Anthropometry and Pancreatic Cancer Risk: An Illustration of the Importance of Microscopic Verification

Bas A.J. Verhage,[1] Leo J. Schouten,[1] R. Alexandra Goldbohm,[2] and Piet A. van den Brandt[1]

[1]Department of Epidemiology (Nutrition and Toxicology Research Institute Maastricht), Maastricht University, Maastricht, the Netherlands and [2]Department Food and Chemical Risk Analysis, TNO Quality of Life, Zeist, the Netherlands

Abstract

Using data collected of a large population-based cohort study, we studied the association between anthropometric factors and the risk of pancreatic cancer. Furthermore, we investigated whether these associations differ among microscopically confirmed pancreatic cancer (MCPC) cases and non-MCPC (NMCPC) cases. The Netherlands Cohort Study on Diet and Cancer started in 1986 (120,852 men and women) and uses the case-cohort methodology. After 13.3 years of follow-up, 446 pancreatic cancer cases (of which 65% was microscopically confirmed) and 4,774 subcohort members were available for analysis. The multivariable incidence rate ratio of MCPC of men was 1.10 per increment of 1 $kg \cdot m^{-2}$ (95% confidence interval, 1.04-1.18). Women had a rate ratio of MCPC of 1.08 (95% confidence interval, 1.03-1.13). Obese men [body mass index (BMI) $\geq$30 $kg \cdot m^{-2}$] had a 2.6-fold increased risk of MCPC compared with men with BMI 23 to 25 $kg \cdot m^{-2}$. For women, this increase in risk was 1.7-fold. Change in BMI between age 20 years and baseline was also associated with MCPC in both men and women. In men and women, none of these associations were observed for NMCPC, with the exception of the increased risk for pancreatic cancer in obese men. We observed statistically significant associations between both BMI, gain in BMI, and pancreatic cancer risk. These associations are observed only in MCPC and not in NMCPC. If MCPC and NMCPC had been considered as one group, the reported associations would not have been detected. These findings stress the need to evaluate heterogeneity among pancreatic cancer cases in etiologic studies. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1449–54)

Introduction

Although pancreatic cancer does not rank among the most common cancers in the Western world, it is the sixth most common cause of cancer death in Europe (1) and fourth in the United States (2). Its prognosis is one of the most dismal of all cancers and in both Europe and the United States (3), 5-year survival rates of only 4% to 5% for all tumors and <1% for nonresectable tumors (4) have been reported. To date, no effective means of early detection, prevention, or treatment are available.

Few risk factors have been implicated in the etiology of pancreatic cancer, with cigarette smoking being the most consistent (5), accounting for ~25% of the incidence (5, 6). Other potentially modifiable lifestyle factors, including body mass index (BMI) or obesity, may influence the risk of pancreatic cancer but thus far studies have produced inconsistent results. Results from both case-control and cohort studies showed positive associations between BMI, or obesity, and pancreatic cancer (7, 8), whereas other studies found no association (7, 9). Among studies reporting a positive association, some presented evidence of this association among both men and women (7, 8), whereas others among men alone (7). One possible explanation for these inconsistent findings, besides other issues of bias, may be differences among studies in the diagnostic criteria used to define ''caseness.'' In epidemiologic studies of pancreatic cancer, contrary to other forms of cancer, microscopic (or cytohistologic) confirmation often lacks for more than 30% to 40% of all cases. In the United States, pancreatic cancer cases without confirmation represent one fourth of the total number of pancreatic cancer cases (10), whereas in certain areas and demographic groups this figure may even be higher (11). In Europe, populations of pancreatic cancer cases having <50% microscopic verification are observed in Czech Republic, Ireland, Italy, Malta, Poland, Portugal, Slovakia, Spain, and the United Kingdom (12).

Cases without pathologic confirmation (but with strong clinical evidence supporting the diagnosis) are often included in epidemiologic studies (13), but may reflect different subtypes of pancreatic cancer or even nonpancreatic cancer.

The aim of the present study, therefore, is 2-fold. Using the data collected in a large population-based cohort study, we study the association between anthropometric factors and the risk of pancreatic cancer. Furthermore, we will investigate whether these associations differ among microscopically confirmed pancreatic cancer (MCPC) cases and non-MCPC (NMCPC) cases.

Materials and Methods

The Cohort. The Netherlands Cohort Study is an ongoing prospective cohort study on diet and cancer among 58,279 men and 62,573 women who were ages 55 to 69 years at baseline. Baseline exposure data were collected by means of a self-administered questionnaire in September 1986.

The study was designed as a case-cohort study: Cases arising from the cohort provide numerator information for the calculation of cancer incidence rates, whereas the accumulated person-years in the entire cohort (denominator information for the rates) are estimated using a random sample of 5,000 from the cohort (subcohort). This subcohort was sampled directly after the identification of all cohort members and has been followed up biennially for vital status information. Further details on The Netherlands Cohort Study on Diet and Cancer study design have been reported elsewhere (14).

Received 3/5/07; revised 4/20/07; accepted 4/30/07.

Grant support: Dutch Cancer Society.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Bas A.J. Verhage, Department of Epidemiology, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, P.O. Box 616, 6200 MD Maastricht, the Netherlands. Phone: 31-43-388-2371; Fax: 31-43-388-4128. E-mail: bas.verhage@epid.unimaas.nl

doi:10.1158/1055-9965.EPI-07-0201

All prevalent cancer cases, other than skin tumors, at baseline (75 men and 151 women) were excluded from the subcohort. The remaining 4,774 subcohort members (2,336 men and 2,438 women) were available for analyses.

