Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Pooled Analysis of Body Mass Index and Pancreatic Cancer Mortality in African Americans

Traci N. Bethea[1], Cari M. Kitahara[2], Jennifer Sonderman[3], Alpa V. Patel[4], Chinonye Harvey[5], Synnøve F. Knutsen[6], Yikyung Park[2], Song Yi Park[7], Gary E. Fraser[6], Eric J. Jacobs[4], Mark P. Purdue[2], Rachael Z. Stolzenberg-Solomon[2], Elizabeth M. Gillanders[5], William J. Blot[3,8], Julie R. Palmer[1], and Laurence N. Kolonel[7]

Abstract

Background: Pancreatic cancer is a leading cause of cancer-related mortality in the United States 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 HRs and 95% confidence intervals (CI) 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 before 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 to 29.9, 1.25 (95% CI, 0.99–1.57) for BMI 30.0 to 34.9, and 1.31 (95% CI, 0.97–1.77) for BMI ≥35.0 among those with ≥5 years of follow-up ($P_{trend} = 0.03$). 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; $P_{interaction} = 0.02$).

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. *Cancer Epidemiol Biomarkers Prev; 23(10); 2119–25. ©2014 AACR.*

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 (CPS-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 in 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 numbers of African American participants 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; ref. 13), Black

[1]Slone Epidemiology Center at Boston University, Boston, Massachusetts. [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland. [3]International Epidemiology Institute, Rockville, Maryland. [4]American Cancer Society, Atlanta, Georgia. [5]Epidemiology and Genomics Research Program, National Cancer Institute, Rockville, Maryland. [6]Loma Linda University, Loma Linda, California. [7]University of Hawaii Cancer Center, Honolulu, Hawaii. [8]Vanderbilt University School of Medicine, Nashville, Tennessee.

Corresponding Author: Traci N. Bethea, Slone Epidemiology Center at Boston University, 1010 Commonwealth Avenue, Boston, MA 02215. Phone: 617-734-6006; Fax: 617-738-5119; E-mail: tnb@bu.edu

doi: 10.1158/1055-9965.EPI-14-0422

Women's Health Study (BWHS; ref. 14), CPS-II (10), Multiethnic Cohort Study (MEC; ref. 15), National Institutes of Health-AARP Diet and Health Study (NIH-AARP; ref. 16), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; ref. 17), and Southern Community Cohort Study (SCCS; ref. 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 to 24.9, 25 to 29.9, 30 to 34.9, and $\geq$35 kg/m^2.

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 the age of 30 years (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, $\geq$16 years), marital status (married, divorced/separated, or widowed, single), alcohol consumption (none, <10, $\geq$10 g/d), 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 HRs and 95% confidence intervals (CI) for the association of pancreatic cancer mortality with categories of BMI relative to BMI 18.5 to 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 before diagnosis (20, 21), preliminary analyses were stratified on length of follow-up (1 to <5 years, $\geq$5 years) and the remaining analyses were restricted to participants with $\geq$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 $\geq$18.5. Because obesity and type II 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 nonmelanoma skin cancer; heart disease/heart attack; or stroke) at baseline. SAS version 9.3 (SAS Institute Inc.) was used for the analyses.

To assess heterogeneity between cohorts, a meta-analysis was performed using study-specific results for 5 kg/m^2 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

Table 1. Characteristics of study participants (African Americans only), by cohort

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)
$\geq$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*)[a]	68	11	67	453	201	35	62	897

Abbreviation: AA, African American.

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

(STATA 12 software, StataCorp). 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 to 34 and BMI ≥35, respectively, in relation to BMI 18.5 to 24.9 ($P_{trend} = 0.03$). 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 5 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 ($P_{interaction} = 0.02$). 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 ($P_{interaction} = 0.72$).

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

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 HR (95% CI)	Multivariable[b] HR (95% CI)	Deaths *N*	Person-years	Age-adjusted HR (95% CI)	Multivariable[b] 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

[a]Results 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.

