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A pooled analysis of body mass index and pancreatic cancer mortality in African Americans

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Abstract

Background—Pancreatic cancer is a leading cause of cancer-related mortality in the U.S. and both incidence and mortality are highest in African Americans. Obesity is also disproportionately high in African Americans, but limited data are available on the relation of obesity to pancreatic cancer in this population.

Methods—Seven large prospective cohort studies pooled data from African American participants. Body mass index (BMI) was calculated from self-reported height and weight at baseline. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for levels of BMI relative to BMI 18.5–24.9, with adjustment for covariates. Primary analyses were restricted to participants with ≥ 5 years of follow-up because weight loss prior to diagnosis may have influenced baseline BMI in cases who died during early follow-up.

Results—In follow-up of 239,597 participants, 897 pancreatic cancer deaths occurred. HRs were 1.08 (95% CI, 0.90–1.31) for BMI 25.0–29.9, 1.25 (95% CI, 0.99–1.57) for BMI 30.0–34.9, and 1.31 (95% CI, 0.97–1.77) for BMI ≥ 35.0 among those with ≥ 5 years of follow-up ($P_{\text{trend}} = 0.03$). The association was evident among both sexes and was independent of a history of diabetes. A stronger association was observed among never-smokers (BMI ≥ 30 vs. referent: HR = 1.44; 95% CI, 1.02–2.03) than among smokers (HR = 1.16; 95% CI, 0.87–1.54; $P_{\text{interaction}} = 0.02$).

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Conclusion—The findings suggest that obesity is independently associated with increased pancreatic cancer mortality in African Americans.

Impact—Interventions to reduce obesity may also reduce risk of pancreatic cancer mortality, particularly among never-smokers.

Keywords

body mass index; obesity; pancreatic cancer mortality; African American

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States and both incidence and mortality are higher in African Americans than in other racial/ethnic groups (1, 2). Pancreatic cancer is usually detected at a late stage and 5-year survival is 5.4% (3). Cigarette smoking (4) and diabetes (5) are the two factors most consistently associated with pancreatic cancer. Evidence from the past decade indicates that overweight and obesity are also associated with pancreatic cancer (6, 7). Chronic pancreatitis is a risk factor for pancreatic cancer but explains only a small proportion of the disease (8).

The prevalence of obesity is disproportionately high in African Americans (9), but only three studies have published on the role of obesity in relation to pancreatic cancer in African Americans, with conflicting findings (10–12). The largest, the Cancer Prevention Study II, found that obesity was associated with an increased risk of pancreatic cancer death among African American men, but not among African American women (10); a second study observed an association in women, but not men (11); and the third, of men only, found no association (12).

In the present study, we combined data from seven U.S. prospective cohort studies with large number of African American participants in order to have greater statistical power to assess the relation of obesity to pancreatic cancer mortality.

Materials and Methods

The following cohort studies contributed data to the analysis: Adventist Health Study 2 (AHS2) (13), Black Women's Health Study (BWHS) (14), Cancer Prevention Study II (CPS-II) (10), Multiethnic Cohort Study (MEC) (15), National Institutes of Health-AARP Diet and Health Study (NIH-AARP) (16), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (17), and Southern Community Cohort Study (SCCS) (18). Enrollment periods and numbers of African American participants for each study are presented in Table 1. Each study was approved by the relevant Institutional Review Board.

Deaths were identified in each study through linkage with the National Death Index. Pancreatic cancer mortality was defined using International Classification of Diseases (ICD) codes for an underlying cause of death of C25 (ICD-10) or 157 (ICD-9). Data on height, weight, and potential risk factors for pancreatic cancer were obtained by self-report at time of enrollment in each cohort. Body mass index (BMI) was calculated as weight in kilograms

divided by squared height in meters and was categorized as <18.5, 18.5–24.9, 25–29.9, 30–34.9, and ≥ 35 kg/m².

Participants were excluded if data on BMI were missing or if BMI was <15 or >60 (N=9,463), if the follow-up period was less than one year (N=7,343), or if the follow-up period ended before the subject reached age 30 (N=33), leaving 239,597 individuals for the present analyses. Similar questions across the seven studies enabled categorization of important covariates as follows: sex (male, female), education (<12, 12–15, 16 years), marital status (married, divorced/separated or widowed, single), alcohol consumption (none, <10, 10 grams per day), cigarette smoking (never, former/quartile 1 of pack-years, former/quartile 2, former/quartile 3, former/quartile 4, current/quartile 1 of pack-years, current/quartile 2, current/quartile 3, current/quartile 4), and physical activity (low, medium, high). Physical activity was categorized by each cohort as low, medium, or high frequency of moderate or vigorous activity.

Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of pancreatic cancer mortality with categories of BMI relative to BMI 18.5–24.9. All statistical tests were two-sided. Participants contributed person-time to the analyses beginning one year after cohort entry and ending with death, last known date alive, or end of active follow-up. Results for persons with BMI <18.5 are not presented because only 1% of participants had a BMI <18.5. Multivariable models were stratified by study and adjusted for age, sex, cigarette smoking, education, marital status, alcohol consumption, and physical activity.

Because pancreatic cancer is often advanced by the time of diagnosis (19) and more than two-thirds of patients suffer weight loss prior to diagnosis (20, 21), preliminary analyses were stratified on length of follow-up (1 to <5 years, ≥ 5 years) and the remaining analyses were restricted to participants with ≥ 5 years of follow-up. Interactions of age, cigarette smoking, and education with BMI were tested by the likelihood ratio test, comparing models with and without interaction terms. For trend tests, the midpoint of each category of BMI was modeled as a continuous variable and the tests were restricted to participants with BMI ≥ 18.5 . Because obesity and Type 2 diabetes are highly correlated, we carried out sensitivity analyses, first by adjusting for history of diabetes and second by excluding participants with diabetes. A third sensitivity analysis further excluded participants with major chronic diseases (cancer, excluding non-melanoma skin cancer; heart disease/heart attack; or stroke) at baseline. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used for the analyses.

To assess heterogeneity between cohorts, a meta-analysis was performed using study-specific results for 5 kg/m² increments of BMI in relation to pancreatic cancer mortality and a Cochran's Q statistic was calculated. The meta-analysis used a random effects model (STATA 12 software, StataCorp, College Station, TX). The corresponding forest plot was created using Forest Plot Viewer (22).

Results

Selected baseline characteristics of the study population are shown in Table 1. Mean age at baseline ranged from 39 to 61 years and was 52 years overall. Seventy-one percent of participants were women. The majority of participants were either overweight (36% with BMI 25–29.9) or obese (33% with BMI ≥ 30). As expected, obese participants were less likely than lean participants to be current smokers or to consume alcohol, and had less education and a higher prevalence of diabetes (data not shown).

In follow-up of 239,597 participants for a mean of 11.6 years, 897 pancreatic cancer deaths occurred. BMI was not associated with pancreatic cancer mortality among participants with <5 years of follow-up (Table 2). Among those with ≥ 5 years of follow-up, multivariable HRs were 1.25 (95% CI, 0.99–1.57) and 1.31 (95% CI, 0.97–1.77) for BMI 30–34 and BMI ≥ 35, respectively, in relation to BMI 18.5–24.9 ($P_{\text{trend}} = 0.03$). The HR for the collapsed category of BMI ≥ 30 was 1.27 (95% CI, 1.03–1.56). Results were generally similar among men and women. All further analyses were conducted in the combined group of men and women and were restricted to follow-up time occurring at least five years after study enrollment.

Table 3 presents results stratified by age, cigarette smoking, and years of education. BMI was more strongly associated with pancreatic cancer mortality among never smokers than among ever smokers ($P_{\text{interaction}} = 0.02$). Results were similar for current smokers and former smokers (data not shown). The association of BMI with pancreatic cancer mortality was more evident in the more educated participants, but there was not a statistically significant interaction ($P_{\text{interaction}} = 0.72$).

Controlling for a history of diabetes did not materially change the estimates; the multivariable HR for BMI ≥ 35 was 1.30 (95% CI, 0.96–1.76) with inclusion of a term for history of diabetes and 1.31 (95% CI, 0.97–1.77) without the term. Excluding participants with diabetes or with other major diseases (cancer, myocardial infarction, and/or stroke) also did not materially affect the results; HRs for BMI ≥ 35 were 1.22 (95% CI, 0.86–1.72) and 1.27 (95% CI, 0.91–1.78), respectively.

