

The Association of Body Mass Index and Pancreatic Cancer in Residents of Southeastern Michigan, 1996–1999

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Increased body mass index has emerged as a potential risk factor for pancreatic cancer. The authors examined whether the association between body mass index and pancreatic cancer was modified by gender, smoking, and diabetes in residents of southeastern Michigan, 1996–1999. A total of 231 patients with newly diagnosed adenocarcinoma of the exocrine pancreas were compared with 388 general population controls. In-person interviews were conducted to ascertain information on demographic and lifestyle factors. Unconditional logistic regression models estimated the association between body mass index and pancreatic cancer. Males' risk for pancreatic cancer significantly increased with increasing body mass index ($p_{\text{trend}} = 0.048$), while no relation was found for women ($p_{\text{trend}} = 0.37$). Among nonsmokers, those in the highest category of body mass index were 3.3 times (95% confidence interval: 1.2, 9.2) more likely to have pancreatic cancer compared with those with low body mass index. In contrast, no relation was found for smokers ($p_{\text{trend}} = 0.94$). While body mass index was not associated with pancreatic cancer risk among insulin users ($p_{\text{trend}} = 0.11$), a significant increase in risk was seen in non-insulin users ($p_{\text{trend}} = 0.039$). This well-designed, population-based study offered further evidence that increased body mass index is related to pancreatic cancer risk, especially for men and nonsmokers. In addition, body mass index may play a role in the etiology of pancreatic cancer even in the absence of diabetes.

body mass index; case-control studies; pancreatic neoplasms; risk factors

Abbreviations: CI, confidence interval; RR, relative rate; SEER, Surveillance, Epidemiology, and End Results.

Exocrine adenocarcinoma of the pancreas has the worst prognosis of any major malignancy, with a 5-year survival of only 4 percent (1). About 30,000 new cases of pancreatic cancer are diagnosed each year (1). For men, it is the fourth most common cause of cancer death, and for women, it is the fifth, but pancreatic cancer is only the 10th and ninth most common cancer diagnosis, respectively. Little is known about the etiology of pancreatic cancer. The most consistent risk factor reported in epidemiologic studies is smoking (2). However, at most, about 20–40 percent of pancreatic cancer

is thought to result from smoking (3). Other studies suggest that diabetes may be associated with pancreatic cancer, but it is not clear whether diabetes is a consequence or a cause of pancreatic cancer. Recently, obesity, as measured by body mass index, has been investigated in a number of case-control and cohort studies (4). It has been suggested that smoking and diabetes may act as either effect modifiers or intermediate steps in the causal pathway of obesity and pancreatic cancer (4–6). In order to understand more fully the relation between obesity and pancreatic cancer, we

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completed a large case-control study of pancreatic cancer in southeast Michigan and ascertained information on a variety of potential exposures related to pancreatic cancer risk, including weight at various points in time, height, smoking habits, and history of diabetes. In earlier reports of this study, we have shown a positive relation with a family history of pancreatic cancer (7). In this report, we evaluated whether increased body mass index was a risk factor for pancreatic cancer and whether this relation was modified by gender, smoking status, or history of diabetes.

MATERIALS AND METHODS

Study population

Subjects were recruited between October 1, 1996, and March 31, 1999. Eligible patients were residents of one of 18 counties in southeastern Michigan (Hillsdale, Lenawee, Monroe, Jackson, Washtenaw, Wayne, Ingham, Livingston, Oakland, Macomb, Shiawassee, Genesee, Lapeer, St. Clair, Bay, Gratiot, Midland, or Saginaw) at the time of diagnosis, aged 30–79 years, and English speaking, with newly diagnosed adenocarcinoma of the exocrine pancreas (*International Classification of Diseases*, Tenth Revision, codes C25.0–C25.3 and C25.7). The study pathologist (J. K. G.) reviewed pathology reports and histology slides and selected medical records to confirm the pancreatic cancer diagnosis. Because survival is short, incident pancreatic cancer patients were ascertained through a rapid case-finding system built in eight large hospital pathology departments, various oncology and surgical physician groups, and hospital-based tumor registries in southeastern Michigan. The median time for eligible cases to be identified by the rapid case-finding system after diagnosis was 19 days (range: from 52 days prior to diagnosis to 180 days after diagnosis), and the median time for interview after identification was 48 days (range: from 0 days to 441 days). To validate our rapid case-finding system, we searched the population-based, metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) Program registry, which also ascertains information on incident pancreatic cancer patients, and found only three additional pancreatic cancer patients, indicating that our rapid case-finding system captured nearly all of the SEER Program registry patients.