Follow-up. The present analyses are restricted to a follow-up of 13.3 years, up to December 1999. Exocrine pancreatic cancer cases (ICD-O-3 code C25, excluding C25.4; $n = 447$) in the cohort were identified through record linkage to the Netherlands cancer registries and the nationwide pathology register PALGA (15). After excluding endocrine subtypes based on histology (islet cell carcinoma, $n = 1$), 446 pancreatic cancers were available for analyses. Of all exocrine pancreatic cancers, 65% was microscopically confirmed (MCPC, $n = 290$), whereas confirmation was missing for 35% (NMCPC, $n = 156$). The diagnosis of the latter group was made by the treating clinician and based on clinical symptoms, physical examination and imaging results, and abstracted and recorded by a trained tumor registrar (16).

Only two subcohort members were lost to follow-up after 13.3 years and completeness of cancer follow-up has been estimated to be at least 96%.

Questionnaire Data. The collected questionnaire data on anthropometry (self-reported height, weight, weight at age 20 years) and other potential risk factors from subcohort and pancreatic cancer cases were key entered twice by research assistants who were blinded with respect to subcohort/case status to minimize observer bias in coding and interpretation of the data.

Rate ratios (RR) for height and weight were presented per centimeter and kilogram, respectively. BMI was calculated by dividing weight (kg) by height squared (m^2). RRs are presented per 1 $kg \cdot m^{-2}$ increment for BMI at baseline, BMI at age 20 years, and BMI gain between age 20 years and baseline. Additional to the analyses with continuous variables, height, weight, BMI, BMI at age 20 years, and BMI gain since age 20 years were also analyzed as categorical variables. Information on BMI at baseline was missing for 4% subcohort; BMI at age 20 years and BMI gain information was missing for 18% of the subcohort.

Energy intake (kcal/d) was calculated from the food frequency questionnaire using the computerized Dutch food composition table. Further details are given elsewhere (17).

Statistical Analysis. Incidence RRs and corresponding 95% confidence intervals (95% CI) for pancreatic cancer were estimated in age-adjusted and multivariable case-cohort analyses using the Cox proportional hazards model processed with the Stata statistical software package (release 9; Stata Corporation). SEs were estimated using the robust Huber-White sandwich estimator to account for additional variance introduced by sampling from the cohort (18). The proportional hazards assumption was tested using the scaled Schoenfeld residuals (19). In case the proportional hazards assumption was not met, time-varying variables were included for those variables that contributed to the violation of the proportional hazards assumption. In none of the cases the main determinant of interest (any of the measures of anthropometry) violated the assumption.

Tests for dose-response trends in risk of pancreatic cancer were assessed by fitting ordinal exposure variables as continuous terms. The following variables were considered as confounders: age at baseline, sex, cigarette smoking (current smoking (yes/no), number of years of smoking, and number of cigarettes smoked per day), and history of diabetes (yes/no) and hypertension (yes/no). All models containing gain in BMI since the age of 20 years were adjusted for BMI at age 20 years. The results are presented for men and women separately as the sex-specific effect estimates differed from the models including both sexes. Two-sided P values are reported throughout the article.

Results

The distributions of determinants and potential confounders (stratified for gender) are presented in Table 1. Among men, only age at diagnosis (69.3 versus 71.2 years) and the medical history of hypertension (18.5% versus 32.4%) were statistically significantly lower for MCPC compared with NMCPC. BMI was higher, although not significantly, among MCPC compared with NMCPC. The percentage of current smokers and medical history of diabetes was higher among cases, both male MCPC and NMCPC, compared with male subcohort members. History of gallstones was more present among male subcohort members compared with pancreatic cancer cases (5.1% versus 2.6% in MCPC and 4.1% in NMCPC).

Female NMCPC were older at baseline and diagnosis, weighed less at baseline and had a lower BMI at age 20 years, and had more often a medical history of high blood pressure and gallstones compared with MCPC. Also in women, more pancreatic cancer cases smoked at baseline compared with subcohort members (30.1% and 24.7% for MCPC and NMCPC, respectively, versus 20.9%).

Table 2 presents the RRs for pancreatic cancer according to height, weight, BMI, BMI at age 20 years, and change in BMI between age 20 years and baseline in men. When considering MCPC and NMCPC as one group, none of the determinants (as continuous variables) showed a statistically significant association with pancreatic cancer. BMI at baseline showed an increased risk for the upper category (BMI $\geq$30 $kg \cdot m^{-2}$; RR, 2.69; 95% CI, 1.47-4.92) compared with the reference category (BMI 23-25 $kg \cdot m^{-2}$). Also, change in BMI since age 20 years shows a significantly increased risk for the upper category (change $\geq$8 $kg \cdot m^{-2}$; RR, 2.21; 95% CI, 1.09-4.49) compared with the reference category (change 0-4 $kg \cdot m^{-2}$). In the MCPC subgroup weight, BMI at baseline and change in BMI were all significantly associated with pancreatic cancer: weight, RR, 1.02 (95% CI, 1.01-1.04); BMI at baseline, RR, 1.10 (95% CI, 1.04-1.18); change in BMI, RR, 1.12 (95% CI, 1.04-1.21). P values for trend were found statistically significant for the categorized variables of weight, BMI at baseline, and change in BMI. For the NMCPC subgroup, none of the associations were significant, although the risk estimates for third, fourth, and fifth BMI quintiles were comparable with those in MCPC. For NMCPC, a RR of 2.62 (95% CI, 1.29-5.31) was observed when comparing the first to the second quintile (reference) of BMI. Because this low BMI could be due to subclinical disease, we excluded the first 2 and 5 years of follow-up. The results, however, did not change (RR, 2.23; 95% CI, 1.08-4.63 and RR, 2.45; 95% CI, 1.14-5.23 for the data set excluding the first 2 and 5 years of follow-up, respectively).

