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

Lauren D. Arnold, Alpa V. Patel, Yan Yan, Eric J. Jacobs, Michael J. Thun, Eugenia E. Calle, and Graham A. Colditz

1Department of Surgery, Washington University in St. Louis, St. Louis, Missouri; 2Department of Epidemiology, American Cancer Society, Atlanta, Georgia; and 3Division of Prevention and Control, Siteman Cancer Center, St. Louis, Missouri

Abstract

Between 2001 and 2005, Blacks from the United States experienced a 32% higher pancreatic cancer death rate than Whites. Smoking, diabetes, and family history might explain some of this disparity, but prospective analyses are warranted. From 1984 to 2004, there were 6,243 pancreatic cancer deaths among Blacks (n = 48,529) and Whites (n = 1,011,864) in the Cancer Prevention Study II cohort. Multivariate Cox proportional hazards models yielded hazards ratios (HR) for known and suspected risk factors. Population attributable risks were computed and their effect on age-standardized mortality rates were evaluated. Blacks in this cohort had a 42% increased risk of pancreatic cancer mortality compared with Whites (HR, 1.42; 95% confidence intervals (CI), 1.28-1.58). Current smoking increased risk by >60% in both races; although Blacks smoked less intensely, risks were similar to Whites (HRBlack, 1.67; 95% CI, 1.28-2.18; HRWhite, 1.82; 95% CI, 1.7-1.95). Obesity was significantly associated with pancreatic cancer mortality in Black men (HR, 1.66; 95% CI, 1.05-2.63), White men (HR, 1.42; 95% CI, 1.25-1.60), and White women (HR, 1.37; 95% CI, 1.22-1.54); results were null in Black women. The population attributable risk 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 effect 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. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2397–405)

Introduction

Pancreatic cancer is the sixth most commonly diagnosed cancer and the fifth leading cause of cancer death in Blacks from the United States (1). Disease trends over the last 30 years illustrate a striking racial disparity. Since the United States 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 Whites (2). Between 2001 and 2005, Blacks were diagnosed with pancreatic cancer at a rate of 15.2 out of 100,000, a 33% excess incidence compared with Whites (11.4/100,000). Five-year mortality trends were similar, with a 32% higher death rate in Blacks. This disparity persists across genders; pancreatic cancer mortality rates are ~27% greater in Black men and 38% greater in Black women as compared with 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).

Although 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; refs. 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; although 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 II (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...
Materials and Methods

Study Population. In September 1982, the American Cancer Society initiated the 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 2-mo 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 y (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 nonmelanoma skin cancer at baseline were excluded, as were those who died of any cause within the first 2 y of follow-up. The later restriction was implemented to reduce misclassification of individuals whose baseline data (e.g., diet, weight, and 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 mo or less) is associated with elimination of individuals whose baseline data (e.g., diet, weight, and exercise habits) may have been influenced by an undiagnosed disease. Of similar concern is the potential misdiagnosis of pancreatic cancer as another illness.

Participants were followed from 1984 to 2004, a total of 20 y, 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, the duration of diabetes and cholecystectomy in patients with pancreatic cancer ranged from a 2-y minimum (pancreatic cancer deaths in 1984) to a 22-y minimum (pancreatic cancer deaths in 2004).

Cigarette smoking was defined as smoking one cigarette a day for at least 1 y; 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 were 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 web site (8).

Variables of interest in our analysis included race, age, 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 CPD as <20, 20, or ≥20; duration smoked was coded as <20 y, 20 to 29 y, and ≥30 y; smoking quit time was coded as ≤10 or ≥10 y; 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” versus “moderate/high activity.”

Outcome Measure. The outcome of interest was pancreatic cancer mortality, defined by International Classification of Diseases-9 codes 157.0 to 157.9. When CPS II began, vital status information was gathered manually every 2 y 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.

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. Nonsmokers were used as the referent group for smoking status and 18.5 ≤ BMI < 25 (normal) served as the referent for BMI. Individuals, 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 effect 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 population-attributable risk (PAR), a sub-data set 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 nonsmokers versus 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) versus 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 effect of predictors on excess Black mortality, PARs were applied to age-standardized mortality rates for each subgroup studied; this was modeled after a method used by Silverman et al. (24). All data analysis was done using SAS v.9.1 with statistical significance determined at \( P < 0.05 \). 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 showed a 45% excess pancreatic cancer mortality compared with Whites (40.32 versus 27.60 per 100,000 women; 56.70 versus 38.82 per 100,000 men).

