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Anthropometry, Physical Activity, and the Risk of Pancreatic Cancer in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Tobacco smoking is the only established risk factor for pancreatic cancer. Results from several epidemiologic studies have suggested that increased body mass index and/or lack of physical activity may be associated with an increased risk of this disease. We examined the relationship between anthropometry and physical activity recorded at baseline and the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (n = 438,405 males and females age 19-84 years and followed for a total of 2,826,070 person-years). Relative risks (RR) were calculated using Cox proportional hazards models stratified by age, sex, and country and adjusted for smoking and self-reported diabetes and, where appropriate, height. In total, there were 324 incident cases of pancreatic cancer diagnosed in the cohort over an average of 6 years of follow-up. There was evidence that the RR of pancreatic cancer was associated with increased height [RR, 1.74; 95% confidence interval (95% CI), 1.20-2.52] for highest quartile compared with lowest quartile (P_{trend} = 0.001). However, this trend was primarily due to a low risk in the lowest quartile, as when this group was excluded, the trend was no longer statistically significant (P = 0.27). A larger waist-to-hip ratio and waist circumference were both associated with an increased risk of developing the disease (RR per 0.1, 1.24; 95% CI, 1.04-1.48; P_{trend} = 0.02 and RR per 10 cm, 1.13; 95% CI, 1.01-1.26; P_{trend} = 0.03, respectively). There was a nonsignificant increased risk of pancreatic cancer with increasing body mass index (RR, 1.09; 95% CI, 0.95-1.24 per 5 kg/m^2), and a nonsignificant decreased risk with total physical activity (RR, 0.82; 95% CI, 0.50-1.35 for most active versus inactive). Future studies should consider including measurements of waist and hip circumference, to further investigate the relationship between central adiposity and the risk of pancreatic cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(5):879–85)

Introduction

Pancreatic cancer is the sixth most common cause of cancer mortality in the European Union countries and is responsible for ~55,000 deaths there every year (1). Tobacco smoking is the only established cause of this invariably fatal disease (2). Diabetes is also probably a cause of pancreatic cancer (3), and it has been hypothesized, therefore, that other factors that are associated with glucose intolerance, such as obesity and lack of physical activity, may also increase the risk of developing pancreatic cancer. Several prospective epidemiologic studies have found that a high body mass index (BMI; refs. 4-6) and/or a lack of physical activity (6, 7) are associated with an increased risk of pancreatic cancer incidence or mortality, and these associations seem to be independent of a prior history of diabetes. Three of these four prospective studies were conducted in the United States (4-6), and the fourth was a study of male smokers in Finland (7).

The purpose of the current study was to examine the relationship between anthropometric factors and physical activity and the risk of developing pancreatic cancer in a large European cohort, the European Prospective Investigation into Cancer and Nutrition. The European Prospective Investigation into Cancer and Nutrition is a multicenter study designed primarily to investigate the relationship between nutrition and cancer in 10 European countries. The study has measured anthropometric variables for most participants at baseline and is one of the first epidemiologic studies of pancreatic cancer to also include measurements of hip and waist circumference.

Materials and Methods

The European Prospective Investigation into Cancer and Nutrition is a multicenter prospective cohort study consisting of 23 centers from Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. The study populations were mostly age 35 to 70 years and were recruited from the general population residing in a specific geographic region (a town or a province). The exceptions were the French cohort (health insurance scheme for school employees), the Utrecht (the Netherlands) and Florence (Italy) cohorts (women attending breast cancer screening), components of the Italian and Spanish cohorts (based on blood donors), and most of the Oxford (United Kingdom) cohort (based on vegetarian and health-conscious volunteers living in the United Kingdom). Eligible subjects were invited to participate in the study, and those who accepted gave informed consent and completed lifestyle questionnaires. In most centers, subjects were then invited to a center to provide a blood sample and to have anthropometric measurements taken. The lifestyle questionnaires included questions on education and socioeconomic status, occupation, history of previous illness, lifetime history of consumption of tobacco and alcoholic beverages, and physical activity. The methods have been reported in full by Riboli et al. (8).

