

Null Results in Brief

Risk Factors for Pancreatic Cancer Mortality: Extended Follow-up of the Original Whitehall Study

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Abstract

Given the well-established links between diabetes and elevated rates of pancreatic cancer, there are reasons to anticipate that other markers of metabolic abnormality (increased body mass index, plasma cholesterol, and blood pressure) and their correlates (physical activity and socioeconomic status) may also confer increased risk. However, to date, the results of a series of population-based cohort studies are inconclusive. We examined these associations in the original Whitehall cohort study of 17,898 men. A maximum of 38 years of follow-up gave rise to 163 deaths due to carcinoma of the pancreas. Although Poisson regression analyses confirmed established

risk factor–disease associations for increasing age, smoking, and type II diabetes, there was essentially no evidence that body mass index (rate ratio, 1.01; 95% confidence interval per 1 SD increase, 0.86–1.18), plasma cholesterol (0.91; 0.78–1.07), diastolic blood pressure (0.93; 0.78–1.09), systolic blood pressure (0.98; 0.83–1.15), physical activity (sedentary versus high: 1.37; 0.89–2.12), or socioeconomic status [clerical (low) versus professional/executive, 0.95; 0.59–1.51] offered any predictive value for pancreatic cancer mortality. These results were unchanged following control for a range of covariates. (Cancer Epidemiol Biomarkers Prev 2009;18(2):673–5)

Introduction

Pancreatic cancer is a relatively rare malignancy but a major cause of cancer mortality worldwide (1, 2). With conventional treatments essentially ineffective (3), <4% of cases survive 5 years after diagnosis (4, 5). Despite the crucial importance of primary prevention for such a near-lethal neoplasm, little is known about its risk factors beyond increased age, family history, smoking, and diabetes (3). Obesity and physical activity, by dint of their link with diabetes, have been implicated in pancreatic cancer etiology, but findings suggest that any increased occurrence of this neoplasm in the obese may be modest (6), particularly in men (7), and evidence for physical exertion is inconclusive with both inverse (8, 9) and null (10–12) associations reported. Other metabolic abnormalities such as increased levels of blood pressure (13–15) and blood cholesterol (15–17), although examined in few studies, generally show no effect. Furthermore, the evidence that socioeconomic disadvantage, by which

all of the afore described risk factors are patterned, may confer increased risk of carcinoma of the pancreas is uncertain with opposing gradients reported (10, 18).

We contribute to this highly inconclusive and scant literature, much of which is derived from underpowered studies, by focusing on the role of obesity, physical activity, increased blood pressure, elevated plasma cholesterol, and socioeconomic disadvantage as potential risk factors for pancreatic cancer in an extended follow-up of a large prospective cohort of male office workers.

Materials and Methods

In the Whitehall Study, data were collected on 19,019 male, nonindustrial, government employees with ages from 40 to 69 years at the time of examination between 1967 and 1970 in London (United Kingdom), representing a 77% response (19). This involved the completion of a study questionnaire and participation in a medical examination, both of which have been described in detail elsewhere (19). In brief, the questionnaire included inquiries regarding civil service employment grade (an indicator of socioeconomic status; ref. 20), smoking habits (21), marital status (22), and physical activity (23, 24). Blood pressure (13), height (25), weight (26), pulmonary function (indexed by forced expiratory volume in 1 s; ref. 27), and, following an overnight fast, plasma cholesterol (17) and post-challenge blood glucose

Received 10/30/08; accepted 11/7/08; published OnlineFirst 02/03/2009.

Grant support: The original screening of the Whitehall study was funded by the Department of Health and Social Security and the Tobacco Research Council. David Batty is a Wellcome Trust Fellow, Michael Marmot is a UK Medical Research Council Research Professor, Martin Shipley is supported by the British Heart Foundation, and Mika Kivimaki by the Academy of Finland.

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doi:10.1158/1055-9965.EPI-08-1032

concentration (28) were all determined using standard protocols (19). Body mass index was computed using the standard formula [weight (kg) / height² (m²)].

A total of 18,863 men (99.2% of participants in the baseline survey) were traced using the U.K. National Health Service Central Registry and pancreatic cancer deaths were ascertained from death certificates (coded as ICD 8/9: 157, ICD 10: C25). The present analyses are based on 17,898 men with complete data. The person years of follow-up for each man was partitioned by age at risk using 5-year age groups. To summarize the relationship between each risk factor and pancreatic cancer, we used Poisson regression, which produced rate ratios with accompanying 95% confidence intervals. These analyses were first adjusted for age at risk and then fully adjusted for all potential confounding and mediating factors.

Results

During a maximum of 38 years of follow-up, there were 12,797 deaths from all causes in the present analytical sample, 163 (1.3%) of which were ascribed to pancreatic cancer. We were able to replicate the few well-established risk factor–disease associations for pancreatic cancer. Thus, in age-adjusted analyses, current (rate ratio, 1.52; 95% confidence interval, 0.94–2.46) and former smokers (1.72; 1.07–2.77) relative to nonsmokers, and

men with type II diabetes (2.47; 0.79–7.75) relative to those who were free of this condition, all experienced an elevated risk of this malignancy. Age itself also revealed the expected positive association with pancreatic cancer mortality (rate ratio per 10-year increase, 2.10; 1.79–2.46).

