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Are Racial Disparities in Pancreatic Cancer Explained by Smoking and Overweight/Obesity?

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Abstract

Between 2001–2005, U.S. Blacks experienced a 32% higher pancreatic cancer death rate than Whites. Smoking, diabetes, and family history may explain some of this disparity, but prospective analyses are warranted. From 1984–2004, there were 6,243 pancreatic cancer deaths among Blacks (n=48,252) and Whites (n=1,011,864) in the Cancer Prevention Study II cohort. Multivariate Cox proportional hazards models yielded hazards ratios for known and suspected risk factors. Population attributable risks were computed and their impact on age-standardized mortality rates evaluated. Blacks in this cohort had a 42% increased risk of pancreatic cancer mortality compared to Whites (HR=1.42; 95% CI 1.28 to 1.58). Current smoking increased risk by >60% in both races; although Blacks smoked less intensely, risks were similar to Whites (HR_{Black}=1.67, 95% CI 1.28 to 2.18; HR_{White}=1.82, 95% CI 1.7 to 1.95). Obesity was significantly associated with pancreatic cancer mortality in Black men (HR=1.66, 95% CI 1.05 to 2.63), White men (HR=1.42; 95% CI 1.25 to 1.60) and White women (HR=1.37; 95% CI 1.22 to 1.54); results were null in Black women. The PAR due to smoking, family history, diabetes, cholecystectomy, and overweight/obesity was 24.3% in Whites and 21.8% in Blacks. Smoking and overweight/obesity play a substantial role in pancreatic cancer. Variation in the impact of these factors underscores the need to evaluate disease on the race-sex level. The inability to attribute excess disease in Blacks to currently known risk factors, even when combined with suspected risks, points to yet undetermined factors that play a role in the disease process.

INTRODUCTION

Pancreatic cancer is the sixth most commonly diagnosed cancer and the fifth leading cause of cancer death¹ in U.S. Blacks (1). Disease trends over the last 30 years illustrate a striking racial disparity. Since the U.S. began monitoring cancer outcomes in 1975, Blacks have been diagnosed with pancreatic cancer at a 48% higher rate than Whites and died from the disease at a 37% higher rate than Whites² (2). Between 2001 and 2005, Blacks were diagnosed with pancreatic cancer at a rate of 15.2/100,000, a 33% excess incidence compared to Whites (11.4/100,000). Five-year mortality trends are similar, with a 32% higher death rate in Blacks. This disparity persists across genders; pancreatic cancer

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¹2004 U.S. Cancer Statistics, Top 10 Cancers: Black males and females combined, <http://apps.nccd.cdc.gov/uscs/>

²SEER Cancer Statistics Review, 1975–2005 Tables XXII-2-4, http://seer.cancer.gov/csr/1975_2005

mortality rates are approximately 27% greater in Black men and 38% greater in Black women as compared to their White counterparts.

Cancer mortality disparities are often correlated with socioeconomic factors, thought to be mediated by differences in screening, early detection, and access to care (3–5). However, the lack of a screening test or other early diagnostic procedure for pancreatic cancer results in a uniformly late diagnosis and subsequently shortened survival time (6). Five-year survival is only at 5%, with little variation across racial or economic groups (2, 6).

While cigarette smoking is a recognized cause of pancreatic cancer (7), diabetes (8–11), family history of pancreatic cancer (8, 11, 12), and elevated body mass index (BMI) (8, 13–15) are suggested to play relatively lesser roles. Associations have been inconsistent for the effects of fruit/vegetable consumption (16–19), alcohol (11, 20–22), gallstones and cholecystectomy (8, 9, 23). Limited research has examined whether differences in these risk factors account for the dramatic racial disparities in incidence and mortality. One case control study indicated that disparities can be explained by different factors at the race-sex sublevel; while diabetes, smoking and family history explained most of the excess disease in Black men, elevated BMI and alcohol consumption added to the excess in Black women (24).

Over a 20-year follow-up period, the American Cancer Society's Cancer Prevention Study (CPS) II cohort yielded more than 6,000 pancreatic cancer deaths. Because of the poor prognosis, mortality often serves as a marker for incidence. Thus, our prospective analysis of CPS II data examined predictors of pancreatic cancer risk in Blacks and Whites using mortality as a surrogate endpoint for incidence. Secondly, we sought to identify factors contributing to the excess occurrence of pancreatic cancer in Blacks based upon what was previously suggested in a smaller case-control study (24).

METHODS

Study Population

In September 1982, the American Cancer Society initiated the Cancer Prevention Study II (CPS II) to prospectively examine factors associated with cancer death through biennial follow-up of participants. Approximately 1.2 million individuals from all 50 states, the District of Columbia, and Puerto Rico were enrolled over a two-month period. Eligible households included those with at least one member aged 45 or older, and all individuals in the home over the age of 30 were asked to complete a questionnaire (8, 25, 26). At enrollment, the cohort was 56.8% female and 4% Black (26), with a median age of 57 years (27).