[b]Multivariable model adjusted for age, sex (where appropriate), cigarette smoking, education, marital status, alcohol consumption, and physical activity.

[c]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.

Table 3. 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[a]
	Deaths *N*	Person-years	HR (95% CI)	Deaths *N*	Person-years	HR (95% CI)
BMI (kg/m^2)						
		Age <60			Age ≥60	
18.5–24.9	19	271,355	1.00 (Referent)	168	278,085	1.00 (Referent)
25–29.9	21	229,905	1.03 (0.55–1.93)	249	395,483	1.09 (0.89–1.32)
≥30	21	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	
18.5–24.9	60	277,883	1.00 (Referent)	117	250,239	1.00 (Referent)
25–29.9	104	297,677	1.21 (0.88–1.67)	147	296,512	1.00 (0.78–1.27)
≥30	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	
18.5–24.9	73	152,338	1.00 (Referent)	111	385,843	1.00 (Referent)
25–29.9	114	215,475	1.09 (0.81–1.46)	150	393,011	1.09 (0.85–1.39)
≥30	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.

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/m^2 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 no significant evidence of between-study heterogeneity ($P_{heterogeneity} = 0.56$). Overall, the HR for a 5 kg/m^2 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 ($P_{trend} < 0.01$), 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 (SE = 0.12) for incidence and 1.36 (SE = 0.10) for

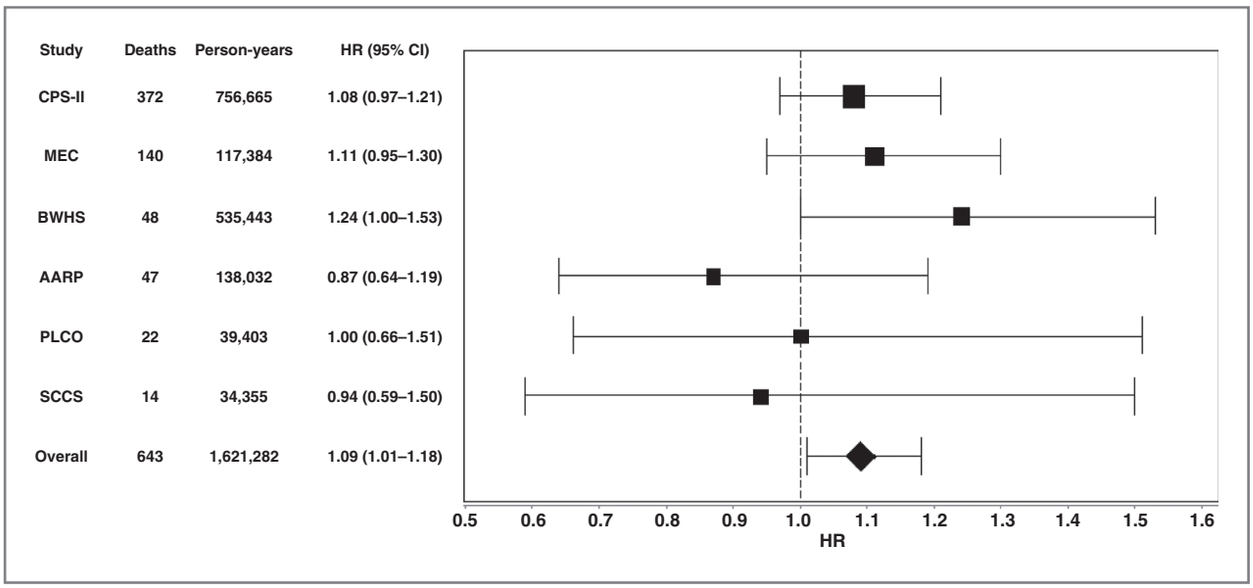

Figure 1. Multivariable HRs and 95% CIs for pancreatic cancer mortality per 5 kg/m^2 increase in BMI among participants with $\geq$5 years of follow-up by study and overall from a random effects meta-analysis. Multivariable models adjusted for age, sex, cigarette smoking, education, marital status, alcohol consumption, and physical activity. 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 $P_{heterogeneity} = 0.67$.