Follow-up and Case Ascertainment

Follow-up was based on population cancer registries in seven of the participating countries: Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. In France, Germany, and Greece, a combination of methods were used, including health insurance records, cancer and pathology registries, and active follow-up through participants and their next of kin. Mortality data were also obtained from either the cancer registry or mortality registries at the regional or national level. Participants were followed from study entry (1991-2000) until first pancreatic cancer diagnosis, death, emigration, or end of the follow-up period. The current analysis was based on the central dataset held at the International Agency for Research on Cancer data set, updated to April 2004. For centers using cancer registry data, censoring dates for complete follow-up were December 1999 (Turin, Italy), December 2000 (Asturias and Murcia, Spain; Cambridge, United Kingdom; Bilthoven, the Netherlands), December 2001 (Florence, Varese, Ragusa, and Naples, Italy; Granada, Norway, Navarra, and San Sebastian, Spain; Oxford, United Kingdom; Malmö, Sweden), December 2002 (Umeå, Sweden; Aarhus and Copenhagen, Denmark), and June 2003 (Utrecht, the Netherlands). Subjects were censored at the date of pancreatic cancer diagnosis, date of death, loss to follow-up, or censoring date, whichever came first. For the three countries using individually based follow-up (France, Greece, and Germany), the end of follow-up was considered to be the date of last known contact, or date of diagnosis, or date of death, whichever came first. The percentage of subjects lost to follow-up was 1.6%.

Cancer incidence data were coded according to *International Classification of Diseases-Oncology 2nd edition* and mortality data according to the *International Classification of Diseases 10th edition*. Incident cases of pancreatic cancer reported to the central database during the follow-up period were eligible to be included in the present study. In total, 356 subjects were diagnosed with incident pancreatic cancer over the follow-up period. Twenty-nine cases were excluded from analyses for the following reasons: cases where the diagnosis date was after the censoring date (n = 1), cases of endocrine or lymphoid origin (n = 14), cases where it was uncertain whether the pancreatic cancer was the primary tumor (n = 14). As there were only three incident cases of pancreatic cancer over the follow-up period reported in the center from Norway, this center was excluded from the current analyses.

Anthropometry

All centers had measured anthropometric factors at baseline with the exception of the centers in France and the Oxford health-conscious volunteers. For the centers in France, self-reported baseline values for height and weight were available but no values for hip and waist circumference. The self-reported measures for the Oxford health-conscious volunteers were corrected for possible reporting bias. The corrections were obtained from age- and sex-specific regression of measured anthropometry onto self-reported anthropometry from the Oxford subjects recruited through general practitioners, for whom both measured and self-reported baseline anthropometry were available (9). The centers in Umeå, Sweden had measured height and weight at baseline but had not collected values for hip and waist circumference either.

Weight and height were recorded to the nearest 0.1 kg and 0.1 or 0.5 cm, respectively (9). Waist circumference was measured either at the narrowest torso circumference (Italy; Cambridge, United Kingdom; and Utrecht, the Netherlands) or at the midpoint between the lower ribs and iliac crest (Bilthoven, the Netherlands; Potsdam, Germany; Malmö, Sweden; and Oxford, United Kingdom). In Spain, Greece, Denmark, and Heidelberg, Germany, a combination of methods was used, although the majority of participants were measured at the narrowest circumference. Hip circumference was measured at the widest circumference (Italy; Spain; Bilthoven, the Netherlands; Greece; and Malmö, Sweden) or over the buttocks (United Kingdom; Utrecht, the Netherlands; Germany; and Denmark).

The anthropometric data were adjusted to reduce heterogeneity due to protocol differences in clothing worn during measurement. In most Italian centers, Spain, Germany, and Denmark, weight was measured in light underwear. In the centers of France; Turin; Umeå, Sweden; and Utrecht, the Netherlands, subjects wore normal clothing without shoes. In the remaining centers (Oxford-GP and Cambridge, United Kingdom; Bilthoven, the Netherlands; Greece; Malmö, Sweden), weighing was undertaken after removal of heavier sweaters or indoor jackets and emptying heavy objects from pockets (light clothing). For subjects who wore normal clothing without shoes, correction factors of –1.5 kg for weight and –2.0 cm for circumferences were adopted. In centers where weight was measured in light clothing, the adjustment for weight was –1.0 kg.

Physical Activity

In each center, work, leisure-time/home, and vigorous physical activity were assessed at baseline as part of the standardized lifestyle questionnaire (10). The core physical activity questionnaire used by most centers included questions on type of physical activity at work and the number of hours spent per week on vigorous physical activity and a number of specific recreational and household activities, including walking, housework, sport, gardening, and do it yourself. A summary "leisure time" physical activity variable was created by summing the number of hours spent per week in summer or winter on recreational and household or do-it-yourself physical activities. The intensities of these recorded activities were estimated from published values, and from these, summary leisure time metabolic equivalent (MET) levels were calculated as the sum of the MET hours/wk. An "overall" physical activity summary was then created by combining levels of physical activity at work with the summary measure of "METs leisure time" physical activity.