Our analysis was restricted to CPS II participants who self-identified as White or Black. Individuals with a positive self-report of cancer other than non-melanoma skin cancer at baseline were excluded, as were those who died of any cause within the first two years of follow-up. The later restriction was implemented to reduce misclassification of individuals whose baseline data (e.g., diet, weight, exercise habits) may have been influenced by an undiagnosed disease. Of similar concern is the potential misdiagnosis of pancreatic cancer as new-onset diabetes or gallbladder disease; it is largely unknown whether pancreatic cancer is causal for these illnesses or if they are indicators of early-stage disease. Studies indicate that new-onset diabetes (36 months or less) is associated with increased diagnosis of pancreatic cancer (28, 29). Most recently, it was reported that this increase is highest within 24 months of new-onset diabetes (30). Thus, elimination of individuals who died from any cause within the first two years of follow-up addresses this concern for misclassification of pancreatic cancer as another illness.

Participants were followed from 1984 through 2004, a total of 20 years, and truncated from the study on December 31, 2004 (the end of the CPS II follow-up) or date of death, whichever occurred first.

Questionnaire and Study Variables

The CPS II baseline questionnaire was a four-page survey that collected self-reported demographic, medical history, environmental/occupational exposure, and lifestyle information. Disease history (e.g., diabetes) was captured by asking participants to review a list and place a checkmark next to any diseases for which they had received a doctor's diagnosis. Surgical history (e.g., cholecystectomy) was indicated by checking a box and writing in the nature of the operation. Diagnosis dates were not recorded. Thus, duration of diabetes and cholecystectomy in pancreatic cancer patients ranged from a two-year minimum (cases diagnosed in 1984) to a 20-year minimum (cases diagnosed in 2004). Cigarette smoking was defined as smoking one cigarette a day for at least one year's time; cigar and pipe smoking data were collected separately. Dietary information was assessed by having participants indicate the number of days per week they ate specific foods. Because neither fruit nor vegetable intake was individually predictive of pancreatic cancer risk in a previous CPS II analysis (8), we used a combined fruit/vegetable intake variable (servings per week) derived from self-reported consumption of carrots, fruit, squash, raw vegetables, green vegetables, tomato, and cabbage and used in other CPS II analyses. The questionnaire is available on the American Cancer Society's website.³

Variables of interest in our analysis included race, age, body mass index (BMI) (computed from self-reported weight and height), family history of pancreatic cancer, diabetes, gallstones, and cholecystectomy, physical activity, alcohol consumption, fruit/vegetable intake, education, and smoking habits. Smoking status was defined as "never cigarette smoker," "current cigarette smoker," "former cigarette smoker," "ever cigarette smoker-baseline status not indicated," and "other smoking," which captured cigar/pipe smokers with or without cigarette smoking. For cigarette smokers only, average number of cigarettes smoked per day (CPD) and number of years smoked was recorded. Former smokers indicated time since quitting.

Continuous variables were recoded into categorical variables as follows: One pack of cigarettes was used as a standard to categorize number of cigarettes smoked per day as < 20, 20, or ≥ 20; duration smoked was coded as < 20 years, 20–29 years, and ≥ 30 years; smoking quit-time was coded as < 10 years or ≥ 10 years; BMI was coded as < 18.5 (underweight), 18.5 to < 25 (normal), 25 to < 30 (overweight), and ≥ 30 (obese); fruit/vegetable intake was recoded into quartiles; and physical activity was recoded into "little/no activity" vs. "moderate/high activity."

Outcome Measure

The outcome of interest was pancreatic cancer mortality, defined by ICD-9 codes 157.0–157.9. When CPS II began, vital status information was gathered manually every two years and confirmed by procurement of death certificates from state health departments (26). Beginning in 1988, the cohort was linked to the National Death Index for automated follow-up, which was shown in a validation study to have 99.9% specificity and 92.9% sensitivity in identifying vital status (27). This update occurred biennially through December 2004 for this analysis.

³CPS II 1982 Baseline Questionnaire: http://www.cancer.org/docroot/RES/RES_6_5.asp

Statistical Analysis

The age-adjusted risk of pancreatic cancer mortality associated with Black race was calculated for the CPS II population. Absolute age-standardized pancreatic mortality rates were generated for Blacks and Whites, as well as each race-sex subgroup (i.e., Black/White men and Black/White women), using the entire CPS II cohort as a standard. Cox proportional hazards modeling was used to calculate hazard rate ratios (HR) and corresponding 95% confidence intervals (CI) to examine the relationship between known or suspected risk factors and pancreatic cancer mortality. Risk estimates were calculated for the total Black and White populations, as well as for the four sex-race subgroups. All Cox models were stratified on exact year of age at enrollment. Variables positively associated with pancreatic cancer mortality were considered for inclusion in the multivariate model. Established risk factors (smoking, family history, diabetes, and BMI) were included in the model, regardless of their univariate results. The final multivariate model was stratified by age at enrollment and adjusted for gender (Black-total and White-total models only), diabetes, family history of pancreatic cancer, smoking status, cholecystectomy, and BMI. Non-smoker was used as the referent group for smoking status and 18.5 BMI < 25 (normal) served as the referent for BMI. Individually, physical activity, education, and fruit/vegetable intake were not predictive of pancreatic cancer risk. Additionally, alcohol consumption had a substantial amount of missing information, and gallstones had a significant interaction with cholecystectomy. Thus, these variables were not included in the final models. The inability to include alcohol information in the analysis and examine the impact of heavy drinking, which has been linked to increased pancreatic cancer risk, is a limitation which is addressed in more detail in the Discussion.

