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Weight Loss, Diabetes, Fatigue, and Depression Preceding Pancreatic Cancer

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Abstract

Objectives—We aimed to determine the severity and co-occurrence of established and potential paraneoplastic conditions in pancreatic cancer (weight loss, new onset diabetes, fatigue, and depression) and their relation to patient characteristics.

Methods—Using information from personal interviews with 510 cases and 463 controls, we obtained adjusted odds ratios for weight loss, long-term and new-onset diabetes, fatigue and depression before diagnosis. Among cases, we investigated the extent to which these factors occurred together and the characteristics of those reporting them.

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Results—The adjusted odds ratio (OR) for weight loss (>3% of usual weight) was 27.0 (95% confidence interval (CI) 17.1-42.6). Severe weight loss was common (21% of cases lost >15%), and was more common in those previously obese. Diabetes was more common in cases and was strongly associated with weight loss (P<0.0001). Diabetes in cases more often led to prescription of insulin, compared to controls.

Fatigue and depression were significantly more common in cases than controls but not related to weight loss or diabetes. These conditions were not related to stage at diagnosis.

Conclusions—Weight loss, often severe, and new onset diabetes frequently occur together before diagnosis of pancreatic cancer. Fatigue and depression are also potential precursors of diagnosis.

Keywords

pancreatic neoplasms; weight loss; diabetes mellitus; depression; fatigue; paraneoplastic conditions

Introduction

Pancreatic cancer is a lethal disease and most patients have very short survival. Patients are usually identified when the disease is advanced and treatment is of little effect. While pancreatic cancer appears to progress rapidly, recent studies have indicated that it may develop slowly over time, perhaps as long as 20 years¹. This may provide a basis for identification of patients at an earlier stage of disease when treatment can be more successful. New-onset diabetes²⁻⁴ and weight loss⁵⁻⁷ are established paraneoplastic features of pancreatic cancer. The severity of these conditions, the degree to which they overlap, and which types of patients they affect, have not been studied in detail. In addition, there are some indications that depression and fatigue may precede a diagnosis of pancreatic cancer, but this has rarely been studied. In this report, we used data from a large hospital- based case-control study of pancreatic cancer to investigate in more detail the severity of weight loss, timing of onset and severity of diabetes, depression/sadness and fatigue prior to diagnosis, and to investigate whether these factors occur together.

Materials and Methods

Study population

The pancreatic cancer case-control study at Memorial Sloan Kettering Cancer Center (MSKCC) is part of the Pancreatic Tumor Registry, established in 2002. Cases are eligible if they have pathologically or cytologically confirmed pancreatic adenocarcinoma and speak English. For this study, we excluded 1 case and 4 controls who did not provide complete data on weight. Cases in this analysis (n=510) were interviewed within 2.5 months of their diagnosis. They were identified when seen by clinicians for initial consultation and diagnosis, follow-up after surgery, or chemotherapy. Controls (n=463) were eligible if they spoke English and had no personal history of cancer other than non-melanoma skin cancer. Controls were either visitors accompanying patients to other MSKCC clinics (n=316) or spouses of patients with pancreatic cancer (n=147). Cases and controls who agreed to take

part signed Informed Consent and were personally interviewed to determine lifestyle and environmental risk factors for pancreatic cancer. Interviews for the present analysis took place between December 2004 and August 2010. Among cases approached, 13% were ineligible (primarily because they did not speak English); of those eligible, 79% took part. Among controls approached, 15% were ineligible (primarily because of history of cancer); of those eligible, 59% took part. The study was reviewed by the institutional review board at MSKCC.

Data collection

Questions on body size included usual adult weight, weight at the time of interview, and height, allowing us to determine weight changes and calculate body mass index (BMI, weight (kg)/height (m²)). We asked whether respondents were ever told they had diabetes, and if so, the age at diagnosis and the type of treatment recommended. We also asked: thinking back over the past year or so (before you got sick, for cases), have you had greater fatigue than usual; found it hard to concentrate; or felt depressed or sad for no apparent reason? Interviewers recorded "yes" or "no" answers for each of these items. In a separate part of the questionnaire on medications, respondents were asked whether they ever used antidepressants. For 492 (96%) cases, we obtained the non- fasting glucose measure (mg/dL) at the time of diagnosis from their medical record.