Figure 1 presents study-specific estimates for each 5 kg/m² increment of BMI in relation to pancreatic cancer mortality. Although HRs varied by cohort, with three studies having HRs of 1.0 or below, there was not significant evidence of between-study heterogeneity ($P_{\text{heterogeneity}} = 0.56$). Overall, the HR for a 5 kg/m² increase in BMI was 1.09 (95% CI, 1.01–1.18).

Discussion

The present findings suggest that obesity is associated with increased pancreatic cancer mortality in African Americans, in both women and men. The association was most apparent in persons who had never smoked, who would have had a lower baseline risk of pancreatic cancer. Study-specific HRs varied, with two slightly below 1.0 and one at 1.0. The variation in results may simply be due to chance variation, given the small number of cases in those three studies. These studies also had the highest proportions of men (43% in AARP, 44% in

PLCO, and 42% in SCCS,) and our overall results showed a weaker association in men than women. We are aware of only three prior studies reporting on the relation of BMI to pancreatic cancer incidence or mortality in African Americans, with mixed results. In an earlier report from the prospective CPS-II including 360 pancreatic cancer deaths, the HR for BMI ≥ 30 was 1.66 (95% CI, 1.05–2.63) for men and 0.82 (95% CI, 0.56–1.18) for women (10). With extended follow-up, 453 pancreatic cancer deaths from CPS-II are included in the present study. In a case-control study involving 159 African American cases, a high BMI was associated with increased risk of pancreatic cancer among women, but not among men (11). Finally, obesity was not associated with risk of pancreatic cancer (83 deaths) among African Americans in a cohort study of U.S. male veterans (12).

BMI has been positively associated with either incidence of or mortality from pancreatic cancer in most (6, 10–12, 23–27), but not all (24–26) studies, which have primarily included White participants (10, 16, 23, 27–38). Estimates from the largest of these studies were similar to the results of the present study. In 900,053 participants from the predominantly White CPS-II, higher BMI was associated with increased risk of pancreatic cancer mortality ($P_{\text{trend}} < 0.01$), with similar results for men and women and a stronger relationship among never smokers (28). In the Million Women Study, a follow-up study of 1.3 million British women, BMI was positively associated with both pancreatic cancer incidence and mortality; the relative risk for BMI ≥ 32.5 was 1.42 (standard error = 0.12) for incidence and 1.36 (standard error = 0.10) for mortality (23). In a meta-analysis that included 9,504 cases of pancreatic cancer from 23 prospective studies, each 5 kg/m² increase in BMI was associated with a 10% increase in risk of pancreatic cancer (38).

In our study and in many of the previous positive studies in predominantly White populations (15, 16, 28, 35, 36), an association was observed only among never smokers or was stronger in never smokers than in smokers. Smokers have an increased risk of pancreatic cancer and it may be more difficult to detect an association of BMI with pancreatic cancer mortality risk in a group at high risk.

The prevalence of obesity is somewhat higher among African Americans than among Whites (9). However, the magnitude of the association between BMI and pancreatic cancer mortality observed in the present study suggests that BMI is likely to be only a modest contributor to the higher rate of pancreatic cancer death among African Americans compared to Whites.

A central mechanism hypothesized to link obesity to pancreatic cancer mortality is inflammation, as described in a recent review (39). Obesity can create chronic inflammation and proinflammatory cytokines have been implicated in cancer progression (6, 39). For example, obesity increases systemic levels of tumor necrosis factor- α (TNF- α) and of interleukin-6 (IL-6) and these cytokines have a positive association with cancer-related death (39). Additionally, obesity tends to reduce serum concentrations of adiponectin, which has anti-inflammatory and insulin-sensitizing properties and can regulate apoptosis and cell proliferation (39).

Our study has several strengths. The data come from prospective cohort studies, which permitted collection of data on exposures prior to diagnosis of pancreatic cancer. Pooling of data across large cohort studies enabled us to accrue a substantial sample size of pancreatic cancer deaths. Further, we were able to harmonize data on the confounding variables and to examine several potential effect modifiers. In particular, we were able to conduct analyses that excluded the first 5 years of follow-up, when results may be influenced by weight loss due to pancreatic cancer.