To calculate PARs, a sub-dataset was created that eliminated 64,400 subjects (6% of the total study population) with missing smoking or BMI information. For the purpose of PARs, smoking and BMI were recoded into dichotomous variables: “ever smoking” categorized non-smokers vs. anyone who had ever smoked (including pipe/cigar smokers) regardless of baseline status (e.g., current, former, unknown); “overweight/obese” described individuals as normal/underweight (BMI < 25) vs. overweight/obese (BMI ≥ 25). PAR calculations had two components: relative risk and distribution of risk factors in the population. Relative risk estimates were obtained for each variable based on the age-stratified Cox proportional hazards model. Distribution of risk factors (or combination of risk factors for summary PARs) in the case population was based on the Bruzzi method (31). Using this information, univariate age-adjusted PARs were calculated for the Black/White total populations and the four sex-race subgroups for all variables included in the Cox models; Black/White PARs were also adjusted for gender. Summary PARs were computed for several combinations of the five risk factors included in the multivariate model (diabetes, family history, “ever” smoker, overweight/obesity, and cholecystectomy). This allowed for characterization of the proportion of disease attributable to each risk factor or combination of factors present in the population.

To assess the impact of predictors on excess Black mortality, PARs were applied to age-standardized mortality rates for each subgroup studied; this was modeled after a method employed by Silverman et al. (24). All data analysis was performed using SAS v.9.1 (Cary, NC) with statistical significance determined at the $p < 0.05$ level. This study was exempt from Institutional Board Review as data did not contain identifiers.

RESULTS

Of the 1,184,507 individuals in the CPS II cohort, 1,060,389 were eligible for analysis (Table 1), 4.6% of whom were Black. There were 6,243 deaths from pancreatic cancer ($n = 360$ Black) during the 20-year follow-up period. The age-adjusted relative risk for Blacks

was 1.42 (95% CI 1.28 – 1.58). Using the CPS II population as the standard, the age-standardized pancreatic cancer death rate was 45.91 per 100,000 Blacks and 32.31 per 100,000 Whites. The racial disparity persisted by gender; Black women and men demonstrated a 45% excess pancreatic cancer mortality compared to Whites (40.32 vs. 27.60 per 100,000 women; 56.70 vs. 38.82 per 100,000 men).

There was racial variation in the prevalence of two risk factors of interest, smoking and body mass index (BMI), in the CPS II population (Table 2). Consistent with expectations, Black men and women were more likely to be overweight/obese (BMI ≥ 25) than their White counterparts. White women had the highest prevalence of “normal” weight (18 BMI < 25), with obesity (BMI ≥ 30) greatest in Black women. Similarly, cigarette smoking trends differed by race. Although nearly 25% of Blacks and Whites were current cigarette smokers at baseline, a higher proportion of Blacks smoked fewer cigarettes per day (CPD) and for a shorter duration than Whites. More than half of Black smokers (53%) smoked < 20 CPD (or less than one pack) compared to 29% of Whites, a trend that persisted by race-sex subgroup. White men had the highest proportion of heavy smokers (> 20 CPD) (48.4%), while Black women had the lowest (7.4%). White men also smoked the longest, with 75% reporting ≥ 30 years of smoking, followed by Black men (64.1%), White women (59.6%), and Black women (44.9%).

Current cigarette smoking was consistently associated with increased risk of pancreatic cancer mortality in both Blacks and Whites (Table 3). Dose-response for CPD and pancreatic cancer mortality was present in Whites but not Blacks. Although associations with smoking varied by duration, confidence intervals for each time-period (< 20 years, 20–29 years, ≥ 30 years) overlapped for both Blacks and Whites. Former smoking was associated with increased risk in Whites with a quit-time of less than 10 years. For both races, there was no apparent residual effect of cigarette smoking after a quit-time of 10 years or longer.

Current cigarette smoking at baseline was the strongest predictor of pancreatic cancer mortality in Whites (HR = 1.82, 95% CI 1.7 – 1.95) and Blacks (HR = 1.67; 95% CI 1.28 – 2.18). Although family history of pancreatic cancer had a stronger association than current smoking in Blacks (HR = 2.89, 95% CI 1.37 – 6.12), this was based on a small number of exposed cases (n = 7) that only occurred in women (Table 4). In Blacks, risk associated with cigarette smoking was comparable to that of cholecystectomy (HR = 1.62, 95% CI 1.02 – 2.55). Dose-response with increasing BMI was evident in both races, although findings for overweight and obesity were only significant in Whites. Significant risks associated with male gender were comparable in both races. Diabetes and “other” smoking risks were only significant in Whites.