Random digit dialing based on established methods (8) was used to recruit general population controls throughout the ascertainment period. Controls were frequency matched by age group (30–44, 45–59, 60–69, 70–79 years), sex, ethnicity (African American, Caucasian, other), and county of residence (counties were grouped into nine different areas on the basis of population size and proximity to each other).

The institutional review boards of the University of Michigan and the participating centers approved the study protocol. All study subjects provided written informed consent before being enrolled.

Data collection

All study subjects underwent a face-to-face interview. The interviewers were unaware of the study hypotheses

and were trained to interview subjects in a standardized manner. Using a structured, pretested questionnaire, interviewers ascertained information on height, weight at various points in time, smoking, specific medical conditions including diabetes, family history of cancer, demographics, and personal history of exposure to selected chemicals. All data were entered using the double-entry method, and computer algorithms were built to detect outliers, logical errors, and omissions.

Statistical analysis

Body mass index (weight (kg)/height (m)²) was categorized into quartiles based on the distribution of body mass index among the controls. Each subject was asked about his/her current weight, weight 1 year ago, weight 5 years ago, and weight 20 years ago. Since the subjects were frequency matched, unconditional logistic regression models were built to estimate the association between body mass index and pancreatic cancer while controlling for potential confounders. Smoking, specific medical conditions including diabetes, family history of cancer, demographics, and personal history of exposure to selected chemicals were considered as possible confounders. The final adjusted models were based on the scientific literature and the statistical significance of explanatory variables in the model, as assessed by the likelihood ratio test. Trend tests were conducted by scoring the categories of body mass index, entering the score as a continuous term in the regression model, and reporting the significance level of the Wald chi-square test (9). All *p* values were based on two-sided tests.

RESULTS

A total of 358 pancreatic cancer patients were eligible for study. Fifty-three died before contact could be made, and 37 were not contacted because their physician would not give permission. The remaining 268 were invited to join the study. Of these, 247 (92 percent) agreed to participate in the study. Of the 597 general population controls eligible for the study, 19 could not be reached by phone, one died before being contacted, and 27 were not contacted because there was an overselection of controls under 45 years of age early in the study period. The remaining 550 people were invited to participate, and 420 (76 percent) agreed. To limit our study to subjects who had an adult weight measurement 20 years prior to the interview, we excluded those subjects (*n* = 28) who were less than 18 years of age 20 years prior to the interview. We also excluded those subjects who had missing weight information (*n* = 20). The final study population for this analysis consisted of 231 pancreatic cancer cases and 388 general population controls.

The characteristics of the pancreatic cancer cases and controls are shown in table 1. Reflecting the matching criteria, pancreatic cancer cases and controls were similar in age (*p* = 0.06), gender (*p* = 0.36), and race (*p* = 0.54). The average age for cases was 62 years (range: 38–80 years) and for controls was 64 years (range: 39–80 years). Both cases

TABLE 1. Characteristics of pancreatic cancer cases and general population controls for a case-control study of pancreatic cancer in residents of southeast Michigan, 1996–1999

