34], Health Professionals Follow-up Study (HPFS) [35], Iowa Women's Health Study (IWHS) [36], Melbourne Collaborative Cohort Study (MCCS) [37], Nurses' Health Study (NHS) [35], New York University Women's Health Study (NYUWHS) [23], Physicians' Health Study (PHS) [38], Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO) [39], Swedish Mammography Cohort (SMC) [34], U.S. Radiologic Technologists Study (USRT) [40], Vitamins and Lifestyle Study (VITAL) [41], Women's Health Study (WHS) [42], and Women's Lifestyle and Health Study (WLHS) [43] (Table 1). We utilized a later questionnaire as the baseline for questionnaire data and the start of follow-up for five cohorts (BCDDP, CPS, NHS, SMC, and USRT), rather than the cohort's first questionnaire, because the later questionnaire was the first time information on key variables (e.g. waist and hip circumference) or comorbidities (e.g. cancer) was available.

exposure assessment

All but one cohort study collected information on height and weight at baseline by self-report; the MCCS measured height and weight [44]. Fourteen studies collected self-reported, recalled weight during early adulthood (between ages 18 and 21). Twelve studies collected self-reported or measured waist and/or hip circumference. Most cohorts ascertained information on important covariates for pancreatic cancer, including smoking history, education, marital status, alcohol consumption, diabetes, and physical activity level.

Table 1. Baseline characteristics and median (interquartile range) values for anthropometric factors by cohort

Cohort	Sex	Follow-up years median (max)	Baseline cohort size[a]	Deaths, *N*	Baseline age range	Median (interquartile range)					
						Waist circumference (cm)	Waist-to-hip ratio	BMI at baseline (kg/m^2)	BMI at early adulthood (kg/m^2)	BMI change (kg/m^2)	Height (cm)
AARP	M	10 (11)	304 632	920	50–71	97 (90–104)	0.95 (0.91–0.99)	27 (24–29)	21 (20–24)	5 (3–8)	178 (173–183)
	F	10 (11)	195 222	439	50–71	83 (75–92)	0.81 (0.76–0.86)	26 (23–30)	20 (19–22)	5 (2–9)	163 (158–168)
AHS-1	M	12 (22)	11 845	36	25–83	**	**	25 (23–27)	**	**	178 (173–183)
	F	12 (22)	16 609	33	25–83	**	**	23 (21–27)	**	**	163 (157–168)
AHS	M	11 (14)	20 536	28	19–83	**	**	27 (25–30)	23 (21–25)	3 (2–6)	178 (175–185)
	F	10 (14)	21 718	19	19–83	**	**	25 (22–28)	21 (19–22)	4 (2–7)	165 (160–170)
BCDDP	F	3 (19)	36 055	162	42–83	81 (74–89)	0.79 (0.74–0.85)	25 (22–28)	**	**	163 (157–168)
CLUE	M	14 (19)	8678	31	19–83	**	**	26 (24–29)	23 (21–25)	3 (1–6)	178 (173–183)
	F	14 (19)	11 696	40	19–83	**	**	25 (22–29)	21 (19–23)	4 (1–7)	163 (157–168)
COSM	M	10 (10)	43 157	134	45–79	95 (90–102)	0.94 (0.90–0.98)	25 (24–28)	22 (20–23)	4 (2–6)	177 (173–182)
CPS	M	10 (11)	54 807	269	46–83	97 (91–105)	**	26 (24–29)	22 (20–24)	4 (2–7)	178 (175–183)
	F	11 (11)	66 113	242	45–83	85 (76–94)	**	25 (22–28)	20 (19–22)	5 (2–8)	163 (160–168)
CTS	F	9 (9)	111 235	124	22–83	79 (72–89)	0.79 (0.75–0.85)	24 (21–27)	21 (19–23)	3 (1–6)	165 (160–168)
HPFS	M	17 (23)	48 066	280	38–78	94 (89–100)	0.93 (0.90–0.97)	25 (24–27)	23 (21–24)	2 (1–4)	178 (172–183)
IWHS	F	19 (19)	37 864	252	52–71	68 (61–76)	0.83 (0.78–0.89)	25 (23–29)	21 (19–22)	5 (2–8)	163 (157–168)
MCCS	M	15 (18)	15 667	39	28–75	93 (87–99)	0.92 (0.88–0.96)	27 (25–29)	22 (21–24)	4 (2–7)	172 (168–178)
	F	15 (18)	22 348	43	31–76	78 (71–87)	0.78 (0.74–0.83)	26 (23–29)	21 (20–23)	5 (2–8)	160 (155–164)
NHS	F	26 (28)	93 843	419	29–56	**	**	23 (21–27)	21 (19–23)	2 (1–5)	163 (160–168)
NYUWHS	F	19 (20)	13 390	41	31–70	73 (67–82)	0.75 (0.71–0.80)	24 (22–27)	**	**	163 (158–168)
PHS	M	22 (26)	28 272	147	39–83	**	**	25 (23–27)	**	**	178 (173–183)
PLCO	M	9 (13)	70 622	273	53–78	**	**	27 (25–30)	23 (21–24)	4 (2–7)	178 (173–183)
	F	9 (13)	69 819	168	50–78	**	**	26 (23–30)	21 (20–22)	5 (3–8)	163 (157–168)
SMC	F	10 (10)	33 936	100	48–83	82 (76–90)	0.81 (0.77–0.85)	24 (22–27)	20 (19–22)	4 (2–6)	165 (161–168)
USRT	M	5 (7)	19 105	16	33–83	**	**	27 (24–29)	**	**	178 (173–183)
	F	6 (7)	63 214	15	31–83	**	**	24 (22–27)	**	**	165 (160–168)
VITAL	M	6 (7)	31 384	41	50–76	**	**	27 (25–30)	22 (20–24)	5 (3–8)	180 (175–183)
	F	6 (7)	31 237	41	50–76	**	**	26 (23–30)	20 (19–22)	6 (3–9)	165 (160–168)
WHS	F	13 (15)	38 927	66	38–83	**	**	25 (22–28)	**	**	165 (160–168)
WLH	F	15 (15)	44 221	27	30–50	75 (70–81)	0.77 (0.74–0.81)	23 (21–25)	20 (19–22)	3 (1–5)	166 (162–170)