In Table 1, we show the associations between a series of other potential risk factors for carcinoma of the pancreas. Body mass index, plasma cholesterol, and socioeconomic position were all unrelated to pancreatic cancer risk. Similarly, neither component of blood pressure predicted the occurrence of this malignancy. There was a modest elevated risk in the least physically active men that, again, did not attain statistical significance at conventional levels, and there was no evidence of a dose-response effect across the exercise groups.

Discussion

In this large prospective cohort study with almost complete follow-up of its members, there was little suggestion that a series of indicators of metabolic abnormalities or their correlates (all of which have been hypothesized, by us and other groups, to influence pancreatic cancer risk), actually revealed any relationship with this malignancy, either with or without adjustment for potential confounders. These results accord with the generally null findings from a series of studies for body

Table 1. Risk factors for pancreatic cancer mortality in the original Whitehall Study (N = 17,898)

	No. deaths/no. men	Rate ratio (95% confidence intervals)	
		Age-adjusted	Multiple adjustment*
Body mass index (kg/m ²)			
Tertile 1	53/5,969	1.0	1.0
Tertile 2	54/5,994	0.98 (0.67–1.43)	1.02 (0.69–1.50)
Tertile 3	56/5,935	1.10 (0.75–1.60)	1.18 (0.79–1.75)
Per 1 SD (2.98 kg/m ²) increase		1.01 (0.86–1.18)	1.03 (0.87–1.23)
Plasma cholesterol (mmol/L)			
Tertile 1	56/6,124	1.0	1.0
Tertile 2	69/5,733	1.32 (0.93–1.88)	1.32 (0.93–1.88)
Tertile 3	38/6,041	0.71 (0.47–1.07)	0.73 (0.48–1.10)
Per 1 SD (1.21 mmol/L) increase		0.91 (0.78–1.07)	0.92 (0.78–1.08)
Diastolic blood pressure (mmHg)			
Tertile 1	63/5,687	1.0	1.0
Tertile 2	50/6,219	0.75 (0.52–1.09)	0.75 (0.52–1.10)
Tertile 3	50/5,991	0.88 (0.61–1.28)	0.89 (0.60–1.31)
Per 1 SD (13.8 mmHg) increase		0.93 (0.78–1.09)	0.92 (0.77–1.10)
Systolic blood pressure (mmHg)			
Tertile 1	59/5,870	1.0	1.0
Tertile 2	57/6,042	0.97 (0.67–1.39)	0.96 (0.67–1.39)
Tertile 3	47/5,986	0.92 (0.63–1.36)	0.93 (0.62–1.38)
Per 1 SD (21.2 mmHg) increase		0.98 (0.83–1.15)	0.98 (0.83–1.17)
Physical activity			
High	33/2,955	1.0	1.0
Moderate	78/9,339	0.93 (0.66–1.33)	0.92 (0.65–1.30)
Sedentary	52/5,604	1.37 (0.89–2.12)	1.32 (0.84–2.06)
Socioeconomic position			
Administrative (highest socioeconomic status)	13/908	1.43 (0.80–2.54)	1.43 (0.80–2.55)
Professional/executive	106/11,652	1.0	1.0
Clerical	21/2,823	0.95 (0.59–1.51)	1.00 (0.62–1.63)
Other (lowest socioeconomic status)	16/1,678	1.29 (0.76–2.18)	1.29 (0.74–2.25)
BC and DS [†]	7/837	0.94 (0.44–2.02)	0.99 (0.46–2.13)

*Excluding the predictor variable of interest, multiple adjustment is adjustment for body mass index, plasma cholesterol, physical activity, socioeconomic status, diabetes/blood glucose, marital status, forced expiratory volume in 1 s, height, age at risk, smoking, and diastolic and systolic blood pressure (estimates for components of blood pressure are not mutually adjusted).

[†] British Council and Diplomatic Service included as separate categories because grade levels are not comparable with other civil service departments.

mass index (in men) (ref. 7), plasma cholesterol (15-17), blood pressure (13-15), physical activity (10-12), and socioeconomic position (18)—including those from earlier follow-ups of the present cohort for some of these risk factors which were based on substantially fewer deaths (13, 20, 23, 26).

This study has several strengths, including its large sample size, which leads to a greater number of pancreatic cancer events than many other studies, prospective design, statistical control of a range of potential mediating and confounding variables, and almost complete follow-up for mortality. Weaknesses include the absence of measurement of other potential risk factors such as dietary characteristics, as well as alcohol and meat consumption (29). Although 3-day food intake diaries were in fact administered in the present study, this was only in a subset of fewer than 2,000 men (26) in which the number of pancreatic cancer deaths is too low to facilitate analyses. A second study limitation is the absence of repeat measurement of these risk factors over time, a common shortcoming in this field. However, given that this data set revealed the established risk factor–disease gradients for age, diabetes, and smoking in relation to pancreatic cancer, there is a suggestion that our null results should be trusted.

In conclusion, although confirming previously well-demonstrated risk factors–disease associations, we found little or no evidence that potentially modifiable physical characteristics (body mass index, plasma cholesterol, blood pressure, physical activity) or socioeconomic status were associated with pancreatic cancer mortality. Examination of other potential risk factors, including dietary characteristics, is important in order to increase our understanding of the etiology of pancreatic cancer and to identify targets for primary prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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BLOOD CANCER DISCOVERY

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Cancer Epidemiol Biomarkers Prev 2009;18:673-675.

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