Statistical analysis

Weight change was the difference in pounds between the usual adult weight and weight at the time of interview. For comparing cases and controls, we considered 3 groups: those whose weight at interview was within $\pm 3\%$ of their usual adult weight (stable weight); those who gained >3%; and those who lost >3%. For examining weight change in relation to other variables among the cases, we considered 3 groups among those who lost weight: lost >3% but <10%; lost 10% but <15%; and lost 15%. We also evaluated weight change in pounds. Individuals who were diagnosed with diabetes when they were the same age as their pancreatic cancer diagnosis (cases) or age at interview (controls), or one or two years younger, were considered to have new-onset diabetes^{6,8}. We determined the degree of association between the variables of interest by cross-tabulating pairs of variables and using X² tests. Among the cases, we determined whether these variables were related to other characteristics: age, gender, education, BMI, smoking history, and stage of disease.

For comparing cases to controls, adjusted odds ratios were estimated from logistic regression. The model included age (continuous), gender, education (high school or less, college, graduate school), smoking (never, former, current), and BMI (<25, 25 to <30, 30, based on usual adult weight). For fatigue, inability to concentrate, and depression/sadness, we included a model with all of these variables to provide an indication of their independence from each other. We repeated these analyses with the exclusion of patients with prior cancer, since there were no controls with prior cancer. Analyses were performed in SAS Version 9.2 (SAS Institute Inc.). Results were considered statistically significant if the two-sided P value was <0.05.

We were concerned that questions on fatigue, concentration, and depression/sadness before diagnosis might be difficult to answer accurately for patients who were likely to have some of these conditions as a result of their diagnosis. To partially address this possibility, we investigated whether the time between diagnosis and interview was related to weight loss, new-onset diabetes, fatigue, concentration, or depression/sadness, as an indication of whether recall of these conditions was different in those who answered these questions further from the time of diagnosis.

Results

Respondent characteristics

Cases were older than controls: the mean age of cases was 64.3 (standard deviation (SD), 11.0) and of controls, 59.5 (SD, 11.6) (Table 1). Controls were somewhat better educated than cases. Usual adult BMI was higher in cases, with 22% classified as obese (BMI 30) compared to 12% of controls. Fifteen per cent of the cases had a history of prior cancer. Pancreatic cancer stage distribution was: 17% stage IA-IIA; 24% Stage IIB; 19% stage III; 41% stage IV.

Weight loss, new-onset diabetes, fatigue, concentration, and depression/sadness in cases and controls

Weight loss from the usual adult weight to weight at the time of interview was highly prevalent in the pancreatic cancer patients, with 71% of the patients losing >3% of their usual adult weight. In contrast, only 7% of controls had lost this much weight (OR=27.0, 95% CI 17.1-42.6). The amount of weight lost by patients was considerable: 42% lost 10% of their body weight or more, including 21% who lost 15% or more (Table 2). In pounds, 22% of patients lost 25 pounds or more. The mean (SD) number of pounds lost by all male patients was 17.1 (17.1), and by all the females, 10.5 (18.4).

New-onset diabetes was common in cases, 15% compared to 3% in controls, with an adjusted odds ratio of 6.40 (95% CI 3.37-12.2) compared to those with no history of diabetes. Longer-standing diabetes was also more common in cases (OR=2.28, 95% CI 1.35-3.86). Glucose measures in cases reflected self-reported diabetes status, with mean values of 133.3 mg/dL (SD 46.9, n=358) among those with no diabetes, 179.3 mg/dL (SD 66.5, n=73) among those with new onset diabetes, and 214.1 mg/dL (SD 69.0, n=61) in those with long-standing diabetes (P<.0001, data not shown in tables).