Studies which have a ** did not ask on their questionnaire or measure that anthropometric factor.

[a]Baseline cohort size determined after specific exclusions (i.e. younger than 18 and older than 85 years at baseline, had less than 1 year of follow-up, had a prevalent cancer, had missing or extreme values of BMI (<15.0 or >59.9 kg/m^2), or had extreme values of height (<122 or >244 cm).

AARP, NIH-AARP Diet and Health study; AHS-1, Adventist Health Study; AHS, Agricultural Health Study; BCDDP, Breast Cancer Detection Demonstration Project follow-up study; CTS, California Teachers Study; CPS, Cancer Prevention Study nutrition cohort II; CLUE, CLUE II; COSM, Cohort of Swedish Men; HPFS, Health Professionals Follow-Up study; IWHS, Iowa Women's Health Study; MCCS, Melbourne Collaborative Cohort Study; NHS, Nurses' Health Study; NYUWHS, New York University Women's Health Study; PHS, Physicians Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening trial; SMC, Swedish Mammography Cohort; USRT, U.S. Radiation Technologists study; VITAL, VITamins And Lifestyle study; WHS, Women's Health study; WLHS, Women's Lifestyle and Health Study; M, male; F, female.

outcome assessment

Participants were followed from the date of completion of the baseline questionnaire for the exposure of interest to date of death, date lost-to-follow-up, or administrative end date, whichever occurred first. Pancreatic cancer death was ascertained from death records or registries and coded according to the *International Classification of Diseases,* Ninth or Tenth Revision [45, 46] (ICD-9:157 and ICD-10:C25).

exclusions

Participants were excluded from all analyses if they were younger than 18 or older than 85 years at baseline ($n = 7317$), had no baseline questionnaire ($n = 4927$), had less than 1 year of follow-up ($n = 19\,727$), or had missing or extreme values of BMI (<15.0 or >59.9 kg/m^2; $n = 79\,739$) or height (<122 or >244 cm; $n = 26\,923$). Participants with extreme values of waist circumference (≤51 or ≥190 cm; $n = 111\,091$), hip circumference (≤51 or ≥190 cm for hip circumference; $n = 118\,550$), or BMI during early adulthood (<15.0 or >40 kg/m^2; $n = 549\,121$) were excluded from analyses in which these exposures were the primary exposure of interest. Those with cancer at baseline were excluded from each analysis, resulting in 55 315 individuals excluded from the waist circumference and waist-to-hip ratio, 84 456 individuals excluded from the BMI during early adulthood and BMI change and 137 837 individuals excluded from the BMI at

baseline and height analyses. Of the 1 564 218 participants in the analytic dataset who had complete data on BMI and height, 647 478 (n = 1947 pancreatic cancer deaths) had information on waist circumference, 528 928 had information on waist-to-hip ratio (n = 1468 pancreatic cancer deaths), and 1 096 492 had information on BMI during early adulthood and BMI change (n = 3223 pancreatic cancer deaths).

statistical methods

Main exposure and covariate data from each of the cohorts were harmonized in a standardized manner across studies and then combined. Individual-level data from each cohort were then combined to create a single aggregated dataset. Anthropometric measures were modeled using continuous variables and categories based on absolute cut points.

For the categorical analyses, waist circumference and waist-to-hip ratio were defined by sex-specific categories using 10-cm increments for waist circumference (for males:<90, 90–99, 100–109, ≥110; for females:<70, 70–79, 80–89, ≥90) and 0.05 increments for waist-to-hip ratio (for males: <0.90, 0.90–0.95, 0.95–109, ≥110; for females:<70, 70–79, 80–89, ≥90) based on the analytic sample's distribution. BMI (kg/m^2) at baseline was modeled using cut points proposed by the World Health Organization (15 to <18.5, 18.5 to <21.0, 21.0 to <23.0, 23.0 to <25.0, 25.0 to <27.5, 27.5 to <30, 30 to <35.0, 35.0 to <60 kg/m^2) [47]. BMI in early adulthood (measured at age 18–21) was modeled using the same categories except that the highest category was 30 to <40 due to lower average BMI values. BMI change (BMI at baseline – BMI in early adulthood) was categorized as: <−2.5, −2.5 to <0, 0 to <2.4, 2.5 to <4.9, 5.0 to <7.4, 7.5 to <9.9, ≥10 kg/m^2 based on the analytic sample's distribution.

