**Annals of Oncology Advance Access published October 3, 2011**

*Annals of Oncology*
doi:10.1093/annonc/mdr398

# Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose–response meta-analysis of prospective studies

D. Aune[1]*, D. C. Greenwood[2], D. S. M. Chan[1], R. Vieira[1], A. R. Vieira[1], D. A. Navarro Rosenblatt[1], J. E. Cade[3], V. J. Burley[3] & T. Norat[1]

[1]*Department of Epidemiology and Biostatistics, Imperial College London, London;* [2]*Biostatistics Unit, Centre for Epidemiology and Biostatistics, University of Leeds, Leeds;* [3]*Nutritional Epidemiology Group, Centre for Epidemiology and Biostatistics, School of Food Science and Nutrition, University of Leeds, Leeds, UK*

*Received 18 May 2011; revised 12 July 2011; accepted 14 July 2011*

**Background:** Questions remain about the shape of the dose–response relationship between body mass index (BMI) and pancreatic cancer risk, possible confounding by smoking, and differences by gender or geographic location. Whether abdominal obesity increases risk is unclear.

**Methods:** We conducted a systematic review and meta-analysis of prospective studies of the association between BMI, abdominal fatness and pancreatic cancer risk and searched PubMed and several other databases up to January 2011. Summary relative risks (RRs) were calculated using a random-effects model.

**Results:** Twenty-three prospective studies of BMI and pancreatic cancer risk with 9504 cases were included. The summary RR for a 5-unit increment was 1.10 [95% confidence interval (CI) 1.07–1.14, $I^2 = 19\%$] and results were similar when stratified by gender and geographic location. There was evidence of a non-linear association, $P_{\text{non-linearity}} = 0.005$; however, among nonsmokers, there was increased risk even within the 'normal' BMI range. The summary RR for a 10-cm increase in waist circumference was 1.11 (95% CI 1.05–1.18, $I^2 = 0\%$) and for a 0.1-unit increment in waist-to-hip ratio was 1.19 (95% CI 1.09–1.31, $I^2 = 11\%$).

**Conclusions:** Both general and abdominal fatness increases pancreatic cancer risk. Among nonsmokers, risk increases even among persons within the normal BMI range.

**Key words:** body mass index, meta-analysis, pancreatic cancer, systematic review, waist circumference, waist-to-hip ratio

## introduction

Pancreatic cancer is the ninth most common cause of cancer with 277 000 new cases diagnosed in 2008 worldwide, accounting for ∼2.2% of all cancer cases [1]. Pancreatic cancer patients have a very low survival, on average only 6 months after diagnosis, because there are few early symptoms and the disease is usually diagnosed in the later stages. Currently, there are no established methods of screening for early detection; thus, at present, primary prevention by altering modifiable risk factors will probably be the most effective way of reducing the pancreatic cancer burden.

Epidemiological studies have suggested that overweight and obesity are associated with increased pancreatic cancer risk. The evidence that body fatness increases pancreatic cancer risk was considered conclusive in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) [2] report from 2007. However, more recent reviews of the evidence suggested an increased risk with higher body mass index (BMI; weight in kilograms divided by height squared in metres) among women but not among men [3], and in addition, there were inconsistencies in the results by geographic location [3]. The exact shape of the dose–response relationship between BMI and pancreatic cancer risk has not been clearly defined. Smoking is an established risk factor for pancreatic cancer and a potentially important confounding factor of the association between BMI and pancreatic cancer risk. Smokers tend to have a lower BMI than nonsmokers and residual confounding by smoking may attenuate or distort the dose–response relationship between BMI and pancreatic cancer risk. The best way to avoid residual confounding by smoking is to restrict the analyses to nonsmokers or never smokers; however, because pancreatic cancer is a relatively uncommon type of cancer, individual studies may have had limited statistical power to examine the association among nonsmokers, thus combining results from several studies in a meta-analysis will increase statistical power to detect significant associations. Hence, we explored whether smoking may have confounded