Cases were significantly more likely than controls to have experienced fatigue (OR=1.67, 95% CI 1.26-2.21), difficulty concentrating (OR=1.41, 95% CI 1.01-1.96), or depression/ sadness (OR=2.18, 95% CI 1.41-3.36) in the year before diagnosis (Table 2). When these variables were included in the same model, ORs were slightly attenuated for fatigue (OR=1.59, 95% CI 1.05-2.41) and depression/sadness (OR=2.0, 95% CI1.09-3.57), while concentration became non-significant (OR=1.13, 95% CI 0.69-1.84). Results were the same when we restricted these analyses to cases who had not had a previous cancer (n=432) (not shown in tables). Among those who reported depression/sadness (102 cases, 38 controls), use of antidepressant medications was considerably less common in cases than controls

(adjusted OR=0.42, 95% CI 0.15-1.15, not shown in tables). There was no indication that reporting of weight change, new-onset diabetes, fatigue, concentration, or depression/ sadness differed according to time between diagnosis and interview (data not shown).

Associations among weight loss, diabetes, fatigue, concentration and depression/ sadness in cases

Weight loss of 10% was strongly related to new-onset diabetes in cases (Table 3). In those with weight gain, stable weight, or loss of <10%, 6-11% were newly diagnosed with diabetes; in contrast, among those with weight loss of 10% to <15% or weight loss of

15%, the proportions newly diagnosed were 18% and 27%, respectively (Table 3, Figure 1). Cases with greater weight loss were also more likely to have long-standing diabetes (overall P<.0001). There were no statistically significant associations between weight loss and measures of fatigue, concentration, or depression/sadness among the cases, except that a higher proportion of those who gained weight mentioned feeling fatigued. There was no relationship between weight loss and stage at diagnosis.

There were no associations between diabetes and fatigue, concentration, or depression/ sadness among the patients (Table 3). Diabetes was not related to stage (Table 3), nor was fatigue, concentration, or depression/sadness (data not shown).

Characteristics of cases with weight loss, diabetes, fatigue, concentration, and depression/sadness

The amount of weight lost was strongly related to usual adult BMI, with 23% of those who lost 10-<15% and 44% of those who lost 15% being obese. Cases who gained weight were more likely to be women. Cases with diabetes, either new-onset or long-standing, were more likely to be males and to have been obese at their usual adult weight (Table 4). Reports of difficulty concentrating and depression/sadness were more common in women than in men. Difficulty concentrating was more often mentioned by those in their fifties, while reports of depression/sadness were more frequent among those who were obese (Table 5). Weight change and diabetes were not related to cases' education or smoking history (data not shown).

Among those who ever were diagnosed with diabetes (n=139 cases, n=35 controls), more controls than cases were advised to go on a diet to lose weight (89% vs 55%, p<0.001), while cases were more likely to have been prescribed insulin (37% vs 9%, p<0.01) (data not shown in tables).

Discussion

Weight loss was frequently reported in the cases in our case-control study: overall, 42% of patients lost at least 10% of their weight, far more than in controls. Our findings on differences between cases and controls in the prevalence of weight loss are generally similar to those in two earlier studies^{5,9}, although our study provides greater detail on the amount of weight lost. Since weight loss is uncommon in adults, this could potentially alert clinicians to the need for consideration of pancreatic cancer.

Fifteen percent of the cases reported diabetes diagnosed within three years of their pancreatic cancer diagnosis, in addition to 13% who had been diagnosed with diabetes at an earlier time. These measures were more common in cases than in controls. Earlier findings from case-control studies have agreed,⁹ although not consistently.⁵ A study among diabetics with and without pancreatic cancer also found more new-onset diabetes in those with cancer¹⁰. The 28% of cases who reported having diabetes (either new-onset or long standing) in our study was similar to that in an earlier study, also based on self-report¹¹. In contrast, a case-control study at Mayo Clinic identified diabetes in 47% of cases, based on elevated fasting blood glucose at the time of interview or usage of diabetic medication⁹, indicating that patients in our study may not have been aware of the presence of diabetes. Our finding that cases with diabetes that their diabetes was more severe and difficult to control; this is similar to findings reported in an earlier study¹². Pancreatic cancer cases with existing diabetes have been found to have both weight loss and worsening of diabetes prior to cancer diagnosis¹⁰.