Pooled multivariable hazard ratios (MVHRs) and 95% confidence intervals (CIs) for pancreatic cancer mortality according to continuous values and predefined categories were calculated by fitting Cox proportional hazards regression models [48]. Multivariable models included age as the underlying time-scale [49], and were stratified by cohort. All multivariable models were adjusted for race, education, marital status, grams of alcohol consumption, overall physical activity level, and smoking status. Waist circumference and waist-to-hip ratio were modeled with and without adjustment for BMI at baseline. We did not adjust for BMI at baseline in the main analysis examining BMI during early adulthood or BMI change as BMI at baseline may be in the causal pathway. Models of BMI change were additionally adjusted for BMI during early adulthood. Models for each anthropometric factor were conducted with and without adjustment for personal history of diabetes.

We also calculated the population attributable fraction (PAF), the proportion of pancreatic cancer deaths that could have been averted in our study population by avoiding levels of BMI during early adulthood, waist circumference (WC), or waist-to-hip ratio (WHR) higher than the referent level in our analyses [50]. The PAF was calculated using multivariable adjusted hazard ratios (unadjusted for BMI at baseline) and the proportion of pancreatic cancer deaths exposed [50].

We examined interactions with linear follow-up time by modeling the cross-product term of linear time and continuous variable of each main anthropometric exposure (waist circumference, waist-to-hip ratio, BMI in early adulthood and change in BMI after early adulthood); we observed no statistically significant interaction. We also modeled cross-product terms for each exposure (coded as continuous variables) and each potential effect measure modifier (age at baseline, smoking status, and sex), coding age at baseline as <60, 60 to <70, ≥70 years, and smoking status as never, former or current; we assessed the statistical significance of the Wald test for the cross-product term.

Models of waist circumference were stratified by categories of BMI at baseline. Analyses of the potential joint effect of combinations of early adult BMI and BMI at baseline were also carried out. All analyses were completed using the SAS statistical software, version 9.0 (SAS Institute).

results

Details of the 20 cohorts included in this analysis are given in Table 1. Median values for age at baseline in individual studies ranged from 40 to 68 years of age. Median values for waist circumference ranged from 68 to 85 cm for female cohorts and 93 to 97 cm for male cohorts. Median values for BMI at baseline and BMI in early adulthood median values ranged from 23 to 27 and 20 to 23 kg/m^2, respectively.

When comparing the highest (M: ≥110 cm; F: ≥90 cm) with the lowest (M: <90 cm; F: <70 cm) category of waist circumference (Table 2), a statistically significant positive association was observed for pancreatic cancer mortality (MVHR = 1.31, 95% CI 1.12–1.54, P value, test for trend <0.0001). When waist circumference was modeled as a continuous variable, a significant 9% increase in risk for pancreatic cancer mortality was observed for every 10 cm increase in waist circumference. Results were similar for men and women (P value, test for interaction = 0.86). When the models were additionally adjusted for BMI at baseline, the results were similar but attenuated (MVHR = 1.07, 95% CI 1.00–1.14; P for trend = 0.05). The highest (M: ≥1.0; F: ≥0.85) compared with lowest (M: <0.90; F: <0.75) category of waist-to-hip ratio was associated with increased risk (MVHR = 1.33, 95% CI 1.14–1.57). We also observed a modest increase in pancreatic cancer mortality (MVHR = 1.11, 95% CI 1.04–1.19) for every 0.1 increment in waist-to-hip ratio. Results were similar when the models were additionally adjusted for BMI at baseline (MVHR = 1.09, 95% CI 1.02–1.17 per 0.1 increment) or when stratified by sex (P value, test for interaction = 0.80).

When the association between waist circumference and pancreatic cancer mortality was stratified by BMI at baseline, a statistically significant positive trend was observed for each 10 cm increment in waist circumference only for individuals within the normal category for BMI at baseline (18.5 to <25 kg/m^2; MVHR = 1.14, 95% CI 1.02–1.17) (Table 3), but a test for interaction by BMI category was not statistically significant (P = 0.70).

An ∼43% increase in pancreatic cancer mortality (MVHR = 1.43, 95% CI 1.11–1.85) was observed for BMI during early adulthood 30 to <40 kg/m^2 compared with 21 to <23 kg/m^2 (Table 4). For each 5 kg/m^2 incremental increase in BMI during early adulthood, an 18% increase in pancreatic cancer mortality was observed; the association was stronger for males (MVHR = 1.25, 95% CI 1.15–1.35) than for females (MVHR = 1.11, 95% CI 1.03–1.21; P value, test for interaction = 0.04). Adjustment of early adult BMI for baseline BMI had negligible impact (MVHR = 1.14, 95% CI 1.07–1.22 per 5 kg/m^2).