	Cases (<i>n</i> = 231)		Controls (<i>n</i> = 388)		<i>p</i> value
	No.	%	No.	%	
Age (years)					
38–52	41	18	74	19	
53–60	45	19	102	26	
61–68	60	26	106	27	
≥69	85	37	106	27	0.064
Gender					
Men	119	52	185	48	
Women	112	48	203	52	0.36
Race					
White	198	86	324	84	
Black	30	13	61	16	
Other	3	1	3	1	0.54
Income (\$)					
≥70,001	58	26	85	23	
40,001–70,000	56	25	82	22	
25,001–40,000	52	24	86	23	
≤25,000	56	25	115	31	0.43
County					
Wayne	89	39	145	37	
Macomb and Oakland	79	34	140	36	
Other	63	27	103	27	0.89
Ever smoke	154	67	246	63	0.41
Relative with pancreatic cancer	22	10	15	4	0.004
Diabetes	65	28	45	12	<0.0001
Insulin users	39	17	16	4	<0.0001

and controls consisted of approximately 50 percent women and 50 percent men. Around 85 percent of the cases and controls were White. Pancreatic cancer cases and controls were similar on reported yearly income ($p = 0.43$), although more controls (31 percent) than cases (25 percent) reported a yearly income of less than or equal to \$25,000. Sixty-seven percent of the cases had smoked compared with 63 percent of the controls ($p = 0.41$). More cases (10 percent) had a relative with pancreatic cancer than did controls (4 percent) ($p = 0.004$). A medical diagnosis of diabetes was also reported significantly more often among cases than controls (28 percent vs. 12 percent; $p < 0.0001$) as was using insulin (17 percent vs. 4 percent; $p < 0.0001$).

It is interesting to note an inverse relation for the association between pancreatic cancer and a body mass index of 25.0 kg/m² or higher and time prior to interview (table 2). At the time of interview, pancreatic cancer cases had a lower body mass index compared with controls (adjusted

odds ratio = 0.1, 95 percent confidence interval (CI): 0.0, 0.2), reflecting the wasting that is part of the disease course (10). At 12 months prior to interview, a similar proportion of cases were in the highest quartile of body mass index compared with controls (adjusted odds ratio = 1.0, 95 percent CI: 0.6, 1.6), but at 20 years prior to interview, the cases were 1.4 times (95 percent CI: 0.8, 2.5) more likely than controls to be in the highest quartile of body mass index.

Table 3 shows the relation between body mass index and pancreatic cancer for a self-reported body mass index 20 years prior to interview stratified by gender, smoking status, diabetes, and use of insulin. Among men, there was a borderline significant gradient in risk with increasing body mass index ($p_{\text{trend}} = 0.048$). Men in the highest quartile of body mass index experienced 2.4 times (95 percent CI: 1.0, 6.2) the risk of pancreatic cancer compared with those in the lowest quartile. The trend in women was less clear ($p = 0.37$) but suggested an association between risk of pancreatic cancer and body mass index. Smoking status modified the relation between increased body mass index and pancreatic cancer. Among smokers, there was no increasing risk in pancreatic cancer with an increasing body mass index ($p_{\text{trend}} = 0.94$). However, nonsmokers with the highest quartile of body mass index had 3.3 times (95 percent CI: 1.2, 9.2) the risk for pancreatic cancer compared with nonsmokers in the lowest quartile of body mass index. There was no clear relation between increasing body mass index and pancreatic cancer among diabetics ($p_{\text{trend}} = 0.58$) or among insulin users ($p_{\text{trend}} = 0.11$). However, a similar increased risk for increasing body mass index was shown for both non-diabetics ($p_{\text{trend}} = 0.065$) and for non-insulin users ($p_{\text{trend}} = 0.039$). Nondiabetics with the highest quartile of body mass index had 1.6 times (95 percent CI: 0.9, 3.0) the risk of pancreatic cancer compared with nondiabetics with the lowest quartile of body mass index. Similarly, non-insulin users with the highest quartile of body mass index had 1.7 times (95 percent CI: 1.0, 3.0) the risk of pancreatic cancer compared with non-insulin users with the lowest quartile of body mass index.

