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Association of body mass index and risk of death from pancreas cancer in Asians: findings from the Asia Cohort Consortium

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The authors have declared no conflict of interest.

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Abstract

Objective—We aimed to examine the association between BMI and the risk of death from pancreas cancer in a pooled analysis of data from the Asia Cohort Consortium.

Methods—The data for this pooled-analysis included 883,529 men and women from 16 cohort studies in Asian countries. Cox proportional-hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreas cancer mortality in relation to BMI. Seven predefined BMI categories (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30) were used in the analysis, with BMI of 22.5–24.9 serving as the reference group. The multivariable analyses were adjusted for known risk factors, including age, smoking, and history of diabetes.

Results—We found no statistically significant overall association between each BMI category and risk of death from pancreas cancer in all Asians, and obesity was unrelated to mortality risk in both East Asians and South Asians. Age, smoking, and history of diabetes did not modify the association between BMI and risk of death from pancreas cancer. In planned subgroup analyses among East Asians, an increased risk of death from pancreas cancer among those with a BMI<18.5 was observed for individuals with a history of diabetes; HR = 2.01(95%CI: 1.01–4.00) (p for interaction=0.07).

Conclusion—The data do not support an association between BMI and risk of death from pancreas cancer in these Asian populations.

Keywords

body mass index; insulin resistance; obesity; overweight; pancreatic cancer

Introduction

Pancreas cancer is one of the most aggressive malignancies in humans, with an all-stage 5-year survival of less than 10% [1]. According to Globocan, pancreas cancer was diagnosed in an estimated 107,810 Asian men and women in 2008 and a similar number (98,214) died from the disease [2]. Although this cancer used to be rare in Asia, incidence rates in East Asia have been increasing over the past decades and now approximate those in Europe and North America [2].

Epidemiologic studies have clearly shown that cigarette smoking and longstanding type-II diabetes are associated with increased risk of pancreas cancer [3–4]. There is also mounting evidence for an association with being overweight or obese [5]. Statistically significant, positive associations were observed in large cohort studies conducted in Western countries [6–8], and corroborated in at least 4 meta-analyses [9–12] and 3 pooled analyses [13–15]. The mechanisms by which obesity confers increased risk are not well understood. Because obesity is closely related to insulin resistance and hyperinsulinemia and because high fasting serum glucose and insulin levels have been shown to predict pancreas cancer risk in diverse ethnic populations [16–18], insulin resistance and hyperinsulinemia are thought to play a central role [19].

Based on a review of the literature, the World Cancer Research Fund concluded that the evidence that greater body fatness is a cause of pancreas cancer is convincing [20]. It is worth noting, however, that this conclusion was based on the summary of findings mainly from cohort studies conducted in Western countries; very few Asian studies were included. The observed differences in body fat distribution, genetic predisposition to obesity, and background lifestyle factors between Caucasians and Asians [21] suggest that the association between BMI and pancreas cancer may differ by ethnic group. To date, 4 cohort studies have examined the BMI-pancreas cancer associations in Asians, but the results have been inconsistent and inconclusive [22–25].

Given the plausible mechanisms underlying an obesity-pancreas cancer association and the paucity of data from Asian populations, we examined the relationship in a pooled analysis of data from the Asia Cohort Consortium (ACC), which involved 883,529 men and women. This pooled analysis allowed us to estimate the risk of death from pancreas cancer in relation to finer BMI categories than would be feasible within any single study.

Methods

Study population

ACC is a consortium of cohort studies in Asian countries, the primary purpose of which is to explore the relationship among genetics, environmental exposures, and the etiology of disease. The details concerning the initiation and conduct of the ACC have been described elsewhere [26, 27]. The ACC has recruited 19 cohorts to date. Sixteen cohorts provided information on death from pancreas cancer during follow-up as well as data on BMI, cigarette smoking, and history of diabetes at baseline; these cohorts were included in this pooled analysis. Of these cohorts, 8 are in Japan, 2 in China, 1 in Taiwan, 2 in Korea, 2 in India, and 1 in Bangladesh. For this pooled analysis, we excluded 50,421 individuals with missing data on age, sex, cigarette smoking, and/or BMI. Also excluded were individuals who had a prior cancer diagnosis at baseline, those who had a BMI >50 or <15, and those with invalid or missing data on survival. The final study population included 799,542 subjects.