Table 2. Multivariable[a] adjusted hazard ratios (MVHRs) and 95% confidence intervals (CIs) for pancreatic cancer mortality according to sex-specific categories of waist circumference and waist-to-hip ratio

Category	Categories of waist circumference (cm)[b]				Continuous (per 10 cm)	*P* value, test for trend	*P* value, Int sex[c]
	1	2	3	4			
Deaths							
M	200	415	262	129	1006		
F	185	245	269	242	941		
MVHR (95% CI)							
M	1.00 (ref)	1.09 (0.92–1.29)	1.16 (0.96–1.40)	1.27 (1.01–1.60)	1.08 (1.02–1.15)	0.008	0.86
F	1.00 (ref)	1.12 (0.91–1.38)	1.38 (1.12–1.71)	1.38 (1.10–1.73)	1.09 (1.03–1.15)	0.002	
M + F	1.00 (ref)	1.11 (0.98–1.27)	1.26 (1.10–1.45)	1.31 (1.12–1.54)	1.09 (1.04–1.13)	<0.0001	
Adj for BMI[d]							
M + F	1.00 (ref)	1.08 (0.94–1.24)	1.19 (1.02–1.40)	1.19 (0.96–1.47)	1.07 (1.00–1.14)	0.05	
Category	Categories of waist-to-hip ratio[e]				Continuous (per 0.1)	*P* value, test for trend	*P* value, Int sex[c]
	1	2	3	4			
Deaths							
M	134	240	176	180	730		
F	107	182	175	274	738		
MVHR (95% CI)							
M	1.00 (ref)	1.05 (0.85–1.30)	1.04 (0.83–1.30)	1.32 (1.05–1.66)	1.12 (1.02–1.23)	0.02	0.80
F	1.00 (ref)	1.20 (0.94–1.52)	1.18 (0.92–1.50)	1.36 (1.08–1.71)	1.10 (1.01–1.21)	0.04	
M + F	1.00 (ref)	1.11 (0.95–1.31)	1.11 (0.94–1.31)	1.33 (1.14–1.57)	1.11 (1.04–1.19)	0.002	
Adj for BMI[d]							
M + F	1.00 (ref)	1.10 (0.94–1.29)	1.08 (0.91–1.28)	1.28 (1.08–1.51)	1.09 (1.02–1.17)	0.02	

[a]Multivariable models were stratified by cohort and used attained age as the underlying time metric. All multivariable models adjusted for race (white, black, Asian, other, or unknown), education (less than high school, high school graduate, some college, college graduate, postgraduate, or unknown), marital status (married, divorced, widowed, single, or unknown), grams of alcohol consumption (quartiles or unknown), overall physical activity level (cohort-specific quintiles or unknown), and smoking status (never smoked, former smoker who quit <20 years ago, former smoker who quit 20 or more years ago, former smoker but unknown number of years since quitting, smoker but unknown if current or former, current smoker, or smoking status unknown).

[b]Male (M)-specific cut points for each category of waist circumference: category 1 (<90), category 2 (90 to <100), category 3 (100 to <110), category 4 (≥110). Female (F)-specific cut points for each category of waist circumference: category 1 (<70), category 2 (70 to <80), category 3(80 to <90), category 4 (≥90).

[c]*P* value, test for interaction by sex.

[d]In addition to the covariates listed in footnote 1, this model was also adjusted for body mass index at baseline (continuous).

[e]Male-specific cut points for each category of waist-to-hip ratio: category 1 (<0.90), category 2 (0.90 to <0.95), category 3 (0.95 to <1.0), category 4 (≥1.0). Female-specific cut points for each category of waist circumference: category 1 (<0.75), category 2 (0.75 to <0.80), category 3 (0.80 to <0.85), category 4 (≥0.85).

A statistically significant increase in risk of pancreatic cancer mortality was observed only for the highest category of BMI gain (≥10 kg/m^2 compared with 0 to <2.4 kg/m^2, MVHR = 1.28, 95% CI 1.12–1.47) for males and females combined (Table 4). A substantial decline in BMI (>2.5 kg/m^2) after early adulthood was also associated with increased risk of pancreatic cancer mortality, although this is potentially attributed to prediagnosis weight loss. BMI gain, measured as a continuous variable, was associated with weakly increased pancreatic cancer mortality overall (per 5 kg/m^2, MVHR = 1.05, 95% CI 1.01–1.10).

We also examined the joint effects of BMI at baseline (mid to late adulthood) and BMI during early adulthood on pancreatic cancer mortality (Table 5). Regardless of their BMI at baseline, individuals who were overweight or obese during early adulthood (BMI 25 to <40 kg/m^2) were at statistically significantly higher risk when compared with those in the referent category of individuals who had a normal BMI category (18.5 to <25.0 kg/m^2) during both early adulthood and baseline. In addition, higher risk was observed for individuals who were obese at baseline and normal weight during early adulthood (MVHR = 1.17, 95% CI 1.03–1.32).