We also found a strong association between weight loss and diabetes, with patients who lost 10% or more of their usual adult weight the most likely to have been diagnosed with diabetes, either within the years shortly before cancer diagnosis or at an earlier time. The study from the Mayo Clinic⁹ also reported that weight loss and diabetes were related, with patients with diabetes experiencing greater weight loss, while a study of pancreatic cancer patients at MD Anderson found a less strong association¹¹. Our more detailed analysis indicates that there may be a threshold effect, with increasing likelihood of new onset diabetes mainly among those with more severe weight loss (10% of usual adult weight).

In our study and others, patients' perceived reasons for weight loss were not queried; they might include loss of appetite⁵ because of mild symptoms, poor absorption leading to weight loss with normal caloric intake¹³, or trying to lose weight as a way of controlling new-onset diabetes. We also do not have information on when the weight loss occurred in the patients in our study.

We noted that cases were more likely than controls to report fatigue and depression/sadness in the year before their diagnosis (cases) or interview (controls). While this has rarely been addressed in large case-control studies, earlier studies using various methods have also reported that depression can precede the appearance of other symptoms or diagnosis in some pancreatic cancer patients¹⁴; fatigue before diagnosis has also been reported as distinguishing cases from controls⁵. In our study, results were similar when we analyzed the data according to the number of weeks between diagnosis and interview. The finding that cases in our study were less likely than controls to be taking antidepressants may indicate that their condition was relatively mild. This is consistent with reports of "malaise" noted in medical records of 5% of patients in the year before diagnosis, about twice as common in cases as in controls⁷.

A potential mechanism for depression and fatigue as precursors of pancreatic cancer diagnosis is the presence of elevated levels of cytokines, produced by cancer cells and inflammatory cells¹⁵⁻¹⁷. IL-6 is linked to both pancreatic cancer¹⁸⁻²⁰ and to fatigue and

depression^{16,19,21}. Elevated levels of IL-6 have been found to be associated with clinical depression in patients with other cancers^{15,22,23,24}. It seems possible that depression and fatigue could represent part of a paraneoplastic syndrome associated with this disease, with cytokines released by an undiagnosed tumor leading to fatigue and depression before diagnosis. In our study presence of these conditions was independent of recognized paraneoplastic conditions, weight loss and new-onset diabetes. Overall, the possibility that depression/sadness and fatigue precede pancreatic cancer warrants further study.

There was no indication that weight loss, new onset diabetes, fatigue, or depression/sadness was related to stage at diagnosis. Similar results have been reported for diabetes in other studies^{9,11}. Gobbi et al²⁵ reported that patients with weight loss at the time of initial presentation had longer delay between first noticing this sign and cancer diagnosis than patients with other symptoms; this may indicate that earlier recognition of weight loss as a symptom might lead to earlier diagnosis. While it is possible that greater awareness of these paraneoplastic conditions on the part of the public or primary care physicians could lead to earlier diagnosis of pancreatic cancer, it is not clear whether this would improve outcomes.

In summary, our study confirms the association of weight loss and diabetes in the years leading up to the clinical presentation of pancreatic ductal adenocarcinoma. Pancreatic cancer patients who were obese demonstrated the greatest weight loss. Unfortunately the onset of weight loss and diabetes is not specific and cannot be used routinely as a reason to evaluate patients for the possibility of pancreatic cancer. Hopefully these findings coupled with the development of biomarkers will enable early detection of this lethal disease.

Acknowledgments

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Abbreviations

BMI	body mass index
CI	confidence interval
IL-6	interleukin-6
mg/dL	milligrams per deciliter
MSKCC	Memorial Sloan Kettering Cancer Center

OR	odds ratio
SD	standard deviation

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Figure 1.