Table 3 presents the RRs for pancreatic cancer according to height, weight, BMI, BMI at age 20 years, and change in BMI between age 20 years and baseline in women. When considering MCPC and NMCPC as one group, height, weight at baseline, and change in BMI since age 20 years were significantly associated with pancreatic cancer (P values for trend of categorized height, weight at baseline, and change in BMI were significant as well).

The association with height was also observed among NMCPC subgroup (RR, 1.05; 95% CI, 1.01-1.09) but not in MCPC. Conversely, weight and change in BMI since age 20 years were associated with pancreatic cancer among MCPC (RR, 1.03; 95% CI, 1.01-1.04 and RR, 1.08; 95% CI, 1.02-1.13, respectively) but not with NMCPC. BMI at baseline was associated with pancreatic cancer among MCPC (RR, 1.08; 95% CI, 1.03-1.13), but not in NMCPC or the total group of pancreatic cancer.

The results of our analyses did not change for men or women after excluding the first 2 and 5 years of follow-up (results not shown).

Table 1. Baseline characteristics of subjects stratified for gender

	Men				Women			
	Pancreatic cancer cases			Subcohort (n = 2,336)	Pancreatic cancer cases			Subcohort (n = 2,438)
	MCPC (n = 157)	NMCPC (n = 74)	P MC-NMCPC		MCPC (n = 133)	NMCPC (n = 82)	P MC-NMCPC	
Age, y (SD)	61.8 (3.9)	62.8 (4.3)	0.085	61.3 (4.2)	61.8 (4.5)	64.1 (3.6)	<0.001	61.5 (4.3)
Age at diagnosis, y (SD)	69.3 (4.7)	71.2 (5.4)	0.007	—	69.8 (5.2)	73.3 (5.4)	<0.001	—
Person-time, y (SD)	2,538 (1,276)	2,867 (1,315)	0.071	4,271 (1,164)	2,729 (1,305)	3,175 (1,279)	0.015	4,553 (860)
Height, cm (SD)	176.3 (6.4)	176.8 (7.1)	0.585	176.4 (6.7)	165.7 (6.0)	166.8 (6.5)	0.224	165.1 (6.2)
Weight, kg (SD)	79.7 (10.6)	77.2 (10.6)	0.099	77.9 (9.5)	71.4 (10.8)	69.7 (9.7)	0.264	68.5 (10.3)
Weight at age 20 y, kg (SD)	68.2 (7.9)	67.7 (9.1)	0.715	67.8 (8.3)	60.1 (10.4)	57.3 (7.3)	0.031	58.2 (7.9)
BMI, $kg \cdot m^{-2}$ (SD)	25.6 (2.8)	24.8 (3.5)	0.102	25.0 (2.6)	26.0 (3.6)	25.1 (3.4)	0.082	25.1 (3.6)
BMI age 20 y, $kg \cdot m^{-2}$ (SD)	21.9 (2.2)	21.7 (2.6)	0.475	21.7 (2.4)	21.9 (3.7)	20.7 (3.0)	0.013	21.4 (2.8)
Change in BMI, $kg \cdot m^{-2}$ (SD)	3.8 (3.0)	3.1 (3.9)	0.253	3.3 (3.0)	4.2 (4.2)	4.4 (4.1)	0.698	3.7 (3.7)
Smoking								
Current smokers (%)	48.7	46.0	0.694	36.7	30.1	24.7	0.395	20.9
n cigarettes/d (SD)	16.5 (10.0)	18.6 (14.2)	0.228	17.1 (10.6)	11.0 (7.0)	13.9 (9.6)	0.096	11.6 (8.3)
n years smoked (SD)	35.4 (12.9)	36.8 (9.8)	0.410	33.8 (11.9)	28.9 (12.4)	29.4 (12.4)	0.843	28.0 (12.4)
Alcohol, g/d (SD)	17.3 (19.5)	18.6 (18.5)	0.645	15.0 (16.8)	7.0 (10.0)	7.5 (12.3)	0.057	5.9 (9.5)
Energy-intake, kcal/d (SD)	2,199 (466)	2,073 (482)	0.649	2,165 (510)	1,684 (381)	1,707 (441)	0.707	1,686 (398)
Vegetable intake, g/d (SD)	196 (95)	186 (80.0)	0.435	192 (85)	214 (82)	207 (85)	0.578	196 (81)
Fruit intake, g/d (SD)	144 (106)	165 (144)	0.233	154 (114)	186 (99)	203 (120)	0.284	196 (121)
Medical history of								
Diabetes (%)	7.6	10.8	0.424	3.5	6.0	2.4	0.227*	4.2
High blood pressure (%)	18.5	32.4	0.019	23.1	25.6	39.0	0.037	29.4
Gallstones (%)	2.6	4.1	0.533	5.1	12.8	24.4	0.029	13.8
Cholecystectomy (%)	3.2	2.7	0.842	4.5	13.5	19.5	0.243	13.3
Educational level								
Low (%)	46.0	46.4		47.8	60.7	55.2		58.8
Medium (%)	33.1	30.4	0.907	34.3	33.0	41.4	0.471	33.0
High (%)	20.9	23.2		17.9	6.3	3.5		8.3

*Cell count <5.

Discussion

In this large prospective study, we found evidence that BMI and BMI change since age 20 years are positively associated with MCPC, both in men and women. These associations were not observed in the NMCPC subgroup, which constituted 35% of our total population of pancreatic cancer cases. Moreover, in the analyses combining MCPC and NMCPC, no association of BMI at baseline with pancreatic cancer was found (except when comparing the upper category of BMI with the reference category).