Limitations include our inability to consider measures of body size other than body mass index, such as waist circumference or waist-hip ratio. We did not have extensive data on comorbidities which could affect the relation of BMI to mortality. Nevertheless, a sensitivity analysis did not show a difference in effect estimates when participants who reported cancer, heart disease, or stroke were excluded. We were unable to differentiate between Type 1 and Type 2 diabetes; however, because Type 2 diabetes comprises 90–95% of diabetes cases (40) and all participants included in our analyses were at least 30 years old, this limitation is unlikely to have materially affected our results. Additionally, we did not observe a change in the HRs when sensitivity analyses controlled for history of diabetes or were restricted to participants who did not report a diabetes diagnosis.

We conclude that obesity is associated with an increased risk of pancreatic cancer death among African American men and women. In addition, consistent with results from other populations, body mass index in African Americans may be more strongly associated with pancreatic cancer mortality among those who have never smoked.

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Figure 1. Multivariable^a hazard ratios and 95% confidence intervals for pancreatic cancer mortality per 5 kg/m² increase in BMI among participants with 5 years of follow-up by study^b and overall from a random effects meta-analysis.

^a Multivariable models adjusted for age, sex, cigarette smoking, education, marital status, alcohol consumption, and physical activity.

^b AHS2 was not included in the meta-analysis due to a small sample size (2 deaths and 11,576 person-years). With AHS2 (HR = 0.68; 95% CI, 0.07–6.38) included, the overall HR is unchanged and $P_{\text{heterogeneity}} = 0.67$.

Table 1

Characteristics of study participants (African Americans only), by cohort^a

Cohort	AARP	AHS2	BWHS	CPS-II	MEC	PLCO	SCCS	TOTAL
Study population	20,399	22,695	58,001	48,712	29,306	7,577	52,906	239,597
Enrollment period	1995–1997	2002–2007	1995	1982–1983	1993–1996	1993–2001	2002–2008	
Years of follow-up								
Mean	11.7	5.0	14.5	20.6	8.9	10.1	4.8	11.6
Age at enrollment								
Mean (range)	61 (50–71)	53 (24–104)	39 (20–70)	55 (29–90)	61 (45–78)	62 (53–77)	51 (40–79)	52 (20–104)
BMI (kg/m ²), N (%)								
<18.5	125 (1)	271 (1)	944 (2)	664 (1)	283 (1)	50 (1)	600 (1)	2,937 (1)
18.5–24.9	4,527 (22)	6,405 (28)	21,269 (37)	17,164 (35)	1,622 (26)	1,622 (21)	12,475 (24)	71,066 (30)
25–29.9	8,547 (42)	8,447 (37)	18,303 (32)	19,840 (41)	2,987 (41)	2,987 (39)	15,695 (30)	85,782 (36)
30–34.9	4,616 (23)	4,493 (20)	9,612 (17)	7,926 (16)	1,773 (20)	1,773 (23)	11,680 (22)	46,081 (19)
35	2,584 (13)	3,080 (14)	7,873 (14)	3,118 (6)	1,145 (12)	1,145 (15)	12,456 (24)	33,731 (14)
Pancreatic cancer deaths (N) ^b	68	11	67	453	201	35	62	897

^a Abbreviations: AA = African American; AARP = NIH-AARP Diet and Health Study; AHS2 = Adventist Health Study 2; BWHS = Black Women's Health Study; CPS-II = Cancer Prevention Study II; MEC = Multiethnic Cohort Study; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCCS = Southern Community Cohort Study.

^b Pancreatic cancer mortality is defined as an underlying cause of death of C25 (ICD-10) or 157 (ICD-9).

Table 2

BMI in relation to pancreatic cancer mortality stratified by duration of follow-up, overall and by sex^a