Race-sex subgroup analyses (Table 5) demonstrated that risk profiles of White men and women generally reflected those of Whites overall, while those of Black men and women deviated from the overall Black population. In Blacks, the overall risk associated with family history of pancreatic cancer was driven by Black women (HR = 4.31, 95% CI 2.02 – 9.19), as no males cases reported a family history. The small but non-significant obesity risk in Blacks overall was influenced by the null effect of BMI in Black women; obesity was a strong predictor in Black men (HR = 1.66, 95% CI 1.05 – 2.63). Current cigarette smoking played a substantial role in all groups. BMI dose-response trends were present for all groups but Black women.

In comparing men, diabetes and family history were significant in Whites but not Blacks. The risk associated with smoking was greater in White men (80% vs. 56% increased risk), and obesity played a more substantial role in Black men (66% vs. 42% increased risk);

however, the 95% CIs for these variables in Black men are wide and encompass those for Whites. With respect to female comparisons, most striking was a 4.31-fold increase (95% CI 2.02–9.19) in risk associated with family history of pancreatic cancer in Black women, nearly three times that seen in their White counterparts. Although White women who were former smokers exhibited a small, significant increase in relative risk (RR = 1.13, 95% CI 1.03–1.25), the effect was null after a quit-time of 10 years or more. Relative risks associated with diabetes and cholecystectomy were only significant in White women.

Population attributable risks (PARs) demonstrated that eliminating smoking and overweight/obesity would have the greatest impact on reducing pancreatic mortality in the population (Table 6). PARs were strongest for “ever” smoking, ranging from 13.5% in White women to 19.7% in Black men. Overweight/obesity (BMI ≥ 25) PARs were about half that of smoking PARs. The exception was in Blacks-total and Black women; because overweight/obesity resulted in a null risk in Black women (Table 5), and because this effect strongly influenced the overall Black population, the overweight/obesity PARs were not reportable in these two groups. By gender, overweight/obesity PARs were comparable in Black men (7.9%), White men (7.7%), and White women (6.1%).

Summary PARs (Table 6) due to smoking, diabetes, and family history accounted for approximately 20% of the population attributable risk, with somewhat higher contributions in Black women (21.7%) and lower contributions in White women (15.4%) and White men (18.4%). When cholecystectomy and overweight/obesity were also considered, PARs increased to nearly 25%, with the greatest impact in Black men (27.9%). There was minimal impact of these additional factors in Black women as overweight/obesity hazards ratio was < 1.0 and thus was not included in the PAR summary model.

The generally similar summary PAR in Blacks and Whites is evidence that known risk factors do not account for the racial disparity in pancreatic cancer mortality rates, either overall or within the race-sex subgroups (Table 6). Eliminating smoking, family history, and diabetes exposure in the CPS II population reduced the Black/White mortality disparity from 42% to 37%; on the race-sex level, the male disparity decrease was minimal (46% to 44%) compared to the disparity decrease in female mortality (46% to 35%). Eliminating all five variables from the male population further reduced the disparity to 39% excess deaths in Blacks. In women, elimination of all variables did not impact the disparity (and actually increased it by 10%, to 45% excess Black deaths) as much as only eliminating smoking, family history, and diabetes; again, this was primarily because overweight/obesity was not included in the PAR summary model for Black women (due to HR < 1.0).

DISCUSSION

This analysis of a large, well-established cohort that yielded 6,243 pancreatic cancer deaths in Blacks and Whites over a 20-year period suggests a substantial role for overweight/obesity in pancreatic cancer risk. We found evidence of racial variation in impact of smoking and BMI and suggest that these modifiable risk factors act differently among race-sex subgroups. However, we were unable to attribute racial disparities in pancreatic cancer incidence and mortality rates to these and other accepted or suspected factors (e.g., diabetes, family history, cholecystectomy, physical activity, diet, etc.).

The primary outcome measure of CPS II is cancer death, as ascertained through linkage of the cohort to the National Death Index; cancer incidence is not measured. Pancreatic cancer has a poor prognosis, with 5-year survival at ~5%. Thus, to examine factors contributing to increased risk of disease in Blacks, we used mortality as a proxy indicator of incidence. This

approach has been used in studies of other rapidly fatal conditions, such as Creutzfeldt-Jakob disease (32) and brain cancer (33).