Although not the focus of this report, higher BMI at baseline was associated with higher pancreatic cancer mortality for both males and females (supplementary Table S1, available at *Annals of Oncology* online). An 8%–9% increase in mortality was observed per 5 kg/m^2 increment in BMI. No statistically significant associations were observed for categories of height (supplementary Table S2, available at *Annals of Oncology* online), but results were marginally statistically significant when height was modeled as a continuous variable.

The estimated PAFs in our study population were 13% for WC and 13% for WHR accounting for categories higher than the referent level (categories 2, 3, and 4) in our analyses. The estimated PAF for early adult BMI was lower (6%), reflecting the relatively low prevalence of early adult BMI levels in the overweight and obese categories (categories of BMI ≥23 kg/m^2) in our study population.

Table 3. Multivariable[a] adjusted hazard ratios (MVHRs) and 95% confidence intervals (95% CIs) for pancreatic cancer mortality according to waist circumference stratified by BMI at baseline[b]

	BMI 18.5 to <25 (normal)		BMI 25 to <30 (overweight)		BMI ≥30 (obese)	
	Deaths	MVHR (95% CI)	Deaths	MVHR (95% CI)	Deaths	MVHR (95% CI)
Waist circumference (cm)[c]						
Category 1	298	1.00 (Ref)	73	1.07 (0.83–1.39)	4	1.62 (0.60–4.35)
Category 2	334	1.12 (0.95–1.32)	284	1.07 (0.91–1.26)	38	1.55 (1.11–2.18)
Category 3	130	1.23 (0.98–1.53)	310	1.30 (1.10–1.53)	89	1.20 (0.95–1.53)
Category 4	29	1.32 (0.89–1.95)	143	1.30 (1.05–1.61)	198	1.32 (1.09–1.60)
Per 10 cm (continuous)[d]		1.14 (1.02–1.27)		1.07 (0.97–1.18)		0.99 (0.87–1.12)

[a]Multivariable models were stratified by cohort and used attained age as the underlying time metric. All multivariable models adjusted for race (white, black, Asian, other, or unknown), education (less than high school, high school graduate, some college, college graduate, postgraduate, or unknown), marital status (married, divorced, widowed, single, or unknown), grams of alcohol consumption (quartiles or unknown), overall physical activity level (cohort-specific quintiles or unknown), and smoking status (never smoked, former smoker who quit <20 years ago, former smoker who quit 20 or more years ago, former smoker but unknown number of years since quitting, smoker but unknown if current or former, current smoker, or smoking status unknown). All models were additionally adjusted for BMI at baseline (continuous).

[b]*P* value, test for interaction for waist circumference and BMI at baseline = 0.70.

[c]Male-specific cut points for each category of waist circumference: category 1 (<90), category 2 (90 to <100), category 3 (100 to <110), category 4 (≥110). Female-specific cut points for each category of waist circumference: category 1 (<70), category 2 (70 to <80), category 3 (80 to <90), category 4 (≥90).

[d]Based on separate models for waist circumference within each BMI category.

Results for the main anthropometric factors of interest were similar when also adjusted for the personal history of diabetes (data not shown). Results for these anthropometric factors were similar when the analytic sample was restricted to non-Hispanic whites, or stratified by smoking status (never, former, current), age at baseline (<60, 60 to <70, ≥70 years) or length of follow-up (<5 years, ≥5 years; data not shown). There was a statistically significant interaction between BMI gain and smoking status ($P = 0.008$ for difference in HRs between never and current smokers), with BMI gain associated with lower pancreatic cancer mortality for current smokers (MVHR = 0.86, 95% CI 0.78–0.95).

discussion

In the largest to date analysis, we observed positive associations among measures of central obesity, waist circumference, and waist-to-hip ratio with pancreatic cancer mortality for both males and females. For waist-to-hip ratio, this association clearly persisted after adjustment for BMI for both males and females. In analyses examining the importance of timing of obesity, being overweight or obese during early adulthood was associated with increased pancreatic cancer mortality, whereas only large gains in BMI (>10 kg/m^2) occurring after early adulthood were associated with pancreatic cancer mortality.

The association between waist-to-hip ratio and higher pancreatic cancer mortality we observed is consistent with the few prior prospective analyses. Waist-to-hip ratio, without adjustment for BMI at baseline, was also associated with increased pancreatic cancer risk in two pooled analyses [7, 13], a meta-analysis [12] and the WCRF systematic review [10]. Our analysis is the first to demonstrate statistically significant higher mortality associated with waist-to-hip ratio even after adjustment for BMI. The only previous analysis of waist-to-hip ratio that adjusted for BMI [13] was a pooled analysis that included some of the cohorts in this analysis (6 of 11 studies), but overall had considerably fewer cases. This previous pooled analysis [13] reported that the association with waist-to-hip ratio was positive, but not statistically significant after adjustment for BMI. Our results suggest that waist-to-hip ratio may predict increased pancreatic cancer mortality independently from BMI.