Statistical Methods

Cox proportional hazards models were used to estimate relative risks (RR) and 95% confidence intervals (95% CI) of pancreatic cancer incidence for each body measure and physical activity category. Age at study entry was used as the underlying (primary dependent) time variable, with entry time defined as the subject's age in days at recruitment and exit time defined as the subject's age in days at pancreatic cancer diagnosis or censoring. Analyses were restricted to subjects who were aged between 19 and 84 years at study entry.

BMI was calculated as weight divided by height squared (kg/m^2). Subjects with BMI between 20.0 and 22.4 kg/m^2 were used as the baseline category and compared with categories of BMI of <20.0, 22.5 to 24.9, 25 to 27.4, 27.5 to 29.9, and ≥30 kg/m^2. The waist and hip circumferences of each participant were used to construct a waist-to-hip ratio. Subjects were categorized according to sex-specific quartiles of height, weight, waist and hip circumference, and waist-to-hip ratio defined over the entire cohort, and the first quartile was used as the reference category. All models were stratified by sex, 5-year age groups at recruitment, and by country, and multivariate models were adjusted for smoking [never, past smokers (time since stopping: <15 and ≥15 years), and current smokers (intensity: <10, 10-19, and ≥20 cigarettes per day)] and self-reported diabetes (yes/no). Analyses of weight, waist and hip circumference, and waist-to-hip ratio were also adjusted for height. Subjects with missing values for smoking status and diabetes were excluded from all analyses (n = 28,532). Trend tests were calculated using the continuous anthropometric variables and across the categories of physical activity. Heterogeneity between countries was tested using the method of empirically weighed least squares with the weights defined as the inverse of the variance of the log relative risk (11).

Results

The analysis cohort included 438,405 subjects age between 19 and 84 years at baseline who were followed up for a total of 2,934,501 person years. Of the 324 included incident cases of pancreatic cancer, 152 cases were in males for which the median age at diagnosis was 61 years, and 172 cases were in females with a median age at diagnosis of 63 years (Table 1). Median height was lowest for Spanish males and for Greek females, and highest for males and females from the Netherlands. Median BMI was lowest in the U.K. health-conscious males and French females and highest in Spanish male and Greek female participants. The lowest proportion of subjects classified as very active were females from France and Swedish males, whereas the highest proportions were males and females from the Netherlands.

Table 1. Distribution of pancreatic cancer cases and noncases and BMI and physical activity according to country and age group

	Pancreatic cancer cases		Noncase subjects		Median height (m)		Median BMI (kg/m^2)		% Very active*	
	Males (%)	Females (%)	Males (%)	Females (%)	Males	Females	Males	Females	Males	Females
Country										
Denmark	45 (30)	27 (16)	25,306 (18)	28,064 (9)	1.77	1.64	26.1	24.8	12	11
France	0 (0)	18 (10)	0 (0)	65,121 (22)	—	1.62	—	22.3	—	3
Germany	27 (18)	18 (10)	21,980 (15)	28,457 (10)	1.75	1.63	26.6	24.7	7	10
Greece	6 (4)	4 (2)	10,198 (7)	14,559 (5)	1.70	1.56	27.6	28.3	5	15
Italy	8 (5)	12 (7)	13,955 (10)	31,099 (11)	1.72	1.59	26.0	25.0	8	11
The Netherlands	6 (4)	18 (10)	9,958 (7)	27,486 (9)	1.78	1.65	25.2	24.5	18	21
Spain	8 (5)	12 (7)	15,414 (11)	25,281 (9)	1.69	1.57	28.2	27.5	8	56
Sweden	29 (19)	43 (25)	21,341 (15)	25,112 (8)	1.77	1.64	25.3	24.1	2	7
U.K. general population	15 (10)	11 (6)	13,799 (10)	17,047 (6)	1.74	1.61	25.9	25.0	10	13
U.K. health conscious	8 (5)	9 (5)	10,105 (7)	33,799 (11)	1.77	1.64	24.4	23.2	9	11
Age (y)										
<45	7 (5)	9 (5)	33,374 (23)	74,243 (25)	1.77	1.63	25.4	23.2	11	19
45-54	38 (25)	42 (24)	50,312 (35)	113,656 (38)	1.75	1.63	26.3	23.9	10	15
55-64	85 (56)	85 (49)	47,330 (33)	86,900 (29)	1.74	1.61	26.6	25.2	8	12
≥65	22 (14)	39 (23)	11,040 (8)	21,226 (7)	1.71	1.59	26.3	25.6	1	3
Total	152 (100)	172 (100)	142,056 (100)	296,025 (100)	1.75	1.62	26.2	24.2	9	14

* Overall physical activity (see Materials and Methods).