This study was approved by the ethics committee overseeing each of the participating cohort studies and by the IRB at the Fred Hutchinson Cancer Research Center.

Exposure measurement and outcome ascertainment

In the majority of the ACC participating cohorts, height and weight at baseline were both self-reported. Outcomes for pancreas cancer mortality were ascertained from the causes of death recorded on death certificates. Information on cigarette smoking, history of diabetes, and other lifestyle factors was collected at baseline.

Statistical analysis

We quantified the association between BMI and risk of death from pancreas cancer based on a meta-analysis of individual data from each cohort and a pooled analysis of aggregated data from all participating cohorts. For the meta-analysis, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each cohort, and a random-effects model was adopted to calculate a summary HR by combining cohort-specific HRs [28]. BMI was modeled categorically, using 7 predefined BMI categories (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30). Individuals with BMIs of 22.5–24.9 served as the reference category because this BMI category has been shown to be associated with the lowest risk of all-cause mortality in East Asian populations [29–31]. Between-study heterogeneity was estimated by a likelihood ratio test. In the pooled analysis, Cox

proportional-hazards models were used to estimate HRs and 95% CIs for pancreas cancer mortality in relation to BMI. The proportional hazards assumption was tested using Schoenfeld residuals..

In the absence of between-study heterogeneity, we present the results from the pooled analysis. The multivariable analyses were adjusted for known risk factors for pancreatic cancer, including age, smoking, and history of diabetes.

Given the differences in genetic background and lifestyle factors as well as pancreas cancer rates, separate analyses were performed for the East Asian population (Chinese, Japanese and Korean) and South Asian population (Indian and Bangladeshi populations). Results are presented for men and women combined, as well as separately. We show results only for all men and women for the South Asian cohorts because they had a short follow-up period and a very small number of pancreas cancer deaths (31 of all 1489 deaths).

In addition, we conducted analyses stratified by age (<55 years, ≥55 years), smoking status (never, former, current), and history of diabetes (yes, no) to examine whether these factors modified the associations between BMI and risk of pancreas cancer mortality. To examine the significance of interaction, we divided the subjects into two BMI groups: <18.5 and ≥18.5, and then generated a cross-product term in the model. We used a likelihood ratio to test the statistical significance of interaction. As a sensitivity analysis, we also excluded all deaths occurring in the first 3 years of follow-up to address the possibility that BMI variation was the result of disease rather than vice versa.

All analyses were performed using R (version 2.11.1). All statistical tests were 2-sided.

Results

Table 1 presents characteristics of the participating cohorts in the ACC. The mean follow-up period ranged from 3.1 to 22.0 years and the mean age at entry from 36.8 to 59.5 years old. Mean BMI ranged from 19.9 to 23.7. Of 1489 pancreas cancer deaths, 1458 (98%) were observed in East Asia.

Table 2 shows the HRs and 95% CIs for pancreas cancer deaths in relation to BMI categories among all Asians, East Asians, and South Asians. In all Asians and East Asians, there were no statistically significant associations between BMI and the risk of death from pancreas cancer in either men or women. In South Asians, those both underweight and overweight were at increased risk of death from pancreas cancer; individuals with a BMI of 27.5–29.9 had 4.9-fold increased risk compared with those with a BMI of 22.5–24.9.