mortality (23). In a meta-analysis that included 9,504 cases of pancreatic cancer from 23 prospective studies, each 5 kg/m^2 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 with 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 TNFα and of IL6, and these cytokines have a positive association with cancer-related death (39). In addition, 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 before diagnosis of pancreatic cancer. Pooling of data across large cohort studies enabled us to accrue a substantial sample size of pancreatic cancer deaths. Furthermore, 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 BMI, 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 I and type II diabetes; however, because type II diabetes comprises 90% to 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. In addition, 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, BMI in African Americans may be more strongly associated with pancreatic cancer mortality among those who have never smoked.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T.N. Bethea, C. Harvey, S.F. Knutsen, Y. Park, G.E. Fraser, E.M. Gillanders, J.R. Palmer, L.N. Kolonel
Development of methodology: G.E. Fraser, E.M. Gillanders, J.R. Palmer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.V. Patel, S.F. Knutsen, Y. Park, G.E. Fraser, E.J. Jacobs, M.P. Purdue, R.Z. Stolzenberg-Solomon, W.J. Blot, J.R. Palmer, L.N. Kolonel
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.N. Bethea, C.M. Kitahara, J.S. Sonderman, Y. Park, E.J. Jacobs, E.M. Gillanders, J.R. Palmer, L.N. Kolonel
Writing, review, and/or revision of the manuscript: T.N. Bethea, C.M. Kitahara, J.S. Sonderman, A.V. Patel, C. Harvey, S.F. Knutsen, Y. Park, S.-Y. Park, G.E. Fraser, E.J. Jacobs, M.P. Purdue, R.Z. Stolzenberg-Solomon, E.M. Gillanders, W.J. Blot, J.R. Palmer, L.N. Kolonel
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T.N. Bethea, C. Harvey

Acknowledgments

The authors thank all of the cohort participants for their many years of dedicated contribution to the studies.

Grant Support

This work was supported by the National Cancer Institute's Intramural Research Program in the Division of Cancer Epidemiology and Genetics and the Epidemiology and Genomics Research Program in the Division of Cancer Control and Populations Sciences. Funding to individual cohorts and investigators included grants from the National Cancer Institute: R01 CA94594 (to G.E. Fraser and S.F. Knutsen), R01 CA058420 (to T.N. Bethea and J.R. Palmer), R37 CA54281 (to L.N. Kolonel and S. Park), R01 CA092447 (to W.J. Blot), R01 CA092447–08S1 (to W.J. Blot and J. Sonderman); the American Cancer Society (to E.J. Jacobs and A. Patel); the Intramural Research Program of the National Cancer Institute (to C.M. Kitahara, Y. Park, M.P. Purdue, and R.Z. Stolzenberg-Solomon); and Epidemiology and Genomics Research Program in the National Cancer Institute's Division of Cancer Control and Population Sciences (to E.M. Gillanders and C. Harvey).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 17, 2014; revised June 17, 2014; accepted July 7, 2014; published OnlineFirst July 13, 2014.