Higher waist circumference was also associated with higher pancreatic cancer mortality in our analysis. This association remained, although somewhat attenuated, after adjustment for BMI. The association between waist circumference and pancreatic cancer has been examined in two previous pooled analyses [8, 13] and a meta-analysis [12], each including about half the number of cases in this analysis. Our results for waist circumference are generally consistent with those of the meta-analysis, which included five cohort studies (three of which are also included in this analysis), and reported a statistically significant association with a continuous measure of waist circumference that was slightly stronger than that observed in our analysis. One of the previous pooled analyses reported a weak association with waist circumference and did not present results adjusted for BMI [8], whereas the other reported a marginally statistically significant association with waist circumference that was eliminated by adjustment for BMI [13]. Our analysis is the first study to examine the association between waist circumference and pancreatic cancer mortality within categories of BMI. The statistically significant increase in mortality associated with waist circumference for individuals within the normal category of BMI at baseline in this analysis suggests an influence of visceral fat [51], which has been associated with insulin resistance and inflammation, two potential pathways to pancreatic cancer [14–19, 52, 53].

Being either overweight (BMI ≥25 to <30 kg/m^2) or obese (BMI ≥30 kg/m^2) during early adulthood, was associated with ~40% higher risk of pancreatic cancer mortality in our analyses, which included over 3200 pancreatic cancer deaths. Notably, even the lower half of the overweight category (BMI = 25.0 to <27.5) was associated with an increased risk (HR = 1.36, 95% CI 1.20–1.55), but there was a statistically significant interaction by

Table 4. Pooled multivariable[a] adjusted hazard ratios (MVHRs) and 95% confidence intervals (CIs) for pancreatic cancer mortality according to body mass index during early adulthood and BMI change

	Categories of BMI during early adulthood (kg/m^2)							Continuous (5 kg/m^2)
	15.0 to <18.5	18.5 to <21.0	21.0 to <23.0	23.0 to <25.0	25.0 to <27.5	27.5 to <30	30 to <40	
Deaths								
M	118	404	398	320	222	59	37	1558
F	258	632	416	190	109	34	26	1665
MVHR[a–d] (95% CI)								
M	0.94 (0.77–1.16)	1.04 (0.90–1.19)	1.00 (Ref)	1.19 (1.03–1.38)	1.39 (1.18–1.64)	1.56 (1.19–2.06)	1.81 (1.29–2.54)	1.25 (1.15–1.35)
F	1.03 (0.88–1.20)	0.94 (0.83–1.06)	1.00 (Ref)	1.04 (0.88–1.24)	1.34 (1.09–1.66)	1.38 (0.97–1.95)	1.09 (0.73–1.62)	1.11 (1.03–1.21)
M + F	1.01 (0.89–1.14)	0.98 (0.89–1.08)	1.00 (Ref)	1.13 (1.01–1.26)	1.36 (1.20–1.55)	1.48 (1.20–1.84)	1.43 (1.11–1.85)	1.18 (1.11–1.25)
	Categories of BMI change [BMI at baseline − BMI during early adulthood (kg/m^2)]							Continuous (5 kg/m^2)
	<−2.5	−2.5 to <0.0′	0 to <2.4	2.5 to <4.9	5.0 to <7.4	7.5 to <9.9	≥10	
Deaths								
M	36	119	345	438	320	186	114	1558
F	81	150	313	390	320	171	240	1665
MVHR[a–d] (95% CI)								
M	0.99 (0.69–1.41)	1.15 (0.93–1.42)	1.00 (Ref)	1.05 (0.91–1.21)	1.04 (0.89–1.22)	1.19 (0.99–1.43)	1.06 (0.85–1.33)	1.03 (0.96–1.11)
F	1.50 (1.15–1.95)	1.12 (0.92–1.36)	1.00 (Ref)	1.10 (0.95–1.28)	1.21 (1.03–1.42)	1.08 (0.89–1.30)	1.49 (1.25–1.78)	1.08 (1.02–1.14)
M + F	1.24 (1.01–1.53)	1.12 (0.97–1.29)	1.00 (Ref)	1.07 (0.97–1.19)	1.11 (0.99–1.24)	1.11 (0.98–1.27)	1.28 (1.12–1.47)	1.05 (1.01–1.10)

[a]Multivariable models were stratified by cohort and used attained age as the underlying time metric. All multivariable models adjusted for race (white, black, Asian, other, or unknown), education (less than high school, high school graduate, some college, college graduate, postgraduate, or unknown), marital status (married, divorced, widowed, single, or unknown), grams of alcohol consumption (quartiles or unknown), overall physical activity level (cohort-specific quintiles or unknown), and smoking status (never smoked, former smoker who quit <20 years ago, former smoker who quit 20 or more years ago, former smoker but unknown number of years since quitting, smoker but unknown if current or former, current smoker, or smoking status unknown).
[b]BMI change results were additionally adjusted for BMI during early adulthood (continuous).
[c]*P* value, test for trend for BMI during early adulthood: M (0.0001), F (0.05), M + F (<0.001); *P* value, test for trend for BMI change: M (0.47), F (0.24), M + F (0.79)
[d]*P* value, interaction by sex for BMI during early adulthood = 0.04 and for BMI change = 0.22.