Association between weight change in patients with pancreatic cancer and presence of long-standing (3 years) and new-onset (<3 years) diabetes.

Table 1

Characteristics of Cases and Controls

	Cases N=510	Controls N=463
	n (%)	n (%)
Age, years		
<50	53 (10)	90 (19)
50-59	107 (21)	129 (28)
60-69	173 (34)	160 (35)
70	177 (35)	84 (18)
Mean age (SD)	64.3 (11.0)	59.5 (11.6)
Gender		
Male	275 (54)	239 (52)
Female	235 (46)	224 (48)
Race		
White	453 (89)	405 (87)
Black	24 (5)	23 (5)
Asian	22 (4)	20 (4)
Other or mixed	11 (2)	15 (3)
Education		
High school or less	113 (22)	78 (17)
College	225 (44)	204 (44)
Graduate school	171 (34)	181 (39)
Smoking		
Never	246 (48)	236 (51)
Former	227 (45)	197 (43)
Current	37 (7)	30 (6)
Usual adult BMI		
<25	176 (35)	230 (50)
25-<30	223 (44)	176 (38)
30	111 (22)	57 (12)
Pancreatic cancer in fir	st degree relati	ve
Yes	47 (9)	22 (5)
No	461 (91)	441 (92)
History of prior cancer		
Yes	78 (15)	NA
No	432 (85)	
Stage of disease		
Stage IA to IIA	84 (17)	NA
Stage IIB	122 (24)	
Stage III	94 (19)	
Stage IV	208 (41)	

Numbers may not add to total because of missing values.

Abbreviations: SD-Standard Deviation, BMI-Body Mass Index, NA-Not Applicable

Table 2

Percent Weight Change, Diabetes, and Fatigue, Difficulty Concentrating, and Depression/ Sadness in Cases and Controls

	Cases N=510	Controls N=463	Adjusted OR ^a	95% CI
	n (%)	n (%)		
Percent weight change				
Gained >3%	55 (11)	209 (45)	0.59	0.39-0.88
Stable weight (±3%)	93 (18)	223 (48)	1	
Lost >3%	362 (71)	31 (7)	27.0	17.1-42.6
>3 - <10%	147 (29)			
10% - <15%	108 (21)			
15%	107 (21)			
Diabetes				
No	371 (73)	428 (92)	1	
3 years before cancer diagnosis/interview	64 (13)	23 (5)	2.28	1.35-3.86
<3 years before cancer diagnosis/interview	75 (15)	12 (3)	6.40	3.37-12.2
Other conditions ^b				
Fatigue	206 (40)	141 (30)	1.67	1.26-2.21
Concentration	116 (23)	90 (19)	1.41	1.01-1.96
Depression/sadness	81 (16)	37 (8)	2.18	1.41-3.36

Abbreviations: OR-Odds Ratio, CI-Confidence Interval

 a ORs adjusted for age, gender, education, smoking, BMI

 ${}^{b}\mathbf{R}$ efference category for each condition is those without that condition

	Gained >3%	Stable weight (±3%)	Lost >3% to <10%	Lost 10% to <15%	Lost 15%	<i>P</i> value	No diabetes	3 years earlier	< 3 years earlier	P value
	N=55	N=93	N=147	N=108	N=107		N=370	N=64	N=75	
	%	%	%	%	%		%	%	%	
No diabetes	85	82	82	67	51	<0.0001				
3 years earlier	6	10	7	16	22					
< 3 years earlier	9	6	11	18	27					
Fatigue	55	38	34	47	37	0.04	38	48	45	0.19
Concentration	29	22	17	29	22	0.18	21	31	24	0.19
Depression/sadness	20	13	12	16	22	0.24	14	22	20	0.15
Stage IA-IIA	11	22	16	18	15	0.48	16	19	17	0.48
Stage IIB	27	16	23	26	28		26	14	21	
Stage III	22	19	20	11	22		19	20	16	
Stage IV	40	43	42	44	36		39	47	45	