There was racial variation in the prevalence of two risk factors of interest, smoking and 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 and for a shorter duration than Whites. More than half of the Black smokers (53%) smoked <20 CPD (or less than one pack) compared with 29% of Whites, a trend that persisted by race-sex subgroup. White men had the highest proportion of heavy smokers (>20 CPD; 48.4%), whereas 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 in Blacks. Although associations with smoking varied by duration, confidence intervals for each time-period (<20, 20-29, and ≥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) showed that risk profiles of White men and women generally reflected those of Whites overall, whereas 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 nonsignificant 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 except Black women.

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

PARs showed that eliminating smoking and overweight/obesity would have the greatest effect 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 ∼20% of the PAR, 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 effect in Black men (27.9%). There was minimal effect of these additional factors in Black women as overweight/obesity HR 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 3. Smoking habits and HR (95% CI) for pancreatic cancer by race in the CPS II cohort (1984-2004)

<table>
<thead>
<tr>
<th>Cigarette smoking status</th>
<th>Black</th>
<th>White</th>
<th>HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoker</td>
<td>124</td>
<td>2,102</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>111</td>
<td>1,393</td>
<td>1.56 (1.13-2.17)</td>
</tr>
<tr>
<td>Amount (cigarettes/d)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>55</td>
<td>366</td>
<td>1.97 (1.32-2.92)</td>
</tr>
<tr>
<td>20</td>
<td>35</td>
<td>448</td>
<td>1.49 (0.77-2.89)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>10</td>
<td>526</td>
<td>1.49 (0.77-2.89)</td>
</tr>
<tr>
<td>Duration (y)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>11</td>
<td>61</td>
<td>1.92 (1.01-3.65)</td>
</tr>
<tr>
<td>20-29</td>
<td>20</td>
<td>216</td>
<td>1.55 (0.94-2.56)</td>
</tr>
<tr>
<td>30+</td>
<td>78</td>
<td>1,102</td>
<td>1.77 (1.31-2.40)</td>
</tr>
<tr>
<td>Former cigarette smoker</td>
<td>45</td>
<td>1,376</td>
<td>0.87 (0.50-1.53)</td>
</tr>
<tr>
<td>Quit &lt; 10 y‡</td>
<td>14</td>
<td>439</td>
<td>0.89 (0.58-1.36)</td>
</tr>
<tr>
<td>Quit ≥ 10 y‡</td>
<td>27</td>
<td>921</td>
<td>1.34 (1.20-1.49)</td>
</tr>
</tbody>
</table>

*HR, stratified by age at enrollment and adjusted for gender, diabetes, and BMI.
†CPD and duration HRs based on total number of cases who were current smokers at baseline; exposed cases may not equal total cases that were current smokers due to missing data.
‡Quit-time HRs based on total number of cases who were former smokers at baseline; exposed cases may not total cases that were former smokers due to missing data.

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 with 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 affect 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 the effect 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 the 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 affected by amount...
### Table 5. HRs for pancreatic cancer in the CPS II cohort by gender and race (1984-2004)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black (151 cases; 17,451 controls)</td>
<td>White (2,968 cases; 441,383 controls)</td>
</tr>
<tr>
<td></td>
<td>No. of exposed cases</td>
<td>HR* (95% CI)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 0.70 (0.38-1.29)</td>
<td>199 1.44 (1.24-1.66)</td>
</tr>
<tr>
<td>Family history of</td>
<td>0 —</td>
<td>67 1.80 (1.41-2.29)</td>
</tr>
<tr>
<td>pancreatic cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>5 2.23 (0.91-5.49)</td>
<td>132 1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Smoking status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never cigarette smoker</td>
<td>35 1.0 (referent)</td>
<td>664 1.0 (referent)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>50 1.56 (1.00-2.43)</td>
<td>696 1.80 (1.62-2.01)</td>
</tr>
<tr>
<td>Former cigarette smoker</td>
<td>22 0.82 (0.48-1.4)</td>
<td>809 1.03 (0.93-1.14)</td>
</tr>
<tr>
<td>Ever cigarette smoker,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unknown status at baseline</td>
<td>13 2.42 (1.27-4.61)</td>
<td>46 1.29 (0.96-1.74)</td>
</tr>
<tr>
<td>Other smoker‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI†</td>
<td>21 0.98 (0.57-1.7)</td>
<td>665 1.22 (1.10-1.36)</td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>0 —</td>
<td>19 0.83 (0.53-1.31)</td>
</tr>
<tr>
<td>18.5 to &lt;25.0</td>
<td>45 1.0 (referent)</td>
<td>1,080 1.0 (referent)</td>
</tr>
<tr>
<td>25.0 to &lt;30.0</td>
<td>65 1.02 (0.69-1.49)</td>
<td>1,479 1.11 (1.02-1.2)</td>
</tr>
<tr>
<td>≥30.0</td>
<td>33 1.66 (1.05-2.63)</td>
<td>336 1.42 (1.25-1.60)</td>
</tr>
</tbody>
</table>

---

*HR, 95% CI; stratified by age at enrollment and adjusted for diabetes, family history of pancreatic cancer, cholecystectomy, smoking status, and BMI.