Table 3 shows the results of subgroup analyses stratified by age, smoking status, and diabetes among East Asians. There were no associations between obesity and the risk of death from pancreas cancer in current smokers, ex-smokers, or non-smokers. In planned analyses stratified by diabetes, we observed a statistically significantly increased risk of death associated with low BMI (BMI <18.5) among individuals with a history of diabetes; the HR was 2.01 (95%CI: 1.01–4.00) (p for interaction=0.07). There were no associations between BMI and risk of death from pancreas cancer among those without a history of diabetes. For both East Asian men and women, the risk estimates remained unchanged after excluding deaths that occurred within the first 3 years of follow-up. Additional adjustment for marital status and education in the multivariate model did not materially alter the results (data not shown).

Discussion

In this pooled analysis of 799,542 Asian men and women, we found no overall associations between BMI and the risk of death from pancreas cancer in Asian populations. The findings were also null when we restricted the analyses to men and women who had never smoked or those who had no history of type-II diabetes.

Epidemiologic research has been inconclusive regarding the association between BMI and pancreas cancer in Asians. No statistically significant increase in pancreas cancer risk among the obese was observed in the JACC study [22] and the JPHC study [23], two representative Japanese cohort studies and also cohorts participating in the ACC. In another cohort study conducted in Miyagi Prefecture [24], the obesity-pancreas cancer associations could not be quantified because no deaths had occurred in the BMI category of 30 or more. In a prospective study of over 1 million Koreans, pancreatic cancer risk was statistically significantly elevated in women who were either overweight or obese; however, no association was observed in men [25]. In China, although a previous case-control study had suggested a positive association between BMI and pancreas cancer [32], no prospective cohort data have been available to examine this association. The available data, together with findings in the present study, do not support a role for obesity in the risk of pancreas cancer in East Asians. It is worth noting that the individual Asian cohort studies may have been underpowered to detect a small-to-moderate association due to very few individuals in the obese category. We, therefore, sought to overcome this limitation by pooling the data from 16 cohort studies across Asian countries, the majority of which are from East Asia; the results remain null. Consistent with our results, a pooled analysis of 424,519 participants in the Asia-Pacific Cohort Studies Collaboration found no increase in pancreas cancer risk among obese Asians [33]. For South Asians, although the results suggested an increase in risk among underweight and overweight individuals, the number of pancreas cancer deaths was too small to draw any firm conclusions. Given a potentially high level of misclassifications for pancreas cancer mortality, improving diagnostic accuracy is also an important issue in further studies. With extended follow-up and improved outcome ascertainment, further studies in these cohorts with a larger sample will be able to better quantify the association in South Asians.

There are several potential explanations for the null findings on the BMI-pancreas cancer association in Asian populations. The main reason may be the very small proportion of obese people in Asia. Although this pooled analysis included the largest number of Asians, the obese accounted for only 2.5%, much lower than that (approximately 16–20%) in the pooled analyses of Western cohort studies [14, 15]. The null findings could also be due to the differences in body fat distribution, in genetic predisposition to obesity, and in lifestyle factors between Caucasians and Asians [21, 34]. For example, diet is thought to play an important role in the development of pancreas cancer and the interaction of BMI with diet is possibly different between Caucasians and Asians. This issue needs to be addressed in additional studies. Finally, we could not exclude the possibility that some heterogeneity may still exist among the participating cohorts, although data were harmonized at the coordinating center using a standardized method and we found no between-study heterogeneity.

An interesting finding is that individuals who had a history of diabetes and a lower BMI were at 2-fold increased risk for pancreas cancer. Longstanding diabetes has been linked to an increased risk of pancreas cancer in numerous epidemiologic studies, including those from Japan and Korea [4]. Because insulin resistance and hyperinsulinemia that characterize diabetes can be either causes or consequences of pancreas cancer, it is difficult to disentangle the complex association among BMI, diabetes, and pancreas cancer risk. A

recent pooled analysis of ACC cohort studies demonstrated that both low BMI and high BMI are associated with increased risk of all-cause mortality in all East Asian populations [26]. There is also evidence suggesting that Asian people are more susceptible to insulin resistance at a lesser degree of obesity than people of European descent [34]. This might increase the likelihood that, indeed, low BMI and diabetes act synergistically in the development of pancreatic cancer in this population. However, this was a subgroup analysis and chance remains a plausible explanation of the results.