Table 5. Multivariable[a] adjusted hazard ratios (MVHRs) and 95% confidence intervals (CIs) for pancreatic cancer mortality according to body mass index (BMI) during early adulthood stratified by BMI at baseline[b]

	BMI at baseline (kg/m^2)					
	18.5 to <25		25 to <30		30 to <60	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)
BMI during early adulthood (kg/m^2)						
15 to <18.5	211	0.99 (0.85–1.15)	123	1.14 (0.95–1.38)	32	1.22 (0.85–1.73)
18.5 to <25.0	996	1.00 (ref)	970	1.05 (0.96–1.15)	367	1.17 (1.03–1.32)
25.0 to <40	69	1.32 (1.03–1.69)	208	1.44 (1.23–1.67)	210	1.48 (1.27–1.73)

P-value, test for interaction = 0.42.
[a]Multivariable models were stratified by cohort and used attained age as the underlying time metric. All multivariable models adjusted for race (white, black, Asian, other, or unknown), education (less than high school, high school graduate, some college, college graduate, postgraduate, or unknown), marital status (married, divorced, widowed, single, or unknown), grams of alcohol consumption (quartiles or unknown), overall physical activity level (cohort-specific quintiles or unknown), and smoking status (never smoked, former smoker who quit <20 years ago, former smoker who quit 20 or more years ago, former smoker but unknown number of years since quitting, smoker but unknown if current or former, current smoker, or smoking status unknown).
[b]Owing to small case numbers (<5), we did not present the estimates for when BMI at baseline was <18.5 kg/m^2.

sex and the positive association appeared stronger for men. Our findings were generally consistent with those observed in an earlier pooled analysis of prospective cohort studies [13] and a recent large cohort study [9]. These previous analyses did not present results for individuals who were overweight but not obese, or obese only. The earlier pooled analysis [13], which included ~1600 cases from eight cohorts (all of which also contributed to our analysis), reported that being overweight or obese (BMI ≥25 kg/m^2) during early adulthood was associated with a 30% higher pancreatic cancer risk. Similarly, the NIH-AARP cohort [9], which included ~1200 cases and also contributed to our pooled analysis, reported a 50% higher pancreatic

cancer risk for early adulthood BMI ≥27.5 kg/m^2, compared with normal BMI.

In our analyses, associations with risk of pancreatic cancer mortality appeared stronger for BMI during early adulthood than for BMI gain after early adulthood. Our analysis and the previous pooled analysis of nine studies [13] observed that only a very large gain in BMI (≥10 kg/m^2) between early adulthood and enrollment in cohort studies was associated with significantly higher pancreatic cancer risk. A recent analysis of the NIH-AARP cohort [9] reported no association between change in BMI between early adulthood and BMI at enrollment (typically in middle age or later). Overall, evidence to date suggests that BMI during early adulthood is a stronger predictor of pancreatic cancer mortality than increases in BMI after early adulthood.

BMI gain was associated with an unexpected reduction in pancreatic cancer mortality among current smokers. The two prior publications [9, 13] that examined BMI change in relation to pancreatic cancer did not report results by smoking status. It is possible this association reflects residual confounding by smoking due to lower BMI gain among smokers with the most intense history of smoking. However, this finding may also reflect chance and requires replication.

The idea that obesity in early adulthood may be particularly important to pancreatic carcinogenesis is consistent with time trends in United States (US) pancreatic cancer mortality rates. After many years of stable rates in the US, pancreatic cancer mortality rates began to increase in the early 2000s, possibly due to a delayed effect of increases in obesity prevalence, particularly at younger ages, over recent decades [4]. The delay between increases in the prevalence of obesity and increases in pancreatic cancer mortality is consistent with a long latency period, implying that obesity during early adulthood may have a stronger influence on pancreatic cancer mortality than obesity arising in later adulthood. Based on mutually adjusted estimates, our findings were consistent with this hypothesis.

If being overweight or obese during early adulthood is associated with substantially higher pancreatic risk and mortality, there are important implications for future pancreatic cancer incidence and mortality rates. In our study, the PAF for BMI during early adulthood was modest; however, being overweight or obese during early adulthood was uncommon in our study sample (10.0% and 1.6%, respectively), consisting predominantly of individuals born before 1960, but is relatively common today as a result of dramatic increases in obesity in recent decades. Recent national data from the United States show that ~23% of men and women aged 18–24 years are already obese [54]. Our results suggest that avoiding obesity during early adulthood may be important for reducing pancreatic cancer mortality, adding to the evidence that avoiding obesity throughout life is important for reducing risk of many diseases [55, 56].