Anthropometry

The associations between anthropometry and smoking and diabetes status, the potential confounding factors, were examined in the cohort overall. There was evidence that being taller was associated with a decreased probability of being diabetic and with a slightly increased probability of being a current or past smoker, whereas higher BMI was associated with an increased probability of being diabetic and of being a past smoker but with a lower probability of being a current smoker (Table 2). A higher waist-to-hip ratio was also associated with an increased probability of being diabetic and with a slightly increased probability of being a current smoker.

Table 2. Associations between anthropometry, physical activity and diabetes and smoking status

	No. subjects	Diabetes (%)	Current smoker (%)	Past smoker (%)
Height (quartile)				
Q1	113,750	4.4	20.9	23.5
Q2	111,546	2.8	22.2	27.1
Q3	110,078	2.2	22.5	28.6
Q4	96,471	1.8	23.4	29.6
BMI (kg/m^2)				
<20	25,768	1.1	24.1	19.9
20-22.4	82,336	1.1	21.9	23.0
22.5-24.9	109,029	1.7	22.5	26.8
25-27.5	93,567	2.7	23.1	30.0
27.5-29.9	59,330	4.0	22.4	30.9
30-34.9	47,313	6.4	20.6	28.9
≥35	13,261	9.7	17.5	25.2
Waist-to-hip ratio				
Q1	84,227	1.0	23.0	27.5
Q2	84,017	1.8	24.9	29.7
Q3	84,193	2.9	25.8	29.6
Q4	85,283	6.7	26.1	28.7
Overall physical activity				
Inactive	72,640	2.2	25.2	30.8
Moderately inactive	136,839	3.1	20.9	28.3
Moderately active	148,378	3.3	21.7	27.2
Very active	50,816	2.8	22.6	22.1

The SR of pancreatic cancer was associated with increased height (RR, 1.74; 95% CI, 1.20-2.52) for the highest to lowest quartile (P_{trend} = 0.001; Table 3). However, this significant trend was primarily due to the low risk in the lowest quartile, as when this group was excluded, the RR per cm increase was no longer statistically significant (P_{trend} = 0.27). After adjustment for confounding factors, there was no significant relationship between increased weight and the risk of pancreatic cancer (RR per 5 kg increase, 1.05; 95% CI, 0.99-1.10; Table 3), neither was there evidence that increased BMI was associated with a significantly increased risk of pancreatic cancer (RR per 5 kg/m^2, 1.09; 95% CI, 0.95-1.24). A higher waist circumference and waist-to-hip ratio were both associated with a slightly increased risk of developing pancreatic cancer, and the trends were statistically significant (RR per 10-cm increase, 1.13; 95% CI, 1.01-1.26; P_{trend} = 0.03 and RR per 0.1 increase, 1.24; 95% CI, 1.04-1.48; P_{trend} = 0.02, respectively; Table 3). There was no significant increase in RR with increasing hip circumference.