†Number of exposed cases may not equal number of total cases due to missing data.

‡Other smokers includes pipe and cigar smokers, with or without cigarette smoking.
and duration smoked (34). In our study, the effect of current smoking on pancreatic cancer risk as measured by HR 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 counterintuitive, these findings mirror what is seen in lung cancer, in which racial differences in smoking run counter to incidence trends and fail to explain excess cancer in Blacks (35). This finding is not unique. The Hawaii-Los Angeles Multi-ethnic Cohort Study reported an inverse relationship between BMI and pancreatic cancer risk. This seemed 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 showed that elevated adolescent BMI was inversely related with risk of postmenopausal breast cancer (41). It is not clear why elevated BMI seems 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). Down-regulation of insulin-like growth factor binding protein may cause excess insulin, which then overstimulates 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 seems 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 patients with pancreatic cancer 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 risk factors associated with pancreatic cancer.}

### Table 6. Age-adjusted PAR for factors associated with pancreatic cancer

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.4%</td>
<td>1.7%</td>
<td>NR*</td>
</tr>
<tr>
<td>Family history of pancreatic cancer</td>
<td>1.2%</td>
<td>1.0%</td>
<td>NR†</td>
</tr>
<tr>
<td>Ever smoker‡</td>
<td>19.1%</td>
<td>15.2%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>2.2%</td>
<td>0.9%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Overweight/obese (BMI ≥ 25)</td>
<td>NR*</td>
<td>7.2%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary PARs</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes, family history, ever smoker</td>
<td>20.3%</td>
<td>17.6%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Pancreatic cancer mortality, CPS II population (per 100,000)</td>
<td>45.91</td>
<td>32.31</td>
<td>56.70</td>
</tr>
<tr>
<td>Pancreatic cancer mortality, unexposed CPS II population (per 100,000)</td>
<td>36.59</td>
<td>26.62</td>
<td>45.53</td>
</tr>
<tr>
<td>Diabetes, family history, ever smoker, cholecystectomy, overweight/obese</td>
<td>21.8%</td>
<td>24.3%</td>
<td>27.9%</td>
</tr>
<tr>
<td>Pancreatic cancer mortality, CPS II population (per 100,000)</td>
<td>45.91</td>
<td>32.31</td>
<td>56.70</td>
</tr>
<tr>
<td>Pancreatic cancer mortality, unexposed CPS II population (per 100,000)</td>
<td>35.90</td>
<td>24.46</td>
<td>40.88</td>
</tr>
</tbody>
</table>

*PARs 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.
†Not reportable as n = 0 male cases reported a family history of pancreatic cancer.
‡ Includes current, former, and ever-baseline status unknown cigarette smokers and pipe/cigar smokers with or without cigarette smoking.
Does not include diabetes or family history as HR < 1.0.
∥ Death rates in the CPS II population had the entire population not been exposed to the risk factors considered in the PAR calculation.
§ Does not include overweight/obese as HR < 1.0.
Smoking, Obesity, and Racial Disparities in Pancreatic Cancer

Factors that explained the disparity in the CPS II population. Although not large compared with the 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 effect 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 reported previously (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 effect of smoking by amount and duration. This supports a rationale for looking at racial variation in tobacco metabolism and sensitivity.

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 and 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). Although 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, whereas a prospective analysis of 1.3 million women found no significant variation in tobacco metabolism and sensitivity.

The strengths of 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 United States, the generalizability of these 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 U.S. population. However, it is unlikely that this compromises the 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 reliance on baseline data, which may underestimate 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 nondiabetic when in fact their status changed prior to the 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 effect of these factors on pancreatic cancer. In particular, variation in the effect of overweight/obesity was most evident when comparing sex-race subgroups and reiterates previous calls to look beyond the larger Black/White population to better understand risks for pancreatic cancer. The suggestion that such risk factors affect 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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.

The authors thank Dr. Dana Flanders (Emory University/American Cancer Society) for his statistical guidance on population-attributable risk calculations; we also thank Christina Clements Newton (American Cancer Society) for reviewing the SAS code and corresponding numbers in the tables and text.

References


Cancer Epidemiology, Biomarkers & Prevention

Are Racial Disparities in Pancreatic Cancer Explained by Smoking and Overweight/Obesity?
Lauren D. Arnold, Alpa V. Patel, Yan Yan, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-09-0080

Cited articles
This article cites 47 articles, 14 of which you can access for free at:
http://cebp.aacrjournals.org/content/18/9/2397.full.html#ref-list-1

Citing articles
This article has been cited by 15 HighWire-hosted articles. Access the articles at:
/content/18/9/2397.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.