For men, a RR of 1.10 per increment of 1 $kg \cdot m^{-2}$ (95% CI, 1.04-1.18) of MCPC was found for BMI at baseline. Obese men (BMI $\geq$30 $kg \cdot m^{-2}$) had a 2.6-fold increased risk compared with men with BMI 23 to 25 $kg \cdot m^{-2}$. For women, this increase in risk was 1.7-fold. Women had a RR of 1.08 (95% CI, 1.03-1.13) of MCPC for BMI at baseline (per $kg \cdot m^{-2}$ increment). For every unit increase in BMI since the age of 20 years, which translates for a male of height 1.75 m to a gain of $\pm$3 kg, a relative increase in risk of MCPC was found of 12%. For women, a relative increase in risk of MCPC was found of 8% for every unit increase in BMI (i.e., female of 1.65 m, a gain of $\pm$2.5 kg). In case preclinical pancreatic cancer was present at baseline, this would conceivably have resulted in weight loss and due to this an underestimation of the effect of BMI. Excluding the first 2 or 5 years of follow-up did not change our results, however.

In a meta-analysis, comprising six case-control studies and eight cohort studies (published before 2004; ref. 7), the summary relative risk per unit increase in BMI was 1.02 per increment of 1 $kg \cdot m^{-2}$ (95% CI, 1.01-1.03); the relative risk for obese subjects (BMI $\geq$30 $kg \cdot m^{-2}$) compared with subjects with normal weight (BMI 22 $kg \cdot m^{-2}$) was 1.19 (95% CI, 1.10-1.29). In a recent meta-analysis by Larsson et al. (20), including 21 prospective studies on BMI and pancreatic risk published from 1966 to November 2006, an estimated summary RR of pancreatic cancer was reported per 5 kg/m^2 increase in BMI of 1.12 (95% CI, 1.06-1.17; $P_{heterogeneity}$ = 0.13) in men and women combined, 1.16 (95% CI, 1.05-1.28; $P_{heterogeneity}$ = 0.001) in men, and 1.10 (95% CI, 1.02-1.19; $P_{heterogeneity}$ = 0.12) in women. The RRs presented in these two meta-analyses are lower compared with the results of the present study in both the total group of pancreatic cancer cases and the MCPC subgroup. Although some studies did report the proportions of NMCPC (8, 21-23), ranging from 20% (23) to almost 100% (21), most studies in the meta-analyses did not distinguish between MCPC and NMCPC or report on the proportion of NMCPC in the total case set. In the studies that reported the proportion of NMCPC, all but one (23) showed increased risks, but only statistically significant for men in one study (21). Differences across studies may, at least in part, be due to different populations with differing proportions of NMCPC in the total case sets.

Obesity may be mechanistically linked to pancreatic cancer because of its association with abnormal glucose metabolism, including insulin resistance, hyperinsulinemia, and impaired glucose tolerance (24-26). Experimental studies showed that insulin has growth-promoting and mitogenic effects on pancreatic cancer cells (27). Also, in epidemiologic studies, positive associations between postload plasma glucose concentration, exposure to higher insulin concentrations, insulin resistance, and pancreatic cancer risk have been reported (28-30).

In our study, we found no statistically significant association between height and pancreatic cancer risk in men. In women, an association was observed among all pancreatic cancer and NMCPC (RR, 1.02; 95% CI, 1.00-1.05 and RR, 1.05; 95% CI, 1.01-1.09, respectively) but not in MCPC. Previously, four cohort studies reported on height and the risk of pancreatic cancer: Two found a statistically significant association (8, 9), whereas two other studies did not (28, 31). 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 (32, 33), and may be a proxy for exposure to circulating growth factor levels during adolescence or childhood, genetic predisposition, or prenatal exposures. Because

Table 2. RRs of pancreatic cancer, with 95% CI, according to anthropometry (men only)