Our study has several strengths. With the largest number of diverse Asian populations included in this pooled analysis, we were able to examine the association of pancreas cancer mortality with narrow BMI categories. In addition, we performed analyses stratified by sex, age, smoking status, and diabetes to examine whether these factors modify or confound the BMI-pancreas cancer association.

We recognize several limitations of our study. First, misclassification derived from collection of exposure data may be a concern. The validity of self-reported BMI data can be questioned in part of East Asian cohorts. However, we consider this may not seriously bias the results because our previous study has shown a similar pattern of association between BMI and death from any cause when either self-reported or measured data on height and weight were used [26]. Some non-differential misclassification may be present because BMI was not updated during the follow-up period. Second, information on pancreas cancer mortality was confirmed solely by death certificates in the majority of the ACC participating cohorts. This may have led to some misclassification of outcome. Third, few participating cohorts included in this pooled analysis measured waist circumference or waist/hip ratio, which may be a better index for adiposity than BMI in the elderly [35]. Cohort studies have shown that waist circumference and waist-hip ratio are associated with pancreas cancer risk in Caucasians [36, 37]; however, very few studies are available for Asians. A comprehensive measure of adiposity will further our understanding of the role of obesity in the development of pancreas cancer.

In summary, unlike the findings in Western countries, we found no overall association between BMI and the risk of death from pancreas cancer in the pooled analysis of Asian men and women. With the increasing prevalence of overweight and obesity and type-II diabetes in Asians [38], additional studies will be needed to further address this possible association.

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Table 1

Characteristics of the participating cohorts in the Asia Cohort Consortium

Cohort	Cohort size at baseline	Period of enrollment (yrs)	Mean follow-up period (Yrs)	Age at entry (Yrs)	BMI	Female (%)	Ever smokers (%)	Pancreatic cancer deaths
East Asia								
Japan								
JPHC1	41,718	1990–1992	14.4	49.5±5.9	23.6±3.0	51.8	40.4	98
JPHC2	54,195	1992–1995	11.5	54.1±8.8	23.5±3.1	52.3	40.2	153
JACC	61,835	1988–1990	12.7	56.7±10.0	22.8±2.9	56.4	37.9	238
Miyagi Cohort Study	38,027	1990	12.7	51.5±7.6	23.6±2.9	45.2	49.7	80
3 Pref Miyagi	21,155	1984	11.5	56.4±11.2	23.2±3.2	52.8	40.2	71
3 Pref Aichi	29,750	1985	11.5	55.9±11.2	22.1±2.9	49.9	50.8	109
Ohsaki National Health Insurance Cohort Study	39,782	1995	10.0	59.5±10.4	23.5±3.1	46.7	48.7	145
RERF	47,513	1963 – 1993	22.0	51.9±13.6	22.0±3.4	59.1	44.4	370
Mainland China								
SWHS	73,258	2001–2006	8.6	52.5±9.1	24.0±3.4	100	2.8	76
SMHS	61,339	1996–2000	3.1	55.3±9.7	23.7±3.1	0	69.6	27
Taiwan								
CBSCP	23,493	1991–1992	15.3	47.3±10.0	24.0±3.4	49.7	28.8	33
Korea								
KMCC	14,436	1993–2004	6.6	55.5±12.1	23.7±3.2	61.4	36.6	23
Seoul Male Cohort	13,732	1992 – 1993	14.7	49.2±5.2	23.4±2.4	0	77.3	35
South Asia								
India								
Mumbai Cohort Study	143,401	1991–1997	5.2	50.7±11.1	22.5±4.0	40.2	18.8	15
TOCS	125,651	1995–2002	7.5	49.3±12.2	22±3.9	61.4	23.4	16
Bangladesh								
HEALS	10,257	2000–2002	6.6	36.8±9.9	19.9±3.1	58.3	33.9	0
Total	799,542							1489