Cigarette smoking is an accepted cause of pancreatic cancer (7), with magnitude of risk impacted by amount and duration smoked (34). In our study, the effect of current smoking on pancreatic cancer risk as measured by hazard ratios and PARs was comparable in Blacks and Whites overall, despite the fact that Blacks smoked fewer cigarettes per day and for a shorter duration. A dose-response effect was only observed in Whites. Although counter-intuitive, these findings mirror what is seen in lung cancer, where racial differences in smoking run counter to incidence trends and fail to explain excess cancer in Blacks (35). This supports exploration of racial differences in tobacco metabolism and toxicity. Although such research is limited, there is some evidence for increased K-ras mutations in Blacks with pancreatic cancer (36); K-ras mutations are also linked to smoking (37).

Overweight and obesity (BMI ≥ 25) account for a substantial excess of U.S. cancer deaths (38). BMI has gained attention as a possible risk factor for pancreatic cancer (8, 15, 18, 38, 39), with a potentially greater role in men (8, 15, 39). Our PARs for excess pancreatic cancer deaths due to overweight/obesity range from 6.1% (White women) to 7.9% (Black men) and are consistent with these reports. These were half the magnitude of smoking PARs, and approximately three to five times those for diabetes, a traditionally accepted risk factor for pancreatic cancer. This suggests that elevated BMI plays a substantial role in contributing to excess pancreatic cancer mortality. As this is a modifiable risk factor, there exists the potential for substantial impact of weight loss on disease rates.

Our BMI findings highlight differences in the relationship between overweight/obesity and pancreatic cancer at the race-sex sublevel. The strongest association between BMI and pancreatic cancer mortality was in Black men. Counter to other subgroups, overweight/obesity had a null effect in Black women. Although surprising, this finding is not unique. The Hawaii-Los Angeles Multiethnic Cohort Study reported an inverse relationship between increasing BMI and pancreatic cancer risk. This appeared to be driven by Black women, but the numbers were too small for definitive conclusions (15). An inverse relationship has been reported between increasing BMI and risk of multiple myeloma in Black women (40), and the Black Women's Health study demonstrated that elevated adolescent BMI was inversely related with risk of post-menopausal breast cancer (41). It is not clear why elevated BMI appears protective (or has a null effect) for certain conditions in Black women, but such findings provide a rationale for investigating the effects of overweight/obesity in light of race and gender.

Insulin as a causative agent in the pancreatic cancer disease process is not fully understood. It is hypothesized that independent of BMI, insulin resistance or abnormal glucose metabolism cause pancreatic cancer (42, 43). Downregulation of insulin-like growth factor binding protein may cause excess insulin, which then over-stimulates pancreatic cell division. Lipid peroxidation may induce DNA adducts that irreparably damage the pancreas (14). There is also support for central adiposity as an independent risk factor for disease; gender variation in adipose distribution may explain some of the differences observed in the relationships between obesity and pancreatic cancer (44). BMI may be an effect modifier of these pathways. With these factors in mind, we strongly advocate for considering gender and racial differences when conducting future research as understanding what appears to be a null effect in Black women may help guide prevention and control methods in other subgroups.

A previous case-control analysis of 434 pancreatic cancer patients reported that nearly all the excess disease risk in Black men was attributable to smoking, diabetes, and family

history (24). These factors plus moderate/high BMI and heavy alcohol consumption explained the excess pancreatic cancer in Black women; in their absence, it was projected that White women would experience a higher rate of pancreatic cancer than Black women. Although, the number of Black female cases was small ($n = 94$), this analysis was important in that it suggested modifiable risk factors account for the substantial excess pancreatic cancer in Blacks and that racial disparities can be reduced with lifestyle changes.

One of the aims in our present analysis was to further investigate these findings using prospective data from a well-established cohort. We were unable to replicate these results and did not identify individual or combinations of factors that explained the disparity in the CPS II population. Although not large compared to number of White cases, our study included a larger number of Black cases than the previous case control study. This may explain some of the variability in associations between the two studies, especially when some variables contain smaller numbers of exposed cases.

Previous work identified diabetes and smoking as the largest contributors to excess pancreatic cancer in Black men. Because our study found a null effect of diabetes in Black men, the combination of diabetes and smoking did not have the same impact on excess disease. It is noted that the finding of a null effect of diabetes in Blacks overall is consistent with past CPS II analyses (45), as well as with a null finding in Black women previously reported (24). As discussed earlier, despite Blacks smoking less intensely than Whites, pancreatic cancer risks were comparable. Even though “ever smoking” did not explain the Black/White difference in men, we did see evidence of racial variation in the impact of smoking by amount and duration. This supports a rationale for looking at racial variation in tobacco metabolism/toxicity.

Earlier, heavy alcohol consumption and BMI were identified as additional contributors to the racial disparity in pancreatic cancer. Again, we were unable to replicate this finding. This may be due, in part, to our inability to include alcohol in the models due to a large amount of missing data (43% women, 31.4% men). It was previously suggested that the “missing alcohol” category includes both nondrinkers and heavy drinkers who may not have wanted to report their alcohol consumption (46). While omitting this variable from the analysis may raise concerns, it is noted that many reports for associations with heavy drinking were based on smaller samples. Recent studies with a larger number of cases still yield inconsistent results; for instance, while a prospective analysis of 1.3 million women found no significant relationship between pancreatic cancer and alcohol, even at the highest levels of drinking (47), a pooled analysis supports an increased risk with higher levels of alcohol consumption (48).