DISCUSSION

This large, population-based, case-control study of pancreatic cancer in southeastern Michigan found that cases had a lower body mass index compared with controls at the time of interview, but cases had a higher body mass index compared with controls 20 years prior to the interview. This is not surprising given that people with pancreatic cancer often exhibit cachexia prior to diagnosis (10) and, thus, body mass index at diagnosis is probably not etiologically relevant. Therefore, the focus for the remainder of the analyses was self-reported body mass index 20 years prior to interview. A high body mass index 20 years prior to the interview may be associated with risk for pancreatic cancer among men and nonsmokers. In addition, stratified analyses revealed that a high body mass index 20 years prior to the interview may also be a risk factor for pancreatic cancer independently of diabetes, as measured by use of insulin.

Some case-control (11–16) and cohort (6, 17–22) studies have reported a weak or modest association between body

TABLE 2. Association between obesity and pancreatic cancer for body mass index at various time periods prior to interview in residents of southeast Michigan, 1996–1999

	No. of cases	No. of controls	Crude odds ratio	Adjusted odds ratio*	95% confidence interval
Current body mass index†					
Q1	33	97	1.0	1.0	Referent
Q2	59	101	0.4	0.4	0.3, 0.7
Q3	22	97	0.2	0.2	0.1, 0.3
Q4	17	93	0.1	0.1	0.0, 0.2
P_{trend}				<0.0001	
Body mass index 6 months prior to interview‡					
Q1	68	103	1.0	1.0	Referent
Q2	59	96	0.9	1.0	0.6, 1.6
Q3	62	94	1.0	1.0	0.6, 1.6
Q4	42	95	0.7	0.5	0.3, 0.9
P_{trend}				0.018	
Body mass index 12 months prior to interview§					
Q1	49	99	1.0	1.0	Referent
Q2	66	102	1.3	1.3	0.8, 2.1
Q3	56	91	1.2	1.2	0.7, 2.0
Q4	60	96	1.3	1.0	0.6, 1.6
P_{trend}				0.77	
Body mass index 5 years prior to interview¶					
Q1	46	98	1.0	1.0	Referent
Q2	56	104	1.1	1.1	0.6, 1.8
Q3	68	91	1.6	1.3	0.8, 2.2
Q4	61	95	1.4	1.0	0.6, 1.8
P_{trend}				0.77	
Body mass index 20 years prior to interview#					
Q1	43	103	1.0	1.0	Referent
Q2	48	95	1.1	1.1	0.6, 1.9
Q3	71	100	1.6	1.6	0.9, 2.6
Q4	69	90	1.4	1.4	0.8, 2.5
P_{trend}				0.15	

* Adjusted for age, gender, race, county group, smoking, relative with pancreatic cancer, income, and medical history of diabetes.

† Body mass index (kg/m^2) quartile 1 (Q1): 0.0–24.2; quartile 2 (Q2): 24.3–27.2; quartile 3 (Q3): 27.3–31.4; quartile 4 (Q4): 31.5–62.9.

‡ Q1: 0.0–24.4; Q2: 24.5–27.3; Q3: 27.4–31.4; Q4: 31.5–67.8.

§ Q1: 0.0–24.2; Q2: 24.3–27.3; Q3: 27.4–31.2; Q4: 31.3–67.8.

¶ Q1: 0.0–24.1; Q2: 24.2–26.5; Q3: 26.6–30.3; Q4: 30.4–68.5.

Q1: 0.0–22.2; Q2: 22.3–24.4; Q3: 24.5–27.4; Q4: 27.5–43.0.

mass index and pancreatic cancer risk, while others have not (23–28). Given that pancreatic cancer is a rapidly fatal disease, one explanation for the inconsistent results among studies may be the reliance on next-of-kin interviews for information on body mass index. Uncontrolled confounding

due to diabetes or other pancreatic cancer risk factors may also contribute to the conflicting results. Further, it has been suggested that insulin resistance may play a role in pancreatic cancer (13, 18, 29–32) and that body mass index may be an inaccurate surrogate measure of total body adiposity and

TABLE 3. Association between obesity and pancreatic cancer for body mass index 20 years ago by gender, smoking status, and diabetes in residents of southeast Michigan, 1996–1999