Table 3. RR and 95% CI of pancreatic cancer according to anthropometric factors

	Cases	RR (95% CI)	
		Unadjusted	Adjusted*
Height (cm)†			
Q1	58	1.00	1.00
Q2	99	1.71	1.71 (1.22-2.39)
Q3	87	1.58	1.57 (1.10-2.23)
Q4	75	1.73	1.74 (1.20-2.52)
Per 10 cm		1.37	1.37 (1.15-1.64)
P_{trend} = 0.001			
$P_{heterogeneity}$ = 0.42			
Weight (kg)‡			
Q1	66	1.00	1.00
Q2	65	0.94	0.90 (0.63-1.28)
Q3	85	1.10	1.02 (0.73-1.44)
Q4	103	1.28	1.14 (0.82-1.61)
Per 5 kg		1.06	1.05 (0.99-1.10)
P_{trend} = 0.06			
$P_{heterogeneity}$ = 0.47			
BMI (kg/m^2)			
<20	9	0.71	0.67 (0.33-1.37)
20-22.9	48	1.00	1.00
23-24.9	85	0.97	0.99 (0.69-1.41)
25-26.9	71	0.79	0.82 (0.56-1.19)
27-29.9	43	0.74	0.76 (0.50-1.16)
30-34.9	50	1.15	1.16 (0.77-1.76)
≥35	13	1.21	1.19 (0.64-2.23)
Per 5 kg/m^2		1.08	1.09 (0.95-1.24)
P_{trend} = 0.24			
$P_{heterogeneity}$ = 0.50			
Hip circumference§ (cm)			
Q1	69	1.00	1.00
Q2	55	0.78	0.78 (0.55-1.12)
Q3	66	0.93	0.92 (0.65-1.30)
Q4	90	1.27	1.20 (0.86-1.68)
Per 10 cm		1.11	1.09 (0.94-1.26)
P_{trend} = 0.27			
$P_{heterogeneity}$ = 0.83			
Waist circumference∥ (cm)			
Q1	51	1.00	1.00
Q2	59	0.90	0.89 (0.61-1.30)
Q3	79	1.12	1.08 (0.75-1.54)
Q4	91	1.26	1.14 (0.79-1.63)
Per 10 cm		1.18	1.13 (1.01-1.26)
P_{trend} = 0.03			
$P_{heterogeneity}$ = 0.43			
Waist-to-hip ratio¶			
Q1	45	1.00	1.00
Q2	59	0.97	0.96 (0.65-1.41)
Q3	73	1.09	1.05 (0.72-1.53)
Q4	103	1.48	1.33 (0.93-1.92)
Per 0.1		1.32	1.24 (1.04-1.48)
P_{trend} = 0.02			
$P_{heterogeneity}$ = 0.38			

NOTE: Both adjusted and unadjusted relative risks were stratified by 5-year age at entry groups, sex, and country. $P_{heterogeneity}$ is a test for heterogeneity in RR between countries.

* Adjusted for smoking and diabetes and by sex-specific height quartile (weight, waist, hip, and waist/hip ratio only).

† Quartiles: males, <170, 170 to <175, 175 to <180, and ≥180 cm; females, <158, 158 to <162, 162 to <167, ≥167 cm.

‡ Quartiles: males, <73, 73 to <80, 80 to <88, and ≥88 kg; females, <58, 58 to <64, 64 to <72, and ≥72 kg.

§ Quartiles: males, <97, 97 to <100, 100 to <105, and ≥105 cm; females, <95, 95 to <101, 101 to <107, and ≥107 cm.

|| Quartiles: males, <88, 88 to <94, 94 to <101, and ≥101 cm; females, <73, 73 to <79, 79 to <88, and ≥88 cm.

¶ Quartiles: males, <0.90, 0.90 to <0.94, 0.94 to <0.98, and ≥0.98; females, <0.75, 0.75 to <0.79, 0.79 to <0.84, and ≥0.84.

Generally, the adjustments for smoking and diabetes, and where appropriate, height, decreased the relative risk estimates slightly (Table 3). There was no evidence of significant effect modification by smoking or diabetic status, although the number of subjects with self-reported diabetes as baseline was relatively small; thus, tests for statistical interaction lacked power (Table 4). The RRs for all the anthropometric factors varied somewhat between males and females, but none of these differences were statistically significant at the 0.05 level when interaction terms were included in the proportional hazards model. The consistency of findings across countries was examined by estimating the relative risks for the continuous variables. There was no evidence of significant heterogeneity between the results from different countries for any of the anthropometric factors (Table 3).

Table 4. RR and 95% CI of pancreatic cancer according to anthropometric factors by smoking and diabetes status