JPHC, Japanese Public Health Center-based Prospective Study, JACC, Japan Collaborative Cohort Study, 3 pref. Three Prefecture Cohort Study, RERF, Radiation Effects Research Foundation Life-span Study, SWHS, Shanghai Women's Health Study, SMHS, Shanghai Men's Health Study CBSCP, Community-based Cancer Screening Project, KMCC, The Korean Multi-Center Cancer Cohort, TOCS, Trivandrum Oral Cancer Screening, HEALS, Health Effects of Arsenic Longitudinal Study, BMI, body mass index

Plus minus values are mean±standard deviation

Table 2
Associations between BMI and the risk of death from pancreas cancer in Asian populations

		BMI						
All Asians		<18.5	18.5–19.9	20.0–22.4	22.5–24.9	25.0–27.4	27.5–29.9	30
Men and women								
No of deaths		116	130	432	454	232	89	36
HR1 (95%CI)		0.99 (0.80–1.22)	0.75 (0.62–0.92)	0.91 (0.80–1.04)	1.00	0.93 (0.79–1.09)	1.04 (0.82–1.30)	0.99 (0.70–1.39)
HR2 (95%CI)		1.04 (0.84–1.30)	0.82 (0.67–1.00)	0.91 (0.80–1.05)	1.00	0.95 (0.80–1.11)	1.01 (0.80–1.29)	0.96 (0.67–1.37)
Women								
No of deaths		53	59	174	213	129	52	28
HR1 (95%CI)		0.82 (0.61–1.12)	0.72 (0.54–0.97)	0.78 (0.63–0.95)	1.00	0.98 (0.78–1.22)	0.99 (0.73–1.35)	1.09 (0.73–1.61)
HR2 (95%CI)		0.89 (0.64–1.24)	0.85 (0.63–1.15)	0.78 (0.63–0.96)	1.00	1.01 (0.81–1.27)	1.02 (0.74–1.39)	1.09 (0.72–1.65)
Men								
No of deaths		63	71	258	241	103	37	8
HR1 (95%CI)		1.18 (0.89–1.57)	0.79 (0.61–1.04)	1.04 (0.87–1.24)	1.00	0.86 (0.68–1.08)	1.06 (0.75–1.50)	0.71 (0.35–1.43)
HR2 (95%CI)		1.20 (0.90–1.61)	0.80 (0.61–1.05)	1.03 (0.86–1.24)	1.00	0.87 (0.69–1.10)	0.99 (0.69–1.42)	0.64 (0.30–1.35)
East Asia								
Men and Women								
No of deaths		108	127	423	450	228	86	36
HR1 (95%CI)		0.97(0.78–1.20)	0.75(0.62–0.92)	0.90(0.79–1.03)	1.00	0.92(0.78–1.08)	1.01(0.80–1.27)	1.00(0.71–1.41)
HR2 (95%CI)		1.03 (0.82–1.29)	0.81(0.66–1.00)	0.90 (0.79–1.04)	1.00	0.93 (0.79–1.10)	0.98(0.77–1.25)	0.97(0.68–1.38)
Women								
No of deaths		53	57	174	212	128	52	28
HR1 (95%CI)		0.83(0.60–1.13)	0.70(0.52–0.94)	0.78(0.64–0.95)	1.00	0.97(0.78–1.21)	1.00(0.74–1.36)	1.10(0.74–1.63)
HR2 (95%CI)		0.90(0.64–1.25)	0.82(0.61–1.12)	0.78(0.63–0.97)	1.00	1.00(0.80–1.26)	1.02(0.74–1.39)	1.09(0.72–1.65)
Men								
No of deaths		55	70	249	238	100	34	8
HR1 (95%CI)		1.14(0.84–1.54)	0.81(0.62–1.06)	1.02(0.85–1.22)	1.00	0.84(0.67–1.07)	1.00(0.10–1.43)	0.73(0.36–1.48)
HR2 (95%CI)		1.18(0.87–1.60)	0.81(0.62–1.07)	1.02(0.85–1.22)	1.00	0.85(0.68–1.08)	0.92(0.63–1.34)	0.66(0.31–1.40)
South Asia								