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**Correspondence to:* Mr D. Aune, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London W2 1PG, UK. Tel: +44-0-20-7594-8478; Fax: +44 20 7594 0768; E-mail: d.aune@imperial.ac.uk

the association between BMI and pancreatic cancer risk. Abdominal obesity may be more strongly associated with insulin resistance than peripheral obesity [4], but there have been relatively few studies of waist circumference and waist-to-hip ratio as measures of abdominal fatness in relation to pancreatic cancer risk. A number of additional large cohort studies have been published since the WCRF/AICR report from 2007 [5–17]; thus, we conducted an updated meta-analysis of BMI, waist circumference and waist-to-hip ratio and pancreatic cancer risk with the aim to clarify whether body fatness is associated with pancreatic cancer in both men and women and in European and Asian populations as well. In addition, we wanted to clarify the dose–response relationship between BMI, waist circumference and waist-to-hip ratio and pancreatic cancer risk by conducting non-linear dose–response analyses and by restricting the analysis to studies among nonsmokers or never smokers.

## methods

### search strategy

Initially, relevant studies of anthropometric measures and pancreatic cancer risk were identified by searching several databases up to December 2005, including PubMed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane Library, CINAHL, AMED, National Research Register and In Process Medline. However, because all the relevant studies were identified by the PubMed search, a change to the protocol was made and in the updated searches only PubMed was searched from 1 January 2006 to 31 January 2011. A pre-specified protocol was followed for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf) and we used standard criteria for meta-analyses of observational studies [18]. In addition, we also searched the reference lists of all the studies that were included in the analysis and the reference lists of published meta-analyses [3, 19, 20].

### study selection

Prospective cohort studies, case-cohort studies or nested case–control studies of the association between BMI, waist circumference or waist-to-hip ratio and pancreatic cancer risk incidence or mortality were included. Relative risk (RR) estimates (hazard ratio, risk ratio) had to be available with the 95% confidence intervals (CIs) in the publication and for the dose–response analysis, a quantitative measure of intake and the total number of cases and person-years had to be available in the publication. We identified 48 potentially relevant full-text publications [5–17, 21–56]. We excluded 14 duplicate publications [13, 25, 29, 30, 32, 33, 40, 41, 43, 45–47, 49, 51, 52], 4 publications that did not present risk estimates [23, 24, 26, 39] and 1 publication using less than three categories for categorisation of BMI [27], leaving 29 publications for inclusion in the analysis [5–12, 14–17, 21, 22, 28, 31, 34–38, 42, 44, 48, 50, 53–56]. Results from two overlapping publications were included only in subgroup analyses stratified by sex [42] or smoking [44] but not in the overall analyses, because the superseding publications did not present sex-specific results [5] or results stratified by smoking in enough detail to be included [16].

### data extraction

We extracted the following information from each study: the first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, assessment method of anthropometric factors (measured versus self-reported), RRs and 95% CIs and variables adjusted for in the analysis. Several reviewers at the University of Leeds conducted the search and data extraction of articles published up to December 2005, during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/downloads/SLR/Pancreas_SLR.pdf). The search and data extraction from January 2006 and up to January 2011 was conducted by one author (DA) and was checked for accuracy by one author (TN).

### statistical analysis

Summary RRs and 95% CIs for a 5-unit increment in BMI, 10-cm increment in waist circumference and 0.1-unit increment in waist-to-hip ratio were estimated using a random-effects model [57]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed $P < 0.05$ was considered statistically significant. If studies reported results separately for men and women, we combined the sex-specific estimates using a fixed-effects model to generate an estimate for both genders combined. We conducted separate analyses for pancreatic cancer incidence and mortality.

The method described by Greenland and Longnecker [58] was used for the dose–response analysis and study-specific slopes (linear trends) and 95% CIs were computed from the natural logs of the RRs and CIs across categories of anthropometric measures. The method requires that the distributions of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these but reported the total number of cases and person-years (supplemental Material 1, available at *Annals of Oncology* online). The mean BMI, waist circumference or waist-to-hip ratio level in each category was assigned to the corresponding RR for each study and for studies that reported these measures by ranges, we estimated the mean in each category using the method described by Chene and Thompson [59]. A potential non-linear dose–response relationship between BMI, waist circumference and waist-to-hip ratio and pancreatic cancer was examined by using fractional polynomial models [60]. We determined the best-fitting second-order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the non-linear and linear models to test for non-linearity [60].