	Never smokers (cases = 114), RR (95% CI)	Ever smokers (cases = 210), RR (95% CI)	$P_{interaction}$	Nondiabetics (cases = 300), RR (95% CI)	Diabetics (cases = 24), RR (95% CI)	$P_{interaction}$
Height (per cm)	1.58 (1.16-2.14)	1.27 (1.02-1.59)	0.45	1.32 (1.09-1.59)	2.46 (1.25-4.84)	0.28
Weight (per 5 kg)	1.08 (0.99-1.16)	1.03 (0.97-1.10)	0.38	1.05 (1.00-1.11)	0.94 (0.80-1.11)	0.82
BMI (per 5 kg/m^2)	1.12 (0.90-1.40)	1.07 (0.90-1.27)	0.67	1.10 (0.95-1.27)	0.83 (0.53-1.30)	0.75
Hip circumference (per 10 cm)	1.15 (0.90-1.48)	1.06 (0.88-1.27)	0.39	1.11 (0.95-1.29)	0.77 (0.47-1.25)	0.53
Waist circumference (per 10 cm)	1.17 (0.96-1.43)	1.12 (0.98-1.27)	0.18	1.15 (1.02-1.29)	0.93 (0.64-1.33)	0.55
Waist-to-hip ratio (per 0.1)	1.22 (0.89-1.69)	1.24 (1.00-1.53)	0.28	1.24 (1.03-1.50)	1.21 (0.64-2.28)	0.82

NOTE: RRs were stratified by 5-year age at entry groups, sex, and country and adjusted for smoking and diabetes (where appropriate) and by sex-specific height quartile (weight, waist, hip, and waist/hip ratio only). $P_{interaction}$ is a test for interaction. (RR, 1.32, 95% CI 0.73-2.37 for women and RR, 1.74, 95% CI 1.00-1.31 among men per 10 cm increase).

All the above analyses were repeated with exclusion of the first 2 years of follow-up to assess whether an association with preexisting disease might have influenced the results. The findings were broadly similar to those from the full analysis, but the magnitude of the risk of developing pancreatic cancer with higher waist circumference and waist-to-hip ratio were increased to some extent after this exclusion (Table 5). The mean waist-to-hip ratio at baseline of the female cases who were diagnosed within 2 years of study entry was 0.80 compared with 0.83 for those cases who were diagnosed >2 years after study entry (*t* test, $P = 0.009$). Similarly, the mean waist circumference of the females cases diagnosed within 2 years of study entry was lower than those diagnosed later (81 cm compared with 86 cm; *t* test, $P = 0.04$). No such differences were present, however, for the male cases (mean waist-to-hip ratio = 0.96 and mean waist circumference = 97 cm for <2 and ≥2 years to diagnosis, respectively).

Table 5. RR and 95% CI of pancreatic cancer according to anthropometric factors, excluding the first 2 years follow-up

	Cases	RR (95% CI)	
		Unadjusted	Adjusted*
Height (cm)†			
Q1	42	1.00	1.00
Q2	72	1.63	1.63 (1.10-2.41)
Q3	62	1.46	1.45 (0.96-2.20)
Q4	60	1.78	1.78 (1.16-2.73)
Per 10 cm		1.37	1.38 (1.12-1.70)
P_{trend} = 0.003			
$P_{heterogeneity}$ = 0.30			
Weight (kg)‡			
Q1	49	1.00	1.00
Q2	48	1.03	1.07 (0.71-1.61)
Q3	62	1.13	1.10 (0.75-1.60)
Q4	77	1.35	1.27 (0.87-1.83)
Per 5 kg		1.07	1.06 (1.00-1.12)
P_{trend} = 0.03			
$P_{heterogeneity}$ = 0.70			
BMI (kg/m^2)			
<20	6	0.59	0.55 (0.23-1.31)
20-22.9	39	1.00	1.00
23-24.9	61	0.85	0.87 (0.58-1.31)
25-26.9	51	0.71	0.74 (0.49-1.14)
27-29.9	33	0.72	0.75 (0.46-1.24)
30-34.9	36	1.07	1.10 (0.69-1.76)
35+	6	1.20	1.22 (0.60-2.49)
Per 5 kg/m^2		1.12	1.14 (0.97-1.33)
P_{trend} = 0.11			
$P_{heterogeneity}$ = 0.34			
Hip circumference§ (cm)			
Q1	48	1.00	1.00
Q2	43	0.88	0.88 (0.58-1.34)
Q3	48	0.98	0.96 (0.64-1.46)
Q4	66	1.35	1.31 (0.88-1.94)
Per 10 cm		1.16	1.15 (0.97-1.36)
P_{trend} = 0.10			
$P_{heterogeneity}$ = 0.61			
Waist circumference‖ (cm)			
Q1	36	1.00	1.00
Q2	42	0.90	0.89 (0.57-1.39)
Q3	58	1.17	1.13 (0.74-1.72)
Q4	69	1.39	1.29 (0.85-1.97)
Per 10 cm		1.24	1.21 (1.07-1.37)
P_{trend} = 0.003			
$P_{heterogeneity}$ = 0.20			
Waist-to-hip ratio¶			
Q1	30	1.00	1.00
Q2	46	1.11	1.10 (0.69-1.75)
Q3	50	1.11	1.08 (0.68-1.71)
Q4	79	1.73	1.62 (1.05-2.50)
Per 0.1		1.42	1.36 (1.11-1.66)
P_{trend} = 0.003			
$P_{heterogeneity}$ = 0.43			

NOTE: Both adjusted and unadjusted RRs were stratified by 5-year age at entry groups, sex, and country. $P_{heterogeneity}$ is a test for heterogeneity in RR between countries.