	No. of cases	No. of controls	Adjusted odds ratio	95% confidence interval
Gender*				
Men†				
Q1	8	34	1.0	Referent
Q2	25	54	1.6	0.6, 4.1
Q3	43	54	2.6	1.0, 6.4
Q4	43	43	2.4	1.0, 6.2
<i>p</i> _{trend}			0.048	
Women				
Q1	35	69	1.0	Referent
Q2	23	41	1.2	0.6, 2.5
Q3	28	46	1.5	0.7, 3.0
Q4	26	47	1.4	0.7, 3.0
<i>p</i> _{trend}			0.37	
Ever smoke‡				
Yes				
Q1	34	70	1.0	Referent
Q2	32	61	1.0	0.5, 1.8
Q3	52	55	1.7	0.9, 3.1
Q4	36	60	0.9	0.5, 1.8
<i>p</i> _{trend}			0.94	
No				
Q1	9	33	1.0	Referent
Q2	16	34	1.6	0.6, 4.6
Q3	19	45	1.5	0.5, 4.0
Q4	33	30	3.3	1.2, 9.2
<i>p</i> _{trend}			0.014	

Table continues

body fat distribution, the specific parameters of interest with regard to increased insulin resistance (14).

In our study, increased body mass index was associated with pancreatic cancer in both men and women. However, the association with high body mass index 20 years prior to the interview was more pronounced and borderline significant in men. This finding was supported by one other case-control study (15) and two cohort studies (6, 18). A few studies have examined body mass index by smoking status. In a large case-control study of numerous cancer sites in Canada, Pan et al. (16) found that smoking status did not modify pancreatic risk for a body mass index of 30 kg/m² or higher. In contrast, we found that a high body mass index 20 years prior to the interview was associated with pancreatic cancer among non-smokers but not among smokers. This was confirmed by a large cohort of US men who had never smoked (21), which saw an increased risk for pancreatic cancer with a high body mass index (relative rate (RR) = 2.61, 95 percent CI: 1.27, 5.35), and by a Finnish study of men who smoked (5), which

TABLE 3. Continued

	No. of cases	No. of controls	Adjusted odds ratio	95% confidence interval
Diabetes§				
Yes				
Q1	7	4	1.0	Referent
Q2	11	5	1.1	0.2, 6.1
Q3	16	13	0.7	0.2, 3.6
Q4	31	23	0.7	0.2, 3.2
<i>p</i> _{trend}			0.58	
No				
Q1	35	99	1.0	Referent
Q2	37	90	1.1	0.6, 2.0
Q3	55	87	1.7	1.0, 3.0
Q4	38	67	1.6	0.9, 3.0
<i>p</i> _{trend}			0.065	
Insulin users§				
Yes				
Q1	5	1	1.0	Referent
Q2	6	1	0.2	0.0, 9.2
Q3	9	4	0.1	0.0, 2.7
Q4	19	10	0.1	0.0, 1.7
<i>p</i> _{trend}			0.11	
No				
Q1	37	102	1.0	Referent
Q2	42	94	1.1	0.6, 2.0
Q3	62	96	1.7	1.0, 2.9
Q4	50	80	1.7	1.0, 3.0
<i>p</i> _{trend}			0.039	

* Adjusted for age, race, county group, relative with pancreatic cancer, income, smoking, and medical history of diabetes.

† Body mass index (kg/m²) quartile 1 (Q1): 0.0–22.2; quartile 2 (Q2): 22.3–24.4; quartile 3 (Q3): 24.5–27.4; quartile 4 (Q4): 27.5–43.0.

‡ Adjusted for age, gender, race, county group, relative with pancreatic cancer, income, and medical history of diabetes.

§ Adjusted for age, gender, race, county group, relative with pancreatic cancer, income, and smoking.

found no association between high body mass index and pancreatic cancer (RR = 0.91, 95 percent CI: 0.48, 1.23). Our finding that smoking modifies the risk associated with high body mass index is not surprising given that smokers typically have a lower body mass index and body weight than do nonsmokers (33–35), as nicotine increases the metabolic rate and energy expenditure (36).