Variable	Categorical mean	PYs in subcohort	All pancreatic cancer			MCPC			NMCPC		
			No. cases	RR* (95% CI)	RR† (95% CI)	No. cases	RR* (95% CI)	RR† (95% CI)	No. cases	RR* (95% CI)	RR† (95% CI)
Height at baseline (cm)											
<170‡	166.1	3,910	34	1	1	23	1	1	11	1	1
170-<175	171.9	6,952	46	0.77 (0.48-1.23)	0.68 (0.41-1.12)	29	0.71 (0.40-1.25)	0.55 (0.30-1.00)	17	0.91 (0.42-1.98)	1.07 (0.44-2.60)
175-<180	176.7	8,182	75	1.09 (0.71-1.68)	1.14 (0.72-1.82)	55	1.17 (0.70-1.95)	1.10 (0.65-1.87)	20	0.94 (0.45-1.98)	1.25 (0.53-2.95)
180-<185	181.7	5,632	42	0.87 (0.54-1.40)	0.80 (0.48-1.34)	31	0.94 (0.54-1.65)	0.79 (0.44-1.42)	11	0.73 (0.31-1.73)	0.86 (0.33-2.27)
≥185	188.0	3,371	26	0.92 (0.53-1.58)	0.99 (0.56-1.75)	14	0.71 (0.36-1.41)	0.71 (0.36-1.42)	12	1.42 (0.61-3.30)	1.82 (0.69-4.81)
P_{trend}				0.947	0.715		0.868	0.896		0.701	0.435
Continuous, per cm		28,046	223	1.00 (0.98-1.02)	1.01 (0.99-1.03)	152	1.00 (0.98-1.02)	1.00 (0.97-1.02)	71	1.01 (0.99-1.05)	1.02 (0.98-1.06)
Weight at baseline (kg)											
<75§	68.5	10,272	74	1	1	47	1	1	27	1	1
75-<80	76.4	5,553	47	1.16 (0.79-1.71)	1.16 (0.76-1.76)	35	1.37 (0.87-2.15)	1.41 (0.87-2.28)	12	0.80 (0.40-1.60)	0.73 (0.34-1.58)
80-<85	81.4	5,860	46	1.09 (0.74-1.60)	1.13 (0.75-1.70)	30	1.12 (0.70-1.79)	1.23 (0.75-2.02)	16	1.04 (0.55-1.95)	0.95 (0.48-1.86)
85-<90	86.2	3,120	21	0.95 (0.57-1.58)	0.92 (0.53-1.59)	13	0.91 (0.48-1.71)	0.96 (0.49-1.88)	8	1.01 (0.45-2.26)	0.82 (0.33-2.05)
≥90	95.1	3,436	36	1.49 (0.97-2.27)	1.55 (0.99-2.45)	29	1.89 (1.16-3.06)	2.07 (1.24-3.47)	7	0.79 (0.34-1.85)	0.77 (0.32-1.88)
P_{trend}				0.206	0.182		0.090	0.047		0.796	0.605
Continuous, per kg		28,270	224	1.01 (0.99-1.03)	1.01 (0.99-1.03)	154	1.02 (1.01-1.04)	1.02 (1.01-1.04)	70	0.99 (0.96-1.02)	0.99 (0.96-1.02)
BMI at baseline ($kg \cdot m^{-2}$)											
<23	21.5	5,484	44	1.11 (0.75-1.66)	1.10 (0.72-1.69)	21	0.67 (0.40-1.14)	0.66 (0.38-1.16)	23	2.63 (1.36-5.09)	2.62 (1.29-5.31)
23-<25§	24.1	9,088	67	1	1	52	1	1	15	1	1
25-<27	25.9	7,430	50	0.91 (0.62-1.34)	0.93 (0.61-1.39)	35	0.82 (0.53-1.28)	0.90 (0.57-1.44)	15	1.22 (0.59-2.53)	0.98 (0.44-2.16)
27-<30	28.1	4,672	39	1.14 (0.75-1.73)	1.17 (0.75-1.81)	29	1.10 (0.69-1.77)	1.20 (0.73-1.97)	10	1.26 (0.56-2.85)	1.12 (0.47-2.63)
≥30	31.5	1,166	20	2.54 (1.47-4.41)	2.69 (1.47-4.92)	14	2.23 (1.19-4.18)	2.57 (1.30-5.10)	6	3.36 (1.27-8.92)	2.87 (0.94-8.70)
P_{trend}				0.139	0.141		0.018	0.008		0.517	0.312
Continuous, per $kg \cdot m^{-2}$		27,838	220	1.05 (0.99-1.11)	1.05 (0.99-1.12)	151	1.09 (1.02-1.16)	1.10 (1.04-1.18)	69	0.96 (0.85-1.10)	0.94 (0.81-1.08)
BMI at age 20 y ($kg \cdot m^{-2}$)											
<20‡	18.5	4,360	35	1	1	22	1	1	13	1	1
20-<21	20.5	4,095	26	0.78 (0.46-1.32)	0.80 (0.46-1.40)	19	0.92 (0.49-1.73)	0.93 (0.48-1.80)	7	0.55 (0.22-1.41)	0.62 (0.23-1.66)
21-<23	22.0	7,745	60	0.97 (0.62-1.50)	0.99 (0.62-1.59)	42	1.08 (0.64-1.85)	1.16 (0.67-2.04)	18	0.78 (0.38-1.62)	0.73 (0.32-1.64)
≥23	24.6	6,168	52	1.07 (0.68-1.69)	1.07 (0.67-1.73)	40	1.32 (0.77-2.26)	1.33 (0.76-2.34)	12	0.67 (0.30-1.48)	0.68 (0.29-1.63)
P_{trend}				0.541	0.562		0.239	0.226		0.485	0.480
Continuous, per $kg \cdot m^{-2}$		22,368	173	1.03 (0.96-1.09)	1.03 (0.96-1.10)	123	1.04 (0.97-1.11)	1.04 (0.97-1.11)	50	0.99 (0.87-1.13)	1.00 (0.87-1.15)
Change in BMI since age 20 y§ ($kg \cdot m^{-2}$)											
<0	−1.8	1,824	14	0.97 (0.53-1.79)	0.99 (0.53-1.85)	8	0.76 (0.34-1.68)	0.74 (0.33-1.65)	6	1.54 (0.64-3.73)	1.84 (0.74-4.56)
0-<4‡	2.1	12,150	84	1	1	56	1	1	28	1	1
4-<8	5.7	7,103	60	1.30 (0.89-1.90)	1.34 (0.90-1.99)	50	1.75 (1.15-2.67)	1.89 (1.22-2.94)	10	0.54 (0.25-1.20)	0.45 (0.18-1.08)
≥8	10.0	1,231	15	2.17 (1.13-4.15)	2.21 (1.09-4.49)	9	2.10 (0.97-4.55)	2.56 (1.14-5.72)	6	0.93 (0.61-6.15)	1.28 (0.32-5.18)
P_{trend}				0.042	0.052		0.011	0.001		0.617	0.288
Continuous, per $kg \cdot m^{-2}$		22,308	173	1.06 (0.98-1.14)	1.07 (0.99-1.15)	123	1.10 (1.02-1.18)	1.12 (1.04-1.21)	50	1.02 (0.99-1.05)	0.92 (0.76-1.11)

Abbreviation: PYs, person-years.
*Adjusted for age (continuous).
†Adjusted for age (continuous), smoking (current smoker: yes/no; number of cigarettes smoked per day: continuous; number of years smoked: continuous), history of diabetes (yes/no), and history of hypertension (yes/no).
‡Reference category.
§BMI at age 20 y was included in all models for BMI change.

weight and height were self-reported, as in most other large-scale epidemiologic studies, misclassification cannot be ruled out. Systematic underestimation of weight and overestimation of height have been previously reported (34). It is noted that the higher the measured BMI, the greater the underestimation of weight and overestimation of height (34). This tendency, if present in our study, could have led to an underestimation of the effect of BMI.