		BMI						
		<18.5	18.5–19.9	20.0–22.4	22.5–24.9	25.0–27.4	27.5–29.9	30
Men andn women								
No of deaths	8		3	9	4	4	3	0
HR1 (95%CI)	2.09(0.62–6.98)		1.12(0.25–5.00)	1.84(0.57–5.97)	1.00	1.82(0.45–7.27)	3.57(0.80–16.01)	–
HR2 (95%CI)	2.27(0.57–8.85)		1.42(0.28–7.01)	2.12(0.56–7.99)	1.00	2.45(0.54–11.00)	4.93(0.99–24.48)	–

HR: hazard ratio; CI: confidence interval

HR1: Adjusted for age, sex and cohort

HR2: Adjusted for age, sex, cohort, cigarette smoking and history of type II diabetes

Table 3
Hazard ratios for pancreas cancer deaths in relation to BMI in East Asians according to age, smoking status and history of diabetes

		BMI						
		<18.5	18.5–19.9	20.0–22.4	22.5–24.9	25.0–27.4	27.5–29.9	30
Ages<55								
No. of deaths		30	32	125	131	63	29	7
HR (95%CI)		1.12(0.73–1.73)	0.68(0.45–1.01)	0.92(0.71–1.19)	1.00	0.91(0.67–1.25)	1.22(0.80–1.87)	0.73(0.32–1.67)
Ages 55								
No of deaths		78	95	298	319	165	57	29
HR (95%CI)		1.01(0.78–1.32)	0.88(0.70–1.12)	0.91(0.77–1.07)	1.00	0.93(0.77–1.13)	0.87(0.65–1.17)	1.01(0.68–1.50)
Nonsmokers								
No. of deaths		57	58	185	220	131	55	26
HR (95%CI)		1.15(0.84–1.59)	0.90(0.67–1.21)	0.84(0.68–1.04)	1.00	1.00(0.80–1.25)	1.08(0.79–1.47)	1.09(0.71–1.67)
Ex-smokers								
No. of deaths		12	6	65	60	28	6	3
HR (95%CI)		1.34(0.69–2.60)	0.36(0.14–0.90)	1.28(0.89–1.84)	1.00	0.90(0.57–1.41)	0.63(0.27–1.47)	0.67(0.16–2.77)
Current smokers								
No of deaths		39	63	173	170	69	25	7
HR (95%CI)		0.83(0.58–1.19)	0.80(0.59–1.08)	0.86(0.69–1.06)	1.00	0.87(0.65–1.15)	0.97(0.63–1.50)	0.80(0.37–1.70)
Individuals without history of diabetes								
No. of deaths		87	111	347	384	194	72	32
HR (95%CI)		0.96(0.76–1.22)	0.78(0.63–0.97)	0.87(0.75–1.00)	1.00	0.92(0.77–1.09)	1.00(0.77–1.28)	1.07(0.75–1.54)
Individuals with history of diabetes								
No. of deaths		11	11	40	35	24	8	1
HR (95%CI)		2.01(1.01–4.00)	1.24(0.63–2.45)	1.33(0.84–2.10)	1.00	1.11(0.66–1.87)	0.97(0.45–2.09)	0.26(0.04–1.90)
Excluding deaths within the first 3 years of follow-up								
No. of deaths		82	109	368	391	204	75	29
HR (95%CI)		0.84(0.65–1.09)	0.77(0.62–0.96)	0.88(0.76–1.02)	1.00	0.97(0.82–1.16)	1.01(0.78–1.31)	0.90(0.60–1.34)

HR: hazard ratio; CI: confidence interval

Men and women combined

HR: Adjusted for age, sex, cohort, cigarette smoking and history of type II diabetes