* Adjusted for smoking and diabetes and by sex-specific height quartile (weight, waist, hip and waist: hip ratio only).

† Quartiles: males, <170, 170 to <175, 175 to <180, and ≥180 cm; females, <158, 158 to <162, 162 to <167, and ≥167 cm.

‡ Quartiles: males, <73, 73 to <80, 80 to <88, and ≥88 kg; females, <58, 58 to <64, 64 to <72, and ≥72 kg.

§ Quartiles: males, <97, 97 to <100, 100 to <105, and ≥105 cm; females, <95, 95 to <101, 101 to <107, and ≥107 cm.

|| Quartiles: males, <88, 88 to <94, 94 to <101, and ≥101 cm; females, <73, 73 to <79, 79 to <88, and ≥88 cm.

¶ Quartiles: males, <0.90, 0.90 to <0.94, 0.94 to <0.98, and ≥0.98; females, <0.75, 0.75 to <0.79, 0.79 to <0.84, and ≥0.84.

Physical Activity

Overall, subjects who were most active, according to the summary physical activity index, were younger (Table 1) and were less likely to have ever smoked (Table 2). There was no evidence that the reported number of hours of vigorous physical activity or any of the other composite physical activity measures were related to the risk of pancreatic cancer, either before or after adjustment for smoking and diabetes (Table 6) or after exclusion of the first 2 years of follow-up (data not shown). Neither was there evidence of effect modification between physical activity and obesity, as measured by BMI or waist-to-hip ratio (data not shown).

Table 6. RR and 95% CI of pancreatic cancer in relation to physical activity

	Cases	RR (95% CI)	
		Unadjusted	Adjusted*
Vigorous physical activity (hours/wk)			
None	96	1.00	1.00
≤2	51	1.10	1.13 (0.78-1.64)
>2	47	1.18	1.21 (0.83-1.77)
P_{trend} = 0.32			
$P_{heterogeneity}$ = 0.89			
Leisure time physical activity			
Low	98	1.00	1.00
Medium	97	0.91	0.95 (0.71-1.26)
High	104	0.91	0.94 (0.71-1.25)
P_{trend} = 0.69			
$P_{heterogeneity}$ = 0.31			
Leisure time physical activity (METS quartile)			
Q1	75	1.00	1.00
Q2	82	1.09	1.13 (0.82-1.56)
Q3	78	1.00	1.05 (0.75 -1.47)
Q4	64	0.91	0.96 (0.66-1.39)
P_{trend} = 0.86			
$P_{heterogeneity}$ = 0.65			
Physical activity at work			
Sitting	83	1.00	1.00
Standing	48	0.82	0.81 (0.57-1.17)
Manual/heavy manual	40	0.90	0.88 (0.60-1.29)
Unemployed	139	0.94	0.88 (0.64-1.23)
P_{trend} = 0.33			
$P_{heterogeneity}$ = 0.72			
Physical activity (overall level)			
Inactive	54	1.00	1.00
Moderately inactive	102	0.94	0.91 (0.64-1.28)
Moderately active	117	0.87	0.87 (0.61-1.23)
Very active	26	0.82	0.82 (0.50-1.35)
P_{trend} = 0.36			
$P_{heterogeneity}$ = 0.28			

NOTE: Both adjusted and unadjusted relative risks were stratified by 5-year age at entry groups, sex, and country. $P_{heterogeneity}$ is the test for heterogeneity in RR between countries.

* Adjusted for smoking and diabetes.

Discussion

In this large multicenter prospective study, we found that both a higher waist circumference and waist-to-hip ratio were associated with an increased risk of developing pancreatic cancer, but increased BMI and level of physical activity were not significantly associated with the risk of developing the increase. There was also some evidence of an association between increased height and pancreatic cancer risk.