The strengths of this study include the prospective design, large sample size, and detailed information on potential risk factors of pancreatic cancer. The prospective design precluded recall bias and the need to use next-of-kin respondents (which is often needed in the case-control when studying the highly fatal pancreatic cancer). Moreover, because exposure data were collected before the diagnosis of any cases of pancreatic cancer, any error in recall (nondifferential misclassification) would have attenuated rather than exaggerated a true association. Differential follow-up is unlikely to have made a material contribution to these findings, since follow-up in our cohort was high.

In the present study, we stratified for microscopic confirmation, as the lack of such confirmation may be a source of misclassification of disease status. In 1996, Silverman et al. (35) addressed this issue deeper by reanalyzing their data on the association of smoking and pancreatic cancer risk and reevaluating their case series recruited in the years 1986 to 1989 (5). The case series from the original study was subdivided according to both microscopically confirmation of the diagnosis and the degree of diagnostic certainty [classified as ''likely'' if at least one of the following criteria was satisfied: (*a*) a pancreatic mass was known by radiographic visualization or surgery, with a compatible histologic diagnosis; (*b*) a pancreatic mass was known by surgery and, although a biopsy specimen was not obtained, it appeared to be malignant due to either visible hepatic metastasis or local extension; or (*c*) a pancreatic mass was known by radiographic visualization, although a biopsy specimen was not obtained, and there were supporting clinical signs, symptoms, and course (e.g., rapid death)]. They reported an odds ratio for ''ever smoker'' of 1.8 (95% CI, 1.4-2.4) for MCPC considered ''likely'' to have had

pancreatic cancer, 1.3 (95% CI, 0.6-2.8) for NMCPC considered likely to have had pancreatic cancer, and 1.0 (95% CI, 0.4-2.4) for cases considered ''unlikely'' to have had pancreatic cancer. These findings illustrate that when case series include NMCPC, even if they are considered likely, the effect estimate may be attenuated toward the null. Restriction to (likely) cases with microscopic confirmation will generate the most valid estimates of risk, which is of importance especially when considering risk factors that exert small to modest effects, such as BMI.

In our study, the effects of BMI and change of BMI since age 20 years in men would not have been detected without the stratification on microscopic verification (the effect of BMI since age 20 years in women was weaker in all pancreatic cancer compared with MCPC). Conversely, in women, a statistically significant association of height at baseline was found in all pancreatic cancer cases, but not in MCPC. Most of the previous studies on the association of BMI and pancreatic cancer did not distinguish between MCPC and NMCPC nor reported the contribution of NMCPC to the total population of pancreatic cancer cases. This may, in part, explain differences found across studies.

Cases without pathologic confirmation (but with strong clinical evidence supporting the diagnosis) may reflect different subtypes of pancreatic cancer or even nonpancreatic cancer. Whenever these subtypes or nonpancreatic cancers are not, or more strongly, associated with the determinant of interest compared with MCPC, the effect estimates will affected. The practice of including NMCPC in epidemiologic studies is in our view sound provided that risk estimates are computed and reported across strata of microscopic verification, or diagnostic certainty, to exclude heterogeneity.

In summary, we observed associations between both BMI and gain in BMI and pancreatic cancer risk. Another consequence of the increasing epidemic of obesity in the Western society may thus be an increasing incidence of pancreatic cancer in the coming years. However, these associations are observed only in MCPC and not in NMCPC. These findings stress the need to evaluate heterogeneity among pancreatic cancer cases.

Table 3. RRs of pancreatic cancer, with 95% CIs, according to anthropometry (women only)