The role of diabetes in pancreatic cancer risk is not well understood. Diabetes may be an early manifestation of pancreatic cancer, an etiologic factor, or some combination of both. Obesity is often the initial exposure in diabetes, and its role in the etiology of pancreatic cancer in the absence of diabetes is not well understood. Wolk et al. (6) in a study of cancer risk in Sweden found a slightly higher risk for

a hospital discharge diagnosis of obesity and pancreatic cancer risk among diabetics (RR = 2.0, 95 percent CI: 1.3, 3.0) compared with nondiabetics (RR = 1.3, 95 percent CI: 0.9, 1.7), while Samanic et al. (22) in a large cohort study of US veterans with a hospital discharge of obesity found excess risk in nondiabetics (RR = 1.17, 95 percent CI: 1.03, 1.34) but not in diabetics (RR = 0.87, 95 percent CI: 0.73, 1.03). Body mass index was associated with pancreatic cancer in both diabetics and nondiabetics in one population-based, case-control study (13). While the numbers of subjects were too small to make a meaningful comparison among the diabetics or insulin users in our study, we found a borderline significant risk for both nondiabetics and non-insulin users, indicating that a high body mass index may also play a role in the etiology of pancreatic cancer among people without diabetes.

Our study has many strengths. This is one of the few studies to rely on direct interviews of cases with pancreatic cancer. Most studies of pancreatic cancer have relied on surrogate interviews because of poor survival, whereby accurate exposure information is difficult to obtain. In addition, the exposure information was ascertained through in-person interviews, which provide more reliable information than self-administered questionnaires or telephone interviews. We also assessed the completeness of our case-finding system for Wayne, Oakland, and Macomb counties by also searching the regional SEER Program registry to identify eligible cases at participating hospitals who had been missed during the study period. We found only three additional cases, indicating that selection bias was probably not important. The satisfactory participation rate among cases and controls further lessened the likelihood that a significant selection bias had been introduced into the study design. Our study was further strengthened by its strict case definition. Among the controls, nonparticipants were similar to participants on age ($p = 0.15$), sex ($p = 0.047$), and county ($p = 0.19$). However, the proportion of Blacks who were nonparticipants (21 percent) was higher than the proportion of Blacks who were participants (15 percent). If nonparticipation among Blacks was also related to body mass index, then a bias could be present in our study, although we have no reason to believe that this bias would be differential. Pathology slides and reports were reviewed by the study pathologist to ensure that diagnostic inclusion criteria were met and that only patients with histologically confirmed adenocarcinoma of the exocrine pancreas were included. This increased the reliability of our findings, because the results are for a single category of pancreatic cancer. Interview training and a structured interview minimized recall bias.

This was a study of self-reported body mass index. While self-reported height and weight have been shown to be highly correlated with measured height and weight (36, 37), a small systematic error may exist as self-reported weight is often underestimated, particularly at higher weights (38–40). As people with pancreatic cancer typically lose a large amount of weight, cases who were obese in the past may greatly underestimate their weight at various points in time, thus underestimating the effect that a high body mass index has on pancreatic cancer risk. We also had

no information on weight change or weight cycling throughout the subject's lifetime, and we were unable to evaluate any effect that this may have on pancreatic cancer risk. In addition, lifestyle and behavioral factors that are correlated with a high body mass index (e.g., physical inactivity, high caloric intake, high-fat diets) that may also increase the risk for pancreatic cancer could not be evaluated in our study.

In summary, this study offers some evidence that a high body mass index may increase the risk of pancreatic cancer, particularly among men and nonsmokers. In addition, a high body mass index may play a role in the etiology of pancreatic cancer even in the absence of diabetes. Future studies should make better use of different measures of obesity, including direct measures of adiposity or lean body mass or measures of central adiposity such as the waist/hip ratio, although these methods could be utilized only in long-term cohort studies.

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