Subgroup and meta-regression analyses were conducted to investigate potential sources of heterogeneity and heterogeneity between studies was quantitatively assessed by the $Q$ test and $I^2$ [61]. Small study effects, such as publication bias, were assessed by inspecting the funnel plots for asymmetry and with Egger's test [62] and Begg's test [63], with the results considered to indicate small study effects when $P < 0.10$. Sensitivity analyses excluding one study at a time were conducted to clarify whether the results were simply due to one large study or a study with an extreme result.

### role of the funding source

The funding source had no role in the study design; collection, analysis and interpretation of the data; the writing of the report or the decision to submit the paper for publication.

## results

We identified 24 prospective studies (23 publications) [5–12, 14–17, 21, 22, 28, 31, 34–38, 42, 44] that were included in the analyses of BMI and pancreatic cancer incidence (supplemental Table S1, available at *Annals of Oncology* online; Figure 1). Two of these publications were only included in subgroup analyses of sex [42] and stratified by smoking [44] as they overlapped with two more recent publications [5, 16]. Seven cohort studies [16, 48, 50, 53–56] were included in the analysis of pancreatic cancer mortality (supplemental Table S2,

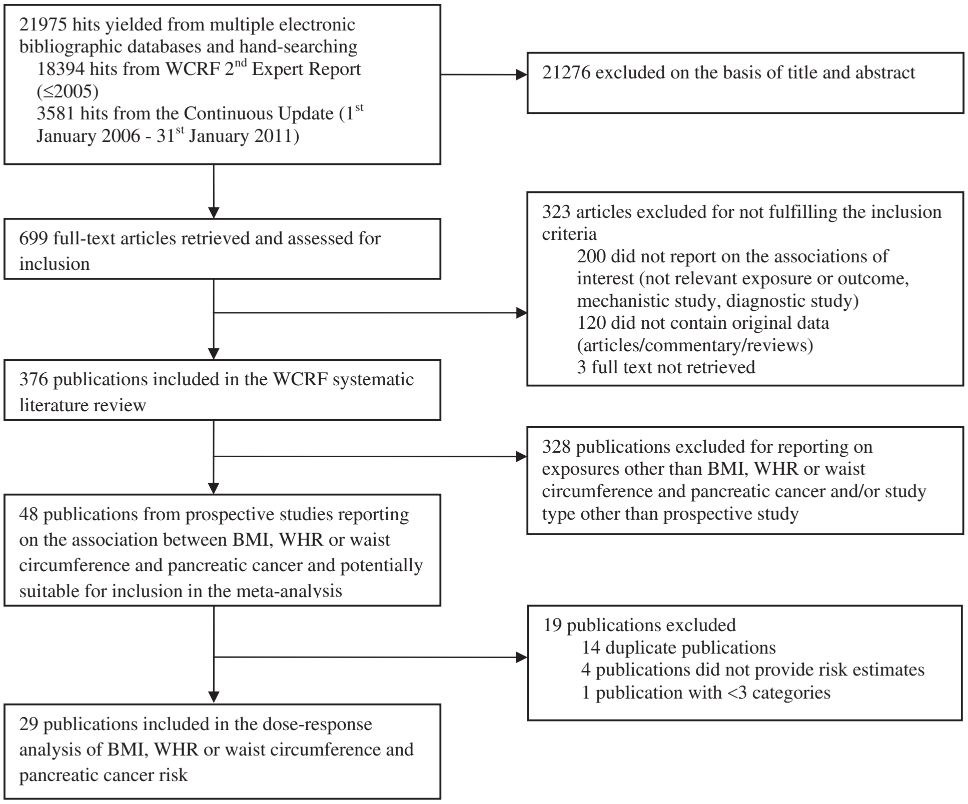

**Figure 1.** Flowchart of study selection.

available at *Annals of Oncology* online). Five cohort studies (four publications) [5, 10, 12, 36] were included in the analysis of waist circumference and four cohort studies [5, 10, 12, 37] were included in the analysis of waist-to-hip ratio and pancreatic cancer incidence. Characteristics of the included studies are provided in supplemental Tables S1 and S2 (available at *Annals of Oncology* online). Most of the studies were from Europe and the United States and used self-reported weight and height (supplemental Tables S1 and S2, available at *Annals of Oncology* online).