Variable	Categorical mean	PYs in subcohort	All pancreatic cancer			MCPC			NMCPC		
			No. cases	RR* (95% CI)	RR† (95% CI)	No. cases	RR* (95% CI)	RR† (95% CI)	No. cases	RR* (95% CI)	RR† (95% CI)
Height at baseline (cm)											
<160‡	155.7	5,156	27	1	1	19	1	1	8	1	1
160-<165	161.9	7,715	39	0.95 (0.57-1.57)	0.93 (0.56-1.57)	28	0.98 (0.54-1.77)	0.90 (0.49-1.65)	11	0.89 (0.35-2.24)	0.98 (0.38-2.50)
165-<170	166.7	10,400	86	1.63 (1.04-2.55)	1.60 (1.02-2.53)	48	1.27 (0.73-2.18)	1.22 (0.70-2.11)	38	2.45 (1.13-5.32)	2.42 (1.11-5.28)
170-<175	171.4	5,289	36	1.35 (0.80-2.27)	1.40 (0.83-2.37)	22	1.13 (0.60-2.12)	1.13 (0.60-2.13)	14	1.88 (0.77-4.56)	2.06 (0.84-5.06)
≥175	177.0	2,248	17	1.52 (0.80-2.86)	1.32 (0.67-2.60)	10	1.22 (0.55-2.67)	0.98 (0.41-2.33)	7	2.21 (0.79-6.21)	2.18 (0.73-6.48)
P_{trend}				0.027	0.044		0.424	0.563		0.007	0.008
Continuous, per cm		30,809	205	1.03 (1.00-1.05)	1.02 (1.00-1.05)	127	1.01 (0.99-1.04)	1.01 (0.98-1.04)	78	1.05 (1.01-1.09)	1.05 (1.01-1.09)
Weight at baseline (kg)											
<65‡	58.5	11,082	59	1	1	36	1	1	23	1	1
65-<70	66.6	6,482	42	1.19 (0.79-1.80)	1.23 (0.81-1.88)	24	1.13 (0.66-1.92)	1.20 (0.70-2.05)	18	1.30 (0.69-2.44)	1.28 (0.66-2.46)
70-<75	71.4	5,687	39	1.29 (0.85-1.97)	1.30 (0.84-1.99)	24	1.30 (0.77-2.21)	1.31 (0.75-2.27)	15	1.29 (0.66-2.50)	1.28 (0.68-2.44)
75-<80	76.2	3,582	31	1.62 (1.03-2.55)	1.58 (0.99-2.52)	20	1.73 (0.98-3.03)	1.77 (1.00-3.17)	11	1.47 (0.71-3.06)	1.37 (0.65-2.89)
≥80	86.1	4,721	39	1.59 (1.04-2.43)	1.64 (1.07-2.52)	26	1.72 (1.02-2.89)	1.88 (1.09-3.22)	13	1.39 (0.70-2.79)	1.34 (0.68-2.61)
P_{trend}				0.011	0.010		0.014	0.009		0.262	0.323
Continuous, per kg		31,555	210	1.02 (1.01-1.03)	1.02 (1.01-1.03)	130	1.03 (1.01-1.04)	1.03 (1.01-1.04)	80	1.01 (0.99-1.03)	1.01 (0.99-1.03)
BMI at baseline ($kg \cdot m^{-2}$)											
<23	21.3	8,307	46	1.03 (0.67-1.57)	1.02 (0.66-1.58)	23	0.82 (0.47-1.44)	0.82 (0.46-1.45)	23	1.35 (0.71-2.55)	1.35 (0.70-2.57)
23-<25‡	24.0	8,328	45	1	1	28	1	1	17	1	1
25-<27	26.0	6,326	55	1.60 (1.06-2.42)	1.69 (1.11-2.58)	36	1.70 (1.02-2.83)	1.91 (1.14-3.23)	19	1.43 (0.73-2.80)	1.38 (0.70-2.70)
27-<30	28.3	4,869	38	1.42 (0.90-2.22)	1.41 (0.89-2.25)	25	1.54 (0.88-2.67)	1.55 (0.87-2.78)	13	1.24 (0.60-2.59)	1.27 (0.61-2.64)
≥30	32.6	2,827	19	1.27 (0.73-2.22)	1.31 (0.74-2.31)	14	1.49 (0.77-2.87)	1.72 (0.87-3.39)	5	0.91 (0.33-2.52)	0.78 (0.28-2.14)
P_{trend}				0.064	0.052		0.006	0.002		0.736	0.539
Continuous, per $kg \cdot m^{-2}$		30,657	203	1.04 (1.00-1.08)	1.04 (1.00-1.08)	126	1.07 (1.02-1.11)	1.08 (1.03-1.13)	77	1.00 (0.94-1.07)	0.99 (0.93-1.05)
BMI at age 20 y ($kg \cdot m^{-2}$)											
<20‡	18.4	8,542	65	1	1	37	1	1	28	1	1
20-<21	20.5	3,966	27	0.87 (0.55-1.40)	0.93 (0.58-1.51)	13	0.75 (0.39-1.43)	0.81 (0.42-1.57)	14	1.04 (0.54-2.02)	1.06 (0.54-2.08)
21-<23	22.0	8,164	42	0.67 (0.45-1.00)	0.69 (0.46-1.04)	28	0.78 (0.47-1.30)	0.80 (0.48-1.33)	14	0.53 (0.27-1.01)	0.55 (0.28-1.06)
≥23	24.9	7,020	52	1.00 (0.68-1.47)	0.97 (0.66-1.44)	37	1.21 (0.76-1.95)	1.21 (0.74-1.96)	15	0.71 (0.37-1.35)	0.66 (0.34-1.30)
P_{trend}				0.606	0.535		0.548	0.590		0.108	0.089
Continuous, per $kg \cdot m^{-2}$		27,691	186	1.02 (0.95-1.09)	1.02 (0.95-1.09)	115	1.07 (1.00-1.14)	1.07 (1.00-1.14)	71	1.03 (1.00-1.06)	1.03 (1.00-1.05)
Change in BMI since age 20 y§ ($kg \cdot m^{-2}$)											
<0	−2.5	3,104	15	0.66 (0.36-1.19)	0.67 (0.37-1.21)	9	0.50 (0.23-1.09)	0.50 (0.23-1.11)	6	0.96 (0.38-2.40)	0.95 (0.38-2.38)
0-<4‡	2.2	12,012	76	1	1	50	1	1	26	1	1
4-<8	5.7	9,287	63	1.09 (0.77-1.53)	1.08 (0.75-1.55)	38	1.09 (0.71-1.67)	1.13 (0.71-1.78)	25	1.07 (0.61-1.85)	1.02 (0.59-1.78)
≥8	10.3	3,187	31	1.63 (1.06-2.52)	1.72 (1.11-2.67)	18	1.58 (0.91-2.74)	1.81 (1.03-3.18)	13	1.55 (0.77-3.10)	1.40 (0.70-2.78)
P_{trend}				0.007	0.004		0.011	0.004		0.290	0.394
Continuous, per $kg \cdot m^{-2}$		27,590	185	1.05 (1.01-1.10)	1.05 (1.01-1.10)	115	1.07 (1.01-1.12)	1.08 (1.02-1.13)	70	1.02 (0.95-1.10)	1.01 (0.94-1.08)

*Adjusted for age (continuous).