Strengths to our study include a prospective analysis, which reduces the chance of recall bias introduced in case control studies. We used data from a large, well-established cohort whose overall disease and incidence trends reflect those of the U.S. population. Case ascertainment in this cohort has high sensitivity and specificity, reducing the possibility of misclassification of death from pancreatic cancer. With 360 cases of pancreatic cancer in Blacks, and nearly 6,000 cases in Whites, we were able to draw comparisons between the two groups and also examine a number of factors on the race-sex sublevel.

Despite the fact that the CPS II cohort includes individuals from across the U.S., generalizability of findings is limited. The cohort is more educated and affluent than the general U.S. population, limiting the ability to directly compare disease and exposure rates to the greater US population. However, it is unlikely that this compromises internal validity of the study (8, 49). In particular, smoking trends are consistent with those of the U.S.

population (26); these data have been used to estimate risks for global tobacco burden (50) and served as the mainstay for Surgeon General tobacco reports.

Other limitations of this study include a small number of exposed Black cases for certain factors (e.g., family history and cholecystectomy in Black men) and the reliance on baseline data, which may under-estimate risk estimates. Specifically, CPS II does not capture changes in BMI and diabetes, the prevalence of which most likely increased over the 20-year follow-up period. Thus, we potentially misclassified cases as normal BMI or non-diabetic when in fact their status changed prior to development of pancreatic cancer. This may explain the weaker association with diabetes from what was previously reported with shorter follow-up in this population (8).

In conclusion, we were unable to attribute racial disparities in pancreatic cancer to smoking, diabetes, family history, BMI, and cholecystectomy. However, risk estimates and PARs for smoking and overweight/obesity indicate racial variation in the impact of these factors on pancreatic cancer. In particular, variation in the effect of overweight/obesity was most evident when comparing sex-race subgroups and reiterate previous calls to look beyond the larger Black/White population to better understand risks for pancreatic cancer. The suggestion that such risk factors impact race-sex subgroups differently may have implications for targeting risk reduction messages and interventions. The inability to attribute excess risk of disease in Blacks to currently accepted or speculative risk factors points to other, yet to be determined, etiologic factors that play a role in the disease process.

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Abbreviations

CI	confidence interval
CPD	Cigarettes per day
CPS	Cancer Prevention Study
HR	Hazards Ratio
PAR	population attributable risk

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Table 1

Cancer Prevention Study II Cohort Exclusion Cascade.

	<u>Total Population</u>	<u>Men</u>		<u>Women</u>	
		<u>Total</u>	<u>Pancreatic Cancer Cases</u>	<u>Total</u>	<u>Pancreatic Cancer Cases</u>
Initial Cohort	1,184,507	508,280	3,609	676,227	3,720
Exclusions					
Cancer at baseline	82,333	25,236	235	57,097	406
Race other than Black/White	25,653	10,935	59	14,718	65
Death from any cause in first two years of follow-up (1982–1984)	16,132	10,156	196	5,976	125
Total included in analysis	1,060,389	461,953	3,119	598,436	3,124
White	1,011,864	444,351	2,968	567,513	2,915
Black	48,525	17,602	151	30,923	209

Table 2Prevalence (%) of Risk Factors at Baseline in the CPS II Cohort, 1984 – 2004.^a

	Total Population		Men		Women	
	Black (n = 48,525)	White (n = 1,011,864)	Black (n = 17,602)	White (n = 444,351)	Black (n = 30,923)	White (n = 567,513)
Male Gender	36.3	43.9	-----	-----	-----	-----
Diabetes	10.2	4.6	10.6	5.3	10.0	4.0
Family history pancreatic cancer	0.7	1.3	0.5	1.2	0.7	1.4
Cholecystectomy	3.5	6.2	1.4	3.7	4.7	8.1
Smoking Status						
Never	40.2	40.8	24.7	25.3	49.1	52.9
Current cigarette smokers	26.5	20.1	30.4	20.4	24.3	19.9
<i>Amount^b</i>						
< 20 cigarettes per day	53.4	29.0	45.8	21.2	58.8	35.3
20 cigarettes per day	27.3	30.9	33.7	28.5	22.7	32.8
> 20 cigarettes per day	10.8	36.6	15.7	48.4	7.4	27.1
<i>Duration^b</i>						
0–19 years	16.8	9.3	10.1	5.9	21.6	12.0
20–29 years	26.5	23.0	21.4	17.4	30.1	27.5
30+ years	52.9	66.8	64.1	75.8	44.9	59.6
Former cigarette smokers	15.6	24.8	19.5	29.8	13.3	20.8
Quit < 10 years ^c	38.1	30.7	38.5	30.6	37.8	31.0
Quit ≥ 10 years ^c	58.5	68.2	58.5	68.7	58.4	67.8
Ever cigarette smokers, unknown status at baseline	3.0	1.6	3.7	1.4	2.5	1.8
Other smoker ^d	5.1	9.0	14.1	20.4	0	0
BMI						
< 18.5	1.4	1.9	1.0	0.8	1.6	2.6
18.5 – <25.0	33.5	49.8	32.3	38.0	34.2	59.1
25.0 – < 30.0	39.1	36.0	46.5	49.1	34.9	25.7
≥ 30.0	21.7	10.3	16.0	10.0	24.9	10.5