## body mass index

Twenty-three prospective studies (21 publications) [5–12, 14–17, 21, 22, 28, 31, 34–38] were included in the overall dose–response analysis of BMI and pancreatic cancer incidence and included a total of 9504 cases among 5 037 555 participants. Ten studies were from the United States, 10 were from Europe and the remaining 3 were from Asia (supplemental Table S1, available at *Annals of Oncology* online). The summary RR for a 5-unit increment in BMI was 1.10 (95% CI 1.07–1.14), with no significant heterogeneity, $I^2 = 19\%$, $P = 0.20$ (Figure 2a). The summary RR was similar among men and women, summary RR = 1.10 (95% CI 1.04–1.16, $I^2 = 46\%$, $P_{\text{heterogeneity}} = 0.03$) for women [7–12, 16, 17, 28, 34–38, 42] and 1.13 (95% CI 1.04–1.22, $I^2 = 42\%$, $P_{\text{heterogeneity}} = 0.05$) for men [6–11, 14, 17, 28, 34–38] (Table 1). Although there was no statistically significant difference in the association between never smokers or nonsmokers [5–7, 10, 44] and ever smokers [5–7, 10] in stratified analyses, the association was restricted to never smokers and nonsmokers (Table 1). In sensitivity analyses excluding one study at a time, the summary RR in the overall analysis ranged from 1.09 (95% CI 1.06–1.12) when the Cancer Prevention Study 2 Nutrition Cohort was excluded to 1.11 (95% CI 1.08–1.14) when the Multiethnic Cohort Study was excluded. There was no evidence of small study effects with Egger's test, $P = 0.36$, or with Begg's test, $P = 0.27$, and when visually inspected the funnel plot showed no sign of asymmetry.

To address the question of reverse causality, for example, whether pre-diagnostic disease may have influenced BMI, we restricted the analyses to the six studies [5, 8, 10, 11, 34, 44] that provided results with exclusion of early follow-up (first 1–4 years of follow-up), but the results were similar, summary RR = 1.11 (95% CI 1.05–1.18, $I^2 = 35\%$, $P_{\text{heterogeneity}} = 0.18$). Further restricting the analyses to the four studies [5, 8, 11, 44] that excluded at least the first 2 years of follow-up did also not materially change the results, summary RR = 1.13 (95% CI 1.05–1.21, $I^2 = 26\%$, $P_{\text{heterogeneity}} = 0.25$; results not shown).

The results were in general consistent across subgroups of duration of follow-up, geographic location, number of cases, adjustment for most confounding factors and adjustment for diabetes (Table 1). Only in the subgroups of studies with and without adjustment for physical activity and red meat was there some evidence of heterogeneity ($P_{\text{heterogeneity}} = 0.03$ for both comparisons), with a stronger association among studies that adjusted for physical activity ($n = 4$) but no association among studies that adjusted for red meat ($n = 2$); however, the number of studies in these subgroup analyses was very low. We also