There have been at least seven prospective and six retrospective studies published on the risk of pancreatic cancer and BMI, and together, they provide evidence that obesity, measured by an increased BMI, may be weakly associated with risk (12). In the current study, although there was no statistically significant relationship between increased BMI and the risk of pancreatic cancer, the relative risk per 5 kg/m^2 of 1.09 (95% CI, 0.95-1.24) was consistent with the combined findings from previous studies (summary RR per 5 kg/m^2, 1.16; ref. 12). Two measures of central adiposity, increased waist circumference and waist-to-hip ratio, however, were significantly related to the risk of developing pancreatic cancer. Two other studies have published results for central adiposity and pancreatic cancer, and both found evidence of increased risks. Larsson et al. found evidence of an increased risk with increasing self-reported waist circumference in a Swedish cohort study. In the U.S. Cancer Prevention Study II, Patel et al. found that subjects who reported a tendency for central weight gain were at increased risk of pancreatic cancer compared with those who reported peripheral weight gain (RR, 1.45; 95% CI, 1.02-2.07; ref. 14). In the current study, the magnitude of the risk and the strength of the trend for these measures of central adiposity increased when the first 2 years of follow-up were excluded, to remove the possible effect of prediagnostic symptoms.

Three prospective studies have directly investigated abnormal glucose metabolism and the risk of pancreatic cancer. All reported increased risks with increasing levels of glucose intolerance not just a raised risk for those who were clinically diabetic (5, 15, 16). Central adiposity is associated with glucose intolerance and is a risk factor for diabetes (17-19), hence concomitantly increased insulin levels may be the mechanism through which central adiposity increases pancreatic cancer risk. Adjustment for self-reported diabetes status did slightly reduce the magnitude of the association between both measures of central adiposity and the risk of pancreatic cancer, but there was still a significant association in those who did not report being diabetic at study entry. This could be evidence that any level of glucose intolerance, not just clinical diabetes, increases risk. If this is the mechanism through which obesity increases the risk of pancreatic cancer, then central adiposity may be a more relevant measure than BMI, despite the fact that it is likely to be measured less accurately. The relationship among central adiposity, glucose intolerance, and pancreatic cancer warrants further investigation.

Three previous cohort studies have also reported on height and the risk of pancreatic cancer: two found no evidence of an association (5, 20), whereas one found an association similar to that reported in the current study (RR, 1.81; 95% CI, 1.31-2.52 for top versus bottom category of height; ref. 6). Of the seven case-control studies that have also investigated this relationship (21-27), only two found evidence of an association between height and the risk of pancreatic cancer (21, 22). Adult height has also been found to be associated with an increased risk of some other cancers, including the breast, prostate, thyroid, colon, and endometrium (28, 29), and may be a proxy for exposure to growth and circulating growth factor levels during adolescence or childhood. However, as only 4 of the 11 epidemiologic studies that have reported on height and pancreatic cancer risk to date have found evidence of an association, and the fact that in the current study the significant trend was due to a reduced risk in the lowest quartile, rather than a consistently increasing risk across quartile, it remains unclear whether there is a real relationship between height and the risk of pancreatic cancer.

Most of the previous studies of pancreatic cancer and anthropometric factors have had to rely on self-reported measurements, which can result in bias due to the fact that weight tends to be underreported by overweight and obese people (30). A strength of the current study, therefore, is that in the majority of centers anthropometric factors were measured rather than self-reported. Measurement rather than self-reporting is particularly important for waist and hip circumferences, which are likely to be reported less accurately than height and weight. Differences between the centers in measurement methods may have resulted in some additional variability in weight, hip, and waist circumference measurements. Attempts were made to correct for these differences, but these adjustments were only possible on a center not an individual basis.

Four prospective studies and one retrospective study have previously investigated physical activity, and three of them have found some evidence that higher levels of physical activity are associated with a decreased risk of pancreatic cancer (5, 6, 31), whereas two of the previous prospective studies did not find any evidence of such an association (32, 33). There was no evidence in the current study that level of physical activity was related to the risk of developing pancreatic cancer. However, there were some differences between centers with respect to the physical activity questionnaires and how the questions were interpreted, which may have introduced additional variability and could have obscured a weak association between physical activity and the risk of pancreatic cancer.

In this large European cohort study, we found evidence that increased central adiposity and possibly height were associated with an increased risk of developing pancreatic cancer. Future studies should consider including measurements of waist and hip circumference to further investigate the relationship between control adiposity and the risk of developing this fatal disease.

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Footnotes

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