1–4 years follow-up							5 years follow-up					
	Deaths N	Person-years	Age-adjusted		Multivariable ^b		Deaths N	Person-years	Age-adjusted		Multivariable ^b	
			HR	(95% CI)	HR	(95% CI)			HR	(95% CI)	HR	(95% CI)
All participants												
BMI (kg/m ²)												
18.5–24.9	85	249,113	1.00	(Referent)	1.00	(Referent)	187	549,440	1.00	(Referent)	1.00	(Referent)
25–29.9	87	312,137	0.71	(0.52–0.96)	0.74	(0.55–1.01)	270	625,387	1.05	(0.87–1.27)	1.08	(0.90–1.31)
30–34.9	39	166,065	0.65	(0.44–0.95)	0.71	(0.48–1.04)	128	290,211	1.14	(0.91–1.43)	1.25	(0.99–1.57)
35	30	117,549	0.84	(0.55–1.28)	0.96	(0.62–1.49)	60	167,820	1.14	(0.85–1.53)	1.31	(0.97–1.77)
P _{trend} ^c				0.11		0.34				0.22		0.03
Men												
BMI (kg/m ²)												
18.5–24.9	41	75,426	1.00	(Referent)	1.00	(Referent)	68	116,269	1.00	(Referent)	1.00	(Referent)
25–29.9	42	109,282	0.71	(0.46–1.11)	0.78	(0.50–1.22)	123	188,968	1.10	(0.82–1.48)	1.15	(0.85–1.55)
30–34.9	13	42,420	0.67	(0.36–1.27)	0.75	(0.40–1.43)	45	61,432	1.30	(0.89–1.90)	1.36	(0.93–2.00)
35	6	16,357	0.93	(0.39–2.21)	1.04	(0.43–2.51)	10	16,913	1.09	(0.56–2.13)	1.14	(0.58–2.24)
P _{trend} ^c				0.22		0.40				0.29		0.20
Women												
BMI (kg/m ²)												
18.5–24.9	44	173,687	1.00	(Referent)	1.00	(Referent)	119	433,171	1.00	(Referent)	1.00	(Referent)
25–29.9	45	202,856	0.72	(0.47–1.09)	0.73	(0.48–1.12)	147	436,419	0.98	(0.77–1.24)	1.03	(0.80–1.31)
30–34.9	26	123,645	0.68	(0.42–1.11)	0.69	(0.42–1.13)	83	228,779	1.06	(0.80–1.41)	1.16	(0.87–1.55)
35	24	101,192	0.93	(0.55–1.55)	0.94	(0.56–1.59)	50	150,907	1.19	(0.85–1.67)	1.34	(0.95–1.89)
P _{trend} ^c				0.61		0.64				0.29		0.08

^aResults for persons with BMI <18.5 are not presented because only 1% of participants had a BMI <18.5, with 11 pancreatic cancer deaths arising from this category.

^bMultivariable model adjusted for age, sex (where appropriate), cigarette smoking, education, marital status, alcohol consumption, and physical activity.

^cTwo-sided trend tests were calculated for the midpoint of each category of BMI. Individuals with BMI <18.5 are excluded from the tests for trend.

BMI in relation to pancreatic cancer mortality among participants with 5 years of follow-up, stratified by age at risk, cigarette smoking, and years of education

Multivariable ^a				Multivariable ^d			
Deaths N	Person-years	HR	(95% CI)	Deaths N	Person-years	HR	(95% CI)
BMI (kg/m ²)							
Age <60				Age 60			
19	271,355	1.00	(Referent)	168	278,085	1.00	(Referent)
21	229,905	1.03	(0.55–1.93)	249	395,483	1.09	(0.89–1.32)
30	197,624	1.40	(0.74–2.65)	167	260,407	1.25	(1.00–1.56)
P _{trend} ^b			0.33				0.05
				P _{interaction} = 0.64			
Never smokers				Ever smokers			
60	277,883	1.00	(Referent)	117	250,239	1.00	(Referent)
104	297,677	1.21	(0.88–1.67)	147	296,512	1.00	(0.78–1.27)
81	240,703	1.44	(1.02–2.03)	93	196,818	1.16	(0.87–1.54)
P _{trend} ^b			0.04				0.33
				P _{interaction} = 0.02			
12 Years of education				13 Years of education			
73	152,338	1.00	(Referent)	111	385,843	1.00	(Referent)
114	215,475	1.09	(0.81–1.46)	150	393,011	1.09	(0.85–1.39)
81	174,134	1.10	(0.79–1.53)	100	273,098	1.39	(1.05–1.83)
P _{trend} ^b			0.57				0.03
				P _{interaction} = 0.72			

^a Multivariable model adjusted for age, cohort, sex, pack-years of cigarette smoking (where appropriate), education (where appropriate), marital status, alcohol consumption, and physical activity

^b Two-sided trend tests were calculated for the midpoint of each category of BMI. Individuals with BMI <18.5 are excluded from the tests for trend.