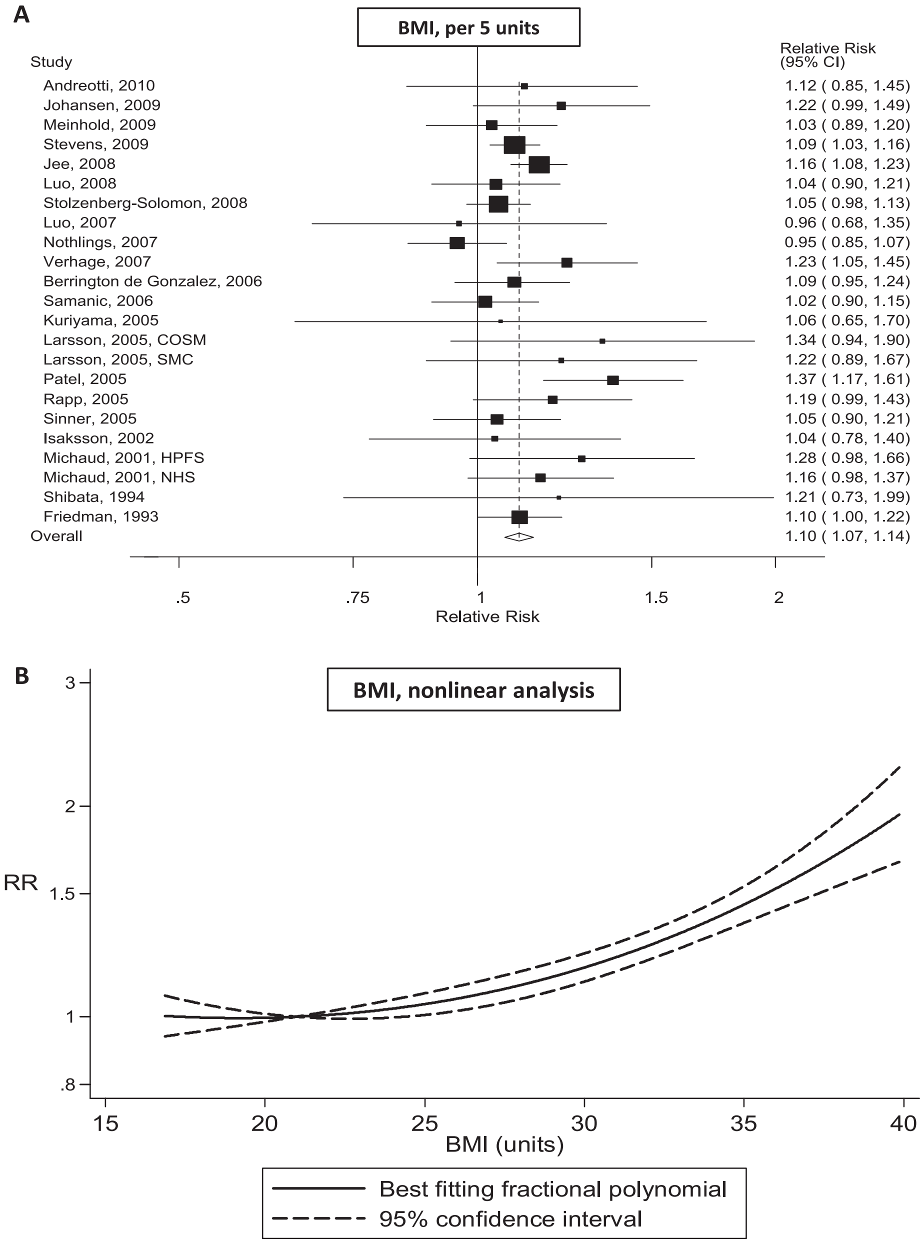

**Figure 2.** BMI and pancreatic cancer incidence, linear (per 5 BMI units) and nonlinear dose–response analyses. BMI, body mass index.

conducted further subgroup analyses within strata of gender to investigate potential sources for the observed heterogeneity for men and women when analysed separately, but only in the analysis among women stratified by adjustment for meat intake was there some evidence of heterogeneity ($P = 0.009$). An inverse association was found in the two studies that adjusted for meat intake (summary RR = 0.86, 95% CI 0.75–0.99), but a positive association was observed in the studies that did not adjust for meat intake (summary RR = 1.10, 95% CI 1.06–1.15; results not shown).

There was evidence of a non-linear association between BMI and pancreatic cancer risk, $P_{\text{non-linearity}} = 0.005$ (Figure 2b), with the lowest risk among persons with a BMI ∼21 and with the most pronounced increase in risk among persons with a BMI > 35. The association between BMI and pancreatic cancer risk appeared to be linear when we further restricted the non-linear analysis to studies of never smokers and nonsmokers [6, 7, 10], $P_{\text{non-linearity}} = 0.61$; however, the shape of the dose–response curve was steeper and there was evidence of an increase in risk even among persons with a BMI in the 'normal' range (BMI 21<25) (Figure 3a). In contrast, there was no evidence of an association between BMI and increased pancreatic cancer risk when we restricted the non-linear analysis to ever smokers (Figure 3b) [7, 10].

Seven cohort studies [16, 48, 50, 53–56] were included in the BMI and pancreatic cancer mortality analysis and included 8869 deaths among 2 537 564 participants. Three of the studies were from the United States, two from Europe and two from Asia (supplemental Table S2, available at *Annals of Oncology* online). The summary RR was 1.16 (95% CI 0.98–1.36) and there was