Similar to prior research, our analyses were mostly limited to self-reported, rather than measured, anthropometric factors. Previous research has shown that self-reported anthropometric factors, particularly height, weight, waist circumference, and hip circumference, are highly correlated with measured anthropometric factors [57–59], even when self-reported assessment occurs years later [60–62]. Any errors in self-reported and recalled weight are unlikely to be strongly associated with later risk of pancreatic cancer mortality; thus, any errors would be expected to be nondifferential and would likely underestimate the risk associated with high BMI during early adulthood. Distinct from the prior pooled analyses, we examined pancreatic cancer mortality instead of incidence. Owing to the high case fatality (>95%) and short median survival time (~6 months), pancreatic cancer mortality is a good surrogate for pancreatic cancer incidence.

A notable strength of this analysis is its large prospective design and the inclusion of geographically diverse populations. To our knowledge, this is the largest analysis to date of measures of central and early adulthood obesity. The large study size enabled us to examine whether central obesity predicted risk independent of BMI, which few studies have done, and to specifically examine joint associations of BMI in early adulthood and BMI at baseline. In addition, information on potential confounding factors was harmonized across studies, allowing results to be adjusted in a standardized way for potentially important risk factors. Owing to our large sample size, we were able to examine whether the associations differed by a priori effect measure modifiers.

Future research should explore the biological mechanisms through which obesity, particularly obesity attained in childhood or early adulthood, influences pancreatic carcinogenesis. In addition, future studies should investigate if sustained weight loss is associated with lower risk of pancreatic cancer and therefore could be useful in preventing pancreatic cancer.

In summary, this analysis within a large international consortium provides strong evidence that central obesity may increase pancreatic cancer mortality, independent of BMI. Our results also suggest that a high BMI during early adulthood may be particularly important in influencing pancreatic cancer mortality later in life. These results are consistent with the hypothesis that increases in the prevalence of overweight and obesity during early adulthood in more recent birth cohorts could be responsible for recent increases in pancreatic cancer mortality rates. Moreover, our results provide evidence that avoiding excess weight gain before early adulthood (during childhood) may be particularly important for pancreatic cancer prevention.

acknowledgements

We thank Dr Christine Berg and Philip Prorok (Division of Cancer Prevention, National Cancer Institute), the Screening Center investigators and staff or the PLCO Cancer Screening Trial, Tom Riley and staff (Information Management Services, Inc.), Barbara O'Brien and staff (Westat, Inc.), and Jackie King (Bioreliance, Rockville) for their contributions to making the PLCO study possible.

funding

This research was supported, in part, by the Intramural Research Program of the National Cancer Institute (Z99 CA999999). The NIH-AARP Diet and Health study was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health. The Adventist Health Study-1 was supported by grant no.: R01-CA14703 from the National Cancer Institute and by grant no.: R01- HL26210 from the National Heart, Lung and Blood Institute. The Agricultural Health Study was funded by the Intramural Program of the NIH, National Cancer Institute (Z01 P010119) and the

National Institute of Environmental Health Sciences (Z01 ES 049030-11). The BCDDP Follow-up Study has been supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health. The CPS-II Nutrition Cohort, including its creation, maintenance, and updating, is funded by the American Cancer Society (ACS). The CTS was supported by National Cancer Institute grant #CA 77398. This research was made possible in part through funding from the National Institute of Aging (grant no.: 5U01AG018033) and National Cancer Institute (grant no.: R01 CA105069). CLUE was supported by the National Institute of Aging; grant no.: U01 AG18033 and National Cancer Institute (NCI): grant no.: CA105069. Cancer incidence data were provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Department of Health and Mental Hygiene, 201 W. Preston Street, Room 400, Baltimore, MD 21201, http://phpa.dhmh.maryland.gov/cancer, 410-767-4055. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the Centers for Disease Control and Prevention for the funds that support the collection and availability of the cancer registry data. The Cohort of Swedish Men was supported by the Swedish Research Council, the Swedish Council for Working Life and Social Research, and the Swedish Cancer Foundation. The Health Professionals Follow-up Study is supported by NIH/NCI P01 CA055075 and UM1 CA167552. The Iowa Women's Health Study is supported by a grant from the National Cancer Institute (R01 CA39742). The Melbourne Collaborative Cohort Study (MCCS) receives core funding from the Cancer Council Victoria and is additionally supported by grants from the Australian NHMRC (209057, 251533, 396414, and 504715). The Nurses' Health Study is supported by NIH/NCI UM1 CA186107, P01 CA87969, and R01 CA49449. The NYU Women's Health Study is supported by grant No.: R01 CA 098661 and Center grant CA 016087 from the National Cancer Institute and by Center grant ES 000260 from the National Institute of Environmental Health Sciences. The Physicians' Health Study was supported by grants CA 97193, CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health. The Swedish Mammography Cohort was supported by the Swedish Research Council, Swedish Council for Working Life and Social Research and the Swedish Cancer Foundation. The USRT was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health. The VITamin And Lifestyle (VITAL) study was supported by National Institutes of Health grant K05 CA154337 (National Cancer Institute and Office of Dietary Supplements). The WHS was supported by CA047988, HL043851, and HL080467. The Women's Lifestyle and Health project was supported by the Swedish Cancer Society and the Swedish Research Council.

disclosure

The authors have declared no conflicts of interest.

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