^aPercentages may not total 100% due missing data and rounding error.^bPercentages based upon total number of current cigarette smokers^cPercentages based upon total number of former cigarette smokers^dOther smokers include pipe and cigar smokers, with or without cigarette smoking

Table 3

Smoking Habits and Hazard Ratios (95% Confidence Interval) for Pancreatic Cancer by Race in the CPS II Cohort, 1984 – 2004.

Cigarette Smoking Status	No. exposed cases		HR (95% CI) ^a	
	Black	White	Black	White
Never Smoker	124	2,102	1.0 (referent)	1.0 (referent)
Current Cigarette Smoker	111	1,393		
Amount^b				
< 20 cigarettes per day	55	366	1.56 (1.13, 2.17)	1.51 (1.35, 1.69)
20 cigarettes per day	35	448	1.97 (1.32, 2.92)	1.91 (1.72, 2.12)
> 20 cigarettes per day	10	526	1.49 (0.77, 2.89)	2.09 (1.89, 2.32)
Duration^b				
0–19 years	11	61	1.92 (1.01, 3.65)	1.52 (1.17, 1.97)
20–29 years	20	216	1.55 (0.94, 2.56)	1.90 (1.63, 2.21)
30+ years	78	1,102	1.77 (1.31, 2.40)	1.83 (1.70, 1.98)
Former Cigarette Smoker	45	1,376		
Quit < 10 yrs ^c	14	439	0.87 (0.50, 1.53)	1.34 (1.20, 1.49)
Quit 10 years ^c	27	921	0.89 (0.58, 1.36)	0.99 (0.92, 1.07)

^aHazard ratio, stratified by age at enrollment and adjusted for gender, diabetes, and BMI

^bCigarettes smoked per day and duration HRs based upon total number of cases who were current smokers at baseline; exposed cases may not equal total cases who were current smokers due to missing data

^cQuit-time HRs based upon total number of cases who were former smokers at baseline; exposed cases may not total cases who were former smokers due to missing data

Table 4

Hazard Ratios for Pancreatic Cancer by Race in the Cancer Prevention Study II Cohort, 1984 – 2004.

	Blacks n = 360 cases; 48,165 controls		Whites n = 5,883 cases; 1,005,981 controls	
	No. exposed cases	HR (95% CI)^a	No. exposed cases	HR (95% CI)^a
Male gender	151	1.39 (1.11, 1.75)	2,968	1.33 (1.26, 1.41)
Diabetes	35	0.97 (0.68, 1.38)	344	1.36 (1.22, 1.51)
Family history of pancreatic cancer	7	2.89 (1.37, 6.12)	136	1.65 (1.4, 1.96)
Cholecystectomy	20	1.62 (1.02, 2.55)	442	1.10 (1.0, 1.22)
Smoking Status^b				
Never cigarette smoker	124	1.0 (referent)	2,102	1.0 (referent)
Current cigarette smoker	111	1.67 (1.28, 2.18)	1,393	1.82 (1.7, 1.95)
Former cigarette smoker	45	0.92 (0.65, 1.3)	1,376	1.07 (1.00, 1.15)
Ever cigarette smoker, unknown status at baseline	22	2.31 (1.46, 3.66)	102	1.24 (1.01, 1.51)
Other smoker ^c	21	1.10 (0.67, 1.80)	665	1.24 (1.12, 1.36)
BMI^b				
< 18.5	2	0.44 (0.11, 1.77)	86	0.93 (0.75, 1.16)
18.5 – <25.0	122	1.0 (referent)	2,644	1.0 (referent)
25.0 – < 30.0	136	0.89 (0.7, 1.4)	2,351	1.15 (1.08, 1.22)
30.0	80	1.06 (0.8, 1.42)	690	1.4 (1.28, 1.52)

^aHazard Ratio, 95% Confidence Interval; stratified by age at enrollment and adjusted for gender, diabetes, family history of pancreatic cancer, cholecystectomy, smoking status, and BMI

^bNumber of exposed cases may not equal total cases due to missing data

^cOther smokers includes pipe and cigar smokers, with or without cigarette smoking

Table 5

Hazard Ratios for Pancreatic Cancer in the Cancer Prevention Study II Cohort by Gender and Race, 1984 – 2004.^a