References

1. SEER. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 18 Regs Public-Use. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2012.
2. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–36.
3. SEER. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2011 Sub (1973–2009 varying). National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch; 2012.
4. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012;23:1880–8.
5. Elena JW, Steplowski E, Yu K, Hartge P, Tobias GS, Brotzman MJ, et al. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Cancer Causes Control 2013;24:13–25.
6. Bracci PM. Obesity and pancreatic cancer: overview of epidemiologic evidence and biologic mechanisms. Mol Carcinog 2012; 51:53–63.
7. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of pancreatic cancer. 2012 [cited Apr. 3, 2014]. Available from: http://www.aicr.org/assets/docs/pdf/education/cup-pancreatic-cancer-2012.pdf.
8. Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2012;23:2964–70.
9. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012;307:491–7.
10. Arnold LD, Patel AV, Yan Y, Jacobs EJ, Thun MJ, Calle EE, et al. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? Cancer Epidemiol Biomarkers Prev 2009;18: 2397–405.
11. Silverman DT, Hoover RN, Brown LM, Swanson GM, Schiffman M, Greenberg RS, et al. Why do Black Americans have a higher risk of pancreatic cancer than White Americans? Epidemiology 2003;14: 45–54.
12. Samanic C, Gridley G, Chow WH, Lubin J, Hoover RN, Fraumeni JFJr. Obesity and cancer risk among white and black United States veterans. Cancer Causes Control 2004;15:35–43.
13. Butler TL, Fraser GE, Beeson WL, Knutsen SF, Herring RP, Chan J, et al. Cohort profile: The Adventist Health Study-2 (AHS-2). Int J Epidemiol 2008;37:260–5.
14. Rosenberg L, Adams-Campbell L, Palmer JR. The Black Women's Health Study: a follow-up study for causes and preventions of illness. J Am Med Womens Assoc 1995;50:56–8.
15. Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Body mass index and physical activity as risk factors for pancreatic cancer: the multiethnic cohort study. Cancer Causes Control 2007;18:165–75.
16. Stolzenberg-Solomon RZ, Adams K, Leitzmann M, Schairer C, Michaud DS, Hollenbeck A, et al. Adiposity, physical activity, and pancreatic cancer in the national institutes of health-AARP diet and health cohort. Am J Epidemiol 2008;167:586–97.
17. Stolzenberg-Solomon RZ, Hayes RB, Horst RL, Anderson KE, Hollis BW, Silverman DT. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. Cancer Res 2009;69:1439–47.
18. Signorello LB, Hargreaves MK, Blot WJ. The southern community cohort study: investigating health disparities. J Health Care Poor Underserved 2010;21:26–37.
19. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975–2010. April 2013 [cited 2013 October 2013]. http://seer.cancer.gov/csr/1975_2010/, based on November 2 SEER data submission, posted to the SEER web site]. Available from: http://seer.cancer.gov/csr/1975_2010/.
20. Bachmann J, Ketterer K, Marsch C, Fechtner K, Krakowski-Roosen H, Buchler MW, et al. Pancreatic cancer related cachexia: influence on metabolism and correlation to weight loss and pulmonary function. BMC Cancer 2009;9:255.
21. Wigmore SJ, Plester CE, Richardson RA, Fearon KC. Changes in nutritional status associated with unresectable pancreatic cancer. Br J Cancer. 1997;75:106–9.
22. Boyles AL, Harris SF, Rooney AA, Thayer KA. Forest plot viewer: a new graphing tool. Epidemiology 2011;22:746–7.
23. Stevens RJ, Roddam AW, Spencer EA, Pirie KL, Reeves GK, Green J, et al. Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. Int J Cancer 2009;124:2400–5.
24. Lee IM, Sesso HD, Oguma Y, Paffenbarger RSJr. Physical activity, body weight, and pancreatic cancer mortality. Br J Cancer 2003;88: 679–83.

25. Batty GD, Kivimaki M, Morrison D, Huxley R, Smith GD, Clarke R, et al. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. Cancer Epidemiol Biomarkers Prev 2009;18: 673–5.
26. Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, Roddam A, Stolzenberg-Solomon R, Halkjaer J, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2006;15:879–85.
27. 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;98:1057–65.
28. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–38.
29. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000;11:915–23.
30. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 2003;89:519–23.
31. Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer 2011;129:1708–17.
32. Jiao L, Berrington de Gonzalez A, Hartge P, Pfeiffer RM, Park Y, Freedman DM, et al. Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts. Cancer Causes Control 2010;21:1305–14.
33. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. Cancer Epidemiol Biomarkers Prev 2005;14: 459–66.
34. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer 2007;120: 1993–8.
35. Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer 2005;93:1310–5.
36. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, 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.
37. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001;286:921–9.
38. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012;23:843–52.
39. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev 2009;18:2569–78.
40. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27:S5–10.