†Adjusted for age (continuous), smoking (current smoker: yes/no; number of cigarettes smoked per day: continuous; number of years smoked: continuous), history of diabetes (yes/no), and history of hypertension (yes/no).

‡Reference category.

§BMI at age 20 y was included in all models for BMI change.

Acknowledgments

We thank the participants of this study; the cancer registries (IKA, IKL, IKMN, IKN, IKO, IKR, IKST, IKW, IKZ, and VIKC); the Netherlands nationwide registry of pathology (PALGA); Drs. A. Volovics and A. Kester for statistical advice; S. van de Crommert, H. Brants, J. Nelissen, C. de Zwart, W. van Dijk, M. Jansen, and A. Pisters for assistance; and H. van Montfort, T. van Moergastel, L. van den Bosch, and J. Berben for programming assistance.

References

1. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002;38:99–166.
2. American Cancer Society. Cancer facts & figures 2006. Atlanta: American Cancer Society Inc; 2006. p. 4.
3. Ries LAG, Eisner MP, Kosary CL, et al. SEER statistics review, 1973-1999. Bethesda (MD): National Cancer Institute; 2002.
4. Bramhall SR, Allum WH, Jones AG, Allwood A, Cummins C, Neoptolemos JP. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. Br J Surg 1995;82:111–5.
5. Silverman DT, Dunn JA, Hoover RN, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst 1994;86:1510–6.
6. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med 1996;156: 2255–60.
7. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 2003;89:519–23.
8. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001;286:921–9.
9. Berrington de Gonzalez A, Spencer EA, Bueno-de-Mesquita HB, et al. Anthropometry, physical activity, and the risk of pancreatic cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2006;15:879–85.
10. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995;75:171–90.
11. Parkin DM, Whelan SL, Ferlay J, Storm H, editors. Cancer incidence in five continents, vol. I to VIII. Lyon: IARC CancerBase No 7; 2005. CD-ROM: I_157.pdf.
12. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, editors. Cancer incidence in five continents, vol. VIII. IARC scientific publications no. 155. Lyon: IARC; 2002. p. 210–1.
13. Soler M, Porta M, Malats N, et al. Learning from case reports: diagnostic issues in an epidemiologic study of pancreatic cancer. J Clin Epidemiol 1998; 51:1215–21.
14. Van den Brandt PA, Goldbohm RA, van 't Veer P, Volovics A, Hermus RJ, Sturmans F. A large-scale prospective cohort study on diet and cancer in The Netherlands. J Clin Epidemiol 1990;43:285–95.
15. Van den Brandt PA, Schouten LJ, Goldbohm RA, Dorant E, Hunen PM. Development of a record linkage protocol for use in the Dutch Cancer Registry for Epidemiological Research. Int J Epidemiol 1990;19:553–8.
16. Van der Sanden GAC, Coebergh JWW, Schouten LJ, Visser O, Van Leeuwen FE. Cancer incidence in the Netherlands in 1989 and 1990: First results of the nationwide Netherlands Cancer Registry. Eur J Cancer 1995;31A: 1822–9.
17. Goldbohm RA, van den Brandt PA, Brants HA, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. Eur J Clin Nutr 1994;48:253–65.
18. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989;84:1074–8.
19. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239–41.
20. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. Int J Cancer 2007;120:1993–8.
21. Rapp K, Schroeder J, Klenk J, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 2005;93:1062–7.
22. Isaksson B, Jonsson F, Pedersen NL, et al. Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. Int J Cancer 2002;98:480–2.
23. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Causes Control 2002;13:417–26.
24. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982;54:254–60.
25. Clausen JO, Borch-Johnsen K, Ibsen H, et al. Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians. Analysis of the impact of gender, body fat, physical fitness, and life-style factors. J Clin Invest 1996;98:1195–209.
26. Kelley DE, Goodpaster BH. Effects of exercise on glucose homeostasis in Type 2 diabetes mellitus. Med Sci Sports Exerc 2001;33:S495–501; discussion S528–9.
27. Kazakoff K, Cardesa T, Liu J, et al. Effects of voluntary physical exercise on high-fat diet-promoted pancreatic carcinogenesis in the hamster model. Nutr Cancer 1996;26:265–79.
28. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. JAMA 2000;283: 2552–8.
29. Stolzenberg-Solomon RZ, Graubard BI, Chari S, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. JAMA 2005;294: 2872–8.
30. Michaud DS, Liu S, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. J Natl Cancer Inst 2002;94:1293–300.
31. Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. Int J Epidemiol 1993;22:30–7.
32. Gunnell D, Okasha M, Smith GD, Oliver SE, Sandhu J, Holly JM. Height, leg length, and cancer risk: a systematic review. Epidemiol Rev 2001;23: 313–42.
33. Okasha M, Gunnell D, Holly J, Davey Smith G. Childhood growth and adult cancer. Best Pract Res Clin Endocrinol Metab 2002;16:225–41.
34. Niedhammer I, Bugel I, Bonenfant S, Goldberg M, Leclerc A. Validity of self-reported weight and height in the French GAZEL cohort. Int J Obes Relat Metab Disord 2000;24:1111–8.
35. Silverman DT, Schiffman M, Devesa S. Diagnostic certainty in pancreatic cancer. J Clin Epidemiol 1996;49:601–3.

Anthropometry and Pancreatic Cancer Risk: An Illustration of the Importance of Microscopic Verification

Bas A.J. Verhage, Leo J. Schouten, R. Alexandra Goldbohm, et al.

Cancer Epidemiol Biomarkers Prev 2007;16:1449-1454.