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Table 3

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 Table 4

 Characteristics of Pancreatic Cancer Cases with Weight Loss and Diabetes

	Gained >3%	Stable weight (±3%)	Lost >3% to <10%	Lost 10% to <15%	Lost 15%		No diabetes	3 years earlier	< 3 years earlier	
	N=55	N=93	N=147	N=108	N=107	P value	N=371	N=64	N=75	P value
	%	%	%	%	%		%	%	%	
Age										
<50	11	11	11	12	7	1.0	11	9	6	0.59
50-59	24	19	20	22	22		21	16	27	
60-69	33	33	34	31	37		34	39	31	
70	33	37	35	34	34		34	39	33	
Gender										
Male	33	53	59	57	56	0.02	51	66	60	0.04
Female	67	47	42	43	44		49	34	40	
Usual adult BMI										
<25	38	40	42	28	24	<0.0001	39	17	27	<0.0001
25-<30	45	48	45	49	32		46	39	39	
30	16	12	13	23	44		15	44	39	
Abbreviation: BMI	I-Body Mass Inde:	×								

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Table 5

Characteristics of Pancreatic Cancer Cases with Fatigue, Difficulty Concentrating, and Depression/Sadness

Yes No. Yes No. Yes No. No. <th></th> <th></th> <th>Fatigue</th> <th></th> <th>Ŭ</th> <th>oncentrati</th> <th>uo</th> <th>Dep</th> <th>ression/Sa</th> <th>adness</th>			Fatigue		Ŭ	oncentrati	uo	Dep	ression/Sa	adness
% %		Yes N=206	No N=303	P value	Yes N=116	No N=393	P value	Yes N=81	No N=428	P value
Age <50 10110.0711100.11179 $<50-59$ 251830182520 $<0-69$ 373235342520 <70 293923383235 <70 293923383235 <70 293923383235 <70 293923383235 <70 293923383235 <70 293923383235 <70 504454445744 <75 340.3035340.5327 <75 30252025213320 <70 252025213320		%	%		%	%		%	%	
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50-59 25 18 30 18 25 20 $60-69$ 37 32 35 34 26 36 70 29 39 23 38 26 36 70 29 39 23 38 32 35 Gender 50 56 0.04 43 56 Male 50 44 57 44 57 44 Female 50 44 57 44 57 44 Usual adult BMI 52 33 32 36 36 $25-530$ 40 45 56 40 57 44 30 $25-530$ 40 40 45 50 32 32 32 30 25 20 25 21 32 20 32 32 32 32	<50	10	Ξ	0.07	Π	10	0.01	17	6	0.07
	50-59	25	18		30	18		25	20	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	60-69	37	32		35	34		26	36	
Gender 50 56 0.15 46 56 0.04 43 56 Male 50 56 0.15 46 56 0.04 43 56 Female 50 44 54 44 57 44 Usual adult BMI 1 2 34 0.30 35 34 36 25-<30	70	29	39		23	38		32	35	
Male 50 56 0.15 46 56 0.04 43 56 Female 50 44 54 44 57 44 Usual adult BMI 50 44 54 44 57 44 <25 35 34 0.30 35 34 0.53 27 36 $<25-30$ 40 46 40 45 40 40 40 40 30 25 20 25 21 33 20 20	Gender									
Female 50 44 54 44 57 44 Usual adult BMI	Male	50	56	0.15	46	56	0.04	43	56	0.04
Usual adult BMI <25 35 34 0.30 35 34 0.53 27 36 25-<30 40 46 40 45 40 44 30 25 20 25 21 33 20	Female	50	44		54	44		57	44	
 <25 35 34 0.30 35 34 0.53 27 36 25-<30 40 46 40 45 40 45 40 44 30 25 20 25 21 33 20 	Usual adult BMI									
25-<30 40 46 40 45 40 45 40 44 30 25 20 25 21 33 20	<25	35	34	0.30	35	34	0.53	27	36	0.02
30 25 20 25 21 33 20	25-<30	40	46		40	45		40	44	
	30	25	20		25	21		33	20	