	Men				Women			
	Black n = 151 cases; 17,451 controls		White n = 2,968 cases; 441,383 controls		Black (209 cases; 30,714 controls)		White (2,915 cases; 564,598 controls)	
	No. exposed cases	HR ^a (95% CI)	No. exposed cases	HR ^a (95% CI)	No. exposed cases	HR ^a (95% CI)	No. exposed cases	HR ^a (95% CI)
Diabetes	11	0.70 (0.38–1.29)	199	1.44 (1.24, 1.66)	24	1.23 (0.80, 1.89)	145	1.26 (1.07, 1.50)
Family history of pancreatic cancer	0	----	67	1.80 (1.41, 2.29)	7	4.31 (2.02, 9.19)	69	1.53 (1.21, 1.94)
Cholecystectomy	5	2.23 (0.91, 5.49)	132	1.05 (0.88, 1.25)	15	1.5 (0.88, 2.54)	310	1.13 (1.00, 1.27)
Smoking Status^b								
Never cigarette smoker	35	1.0 (referent)	664	1.0 (referent)	89	1.0 (referent)	1,438	1.0 (referent)
Current cigarette smoker	50	1.56 (1.00, 2.43)	696	1.80 (1.62, 2.01)	61	1.75 (1.25, 2.45)	697	1.83 (1.67, 2.01)
Former cigarette smoker	22	0.82 (0.48, 1.4)	809	1.03 (0.93, 1.14)	23	0.99 (0.62, 1.57)	567	1.13 (1.03, 1.25)
Ever cigarette smoker, unknown status at baseline	13	2.42 (1.27, 4.61)	46	1.29 (0.96, 1.74)	9	1.95 (0.98, 3.89)	56	1.2 (0.92, 1.56)
Other smoker ^c	21	0.98 (0.57, 1.7)	665	1.22 (1.10, 1.36)	0	----	0	----
BMI^b								
< 18.5	0	----	19	0.83 (0.53, 1.31)	2	0.6 (0.15, 2.44)	67	0.97 (0.76, 1.24)
18.5 – <25.0	45	1.0 (referent)	1,080	1.0 (referent)	77	1.0 (referent)	1,564	1.0 (referent)
25.0 – < 30.0	65	1.02 (0.69, 1.49)	1,479	1.11 (1.02, 1.2)	71	0.82 (0.59, 1.14)	872	1.2 (1.10, 1.30)
30.0	33	1.66 (1.05, 2.63)	336	1.42 (1.25, 1.60)	47	0.82 (0.56, 1.18)	354	1.37 (1.22, 1.54)

^aHazard Ratio, 95% Confidence Interval; stratified by age at enrollment and adjusted for diabetes, family history of pancreatic cancer, cholecystectomy, smoking status, and BMI

^bNumber of exposed cases may not equal total cases due to missing data

^cOther smokers includes pipe and cigar smokers, with or without cigarette smoking

Table 6Age-Adjusted Population Attributable Risk (PAR) for Factors Associated with Pancreatic Cancer.^a

Risk Factors	Total		Men		Women	
	Black	White	Black	White	Black	White
Diabetes	0.4%	1.7%	NR ^a	2.2%	3.6%	1.3%
Family history of pancreatic cancer	1.2%	1.0%	NR ^b	1.0%	2.6%	0.9%
Ever smoker ^c	19.1%	15.2%	19.7%	15.9%	17.0%	13.5%
Cholecystectomy	2.2%	0.9%	2.3%	0.2%	2.2%	1.6%
Overweight/obese (BMI ≥ 25)	NR ^a	7.2%	7.9%	7.7%	NR ^a	6.1%
Summary PARs						
<i>Diabetes, family history, ever smoker</i>	20.3%	17.6%	19.7% ^d	18.4%	21.7%	15.4%
Pancreatic Cancer Mortality, CPS II Population (per 100,000)	45.91	32.31	56.70	38.82	40.32	27.60
Pancreatic Cancer Mortality, Unexposed CPS II Population ^e (per 100,000)	36.59	26.62	45.53	31.68	31.57	23.35
<i>Diabetes, family history, ever smoker, cholecystectomy, overweight/obese</i>	21.8% ^f	24.3%	27.9% ^d	24.3%	23.1% ^f	22.5%
Pancreatic Cancer Mortality, CPS II Population (per 100,000)	45.91	32.31	56.70	38.82	40.32	27.60
<i>Pancreatic Cancer Mortality, Unexposed CPS II Population^e (per 100,000)</i>	35.90	24.46	40.88	29.39	31.01	21.39

^aPARs calculated for variables with HR > 1.0; total PARs adjusted for age and gender; sex-specific PARs adjusted for age; NR = No reportable PAR due to HR < 1.0

^bNot reportable as n = 0 male cases reported a family history of pancreatic cancer

^cIncludes current, former, and ever-baseline status unknown cigarette smokers and pipe/cigar smokers with or without cigarette smoking

^dDoes not include diabetes or family history as HR < 1.0

^eDeaths rates in the CPS II population had the entire population not been exposed to the risk factors considered in the PAR calculation

^fDoes not include overweight/obese as HR < 1.0