**Table 1.** Subgroup analyses of BMI and pancreatic cancer

| | BMI | | | | |
|---|---|---|---|---|---|
| | *n* | RR (95% CI) | $I^2$ (%) | $P_h$[a] | $P_h$[b] |
| All studies | 23 | 1.10 (1.07–1.14) | 19.3 | 0.20 | |
| Sex | | | | | |
| Men | 14 | 1.13 (1.04–1.22) | 45.6 | 0.03 | 0.76 |
| Women | 15 | 1.10 (1.04–1.16) | 41.8 | 0.05 | |
| Assessment of weight/height | | | | | |
| Measured | 7 | 1.11 (1.07–1.15) | 0 | 0.58 | 0.90 |
| Self-reported | 14 | 1.12 (1.05–1.20) | 40.2 | 0.06 | |
| Measured and self-reported | 2 | 1.07 (0.95–1.21) | 0 | 0.49 | |
| Duration of follow-up | | | | | |
| <10 years follow-up | 11 | 1.09 (1.03–1.15) | 38.6 | 0.09 | 0.42 |
| ≥10 years follow-up | 12 | 1.12 (1.08–1.17) | 0 | 0.65 | |
| Geographic location | | | | | |
| Europe | 10 | 1.10 (1.06–1.15) | 0 | 0.60 | 0.96 |
| America | 10 | 1.10 (1.03–1.17) | 45.0 | 0.06 | |
| Asia | 3 | 1.15 (1.08–1.22) | 0 | 0.55 | |
| Number of cases | | | | | |
| Cases <299 | 14 | 1.15 (1.09–1.22) | 0 | 0.59 | 0.14 |
| Cases 300<500 | 5 | 1.07 (0.99–1.16) | 45.5 | 0.12 | |
| Cases ≥500 | 4 | 1.09 (1.04–1.14) | 40.1 | 0.17 | |
| Smoking status | | | | | |
| Never smoker or nonsmoker | 5 | 1.11 (1.04–1.17) | 0 | 0.55 | 0.16 |
| Ever smoker | 4 | 1.03 (0.95–1.10) | 0 | 0.93 | |
| Adjustment for confounders | | | | | |
| Alcohol | | | | | |
| Yes | 4 | 1.14 (0.96–1.37) | 0 | 0.56 | 0.70 |
| No | 19 | 1.10 (1.06–1.14) | 28.1 | 0.12 | |
| Smoking | | | | | |
| Yes | 19 | 1.11 (1.06–1.17) | 29.5 | 0.20 | 0.50 |
| No | 4 | 1.09 (1.04–1.14) | 0 | 0.76 | |
| Diabetes | | | | | |
| Yes | 12 | 1.12 (1.05–1.20) | 46.8 | 0.04 | 0.87 |
| No | 11 | 1.11 (1.07–1.14) | 0 | 0.78 | |
| Physical activity | | | | | |
| Yes | 4 | 1.26 (1.09–1.46) | 16.8 | 0.31 | 0.03 |
| No | 19 | 1.09 (1.06–1.12) | 0 | 0.48 | |
| Red meat, processed meat | | | | | |
| Yes | 2 | 0.96 (0.86–1.07) | 0 | 0.69 | 0.03 |
| No | 21 | 1.11 (1.08–1.14) | 4.7 | 0.40 | |
| Fruit and vegetables | | | | | |
| Yes | 1 | 1.06 (0.65–1.70) | | | 0.86 |
| No | 22 | 1.10 (1.07–1.14) | 22.9 | 0.16 | |
| Energy intake | | | | | |
| Yes | 3 | 1.10 (0.89–1.36) | 84.6 | 0.002 | 0.58 |
| No | 20 | 1.10 (1.07–1.14) | 0 | 0.81 | |

*n* denotes the number of risk estimates.

[a] *P* for heterogeneity within each subgroup.

[b] *P* for heterogeneity between subgroups with meta-regression analysis.

BMI, body mass index; RR, relative risk; CI, confidence interval.

moderate heterogeneity, $I^2 = 56\%$, $P_{\text{heterogeneity}} = 0.04$ (Figure 4a). The summary RR ranged from 1.06 (95% CI 1.01–1.11) when the Cancer Prevention Study 2 was excluded to 1.21 (95% CI 0.97–1.49) when the Million Women's Study was excluded. The Cancer Prevention Study 2 [55] also explained all the heterogeneity and when excluded, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.43$. There was no evidence of small study effects with Egger's test, $P = 0.43$, or with Begg's test, $P = 0.76$. There was evidence that the association between BMI and pancreatic cancer mortality was non-linear, $P_{\text{non-linearity}} = 0.0001$, and the risk was most pronounced above a BMI of 35 (Figure 4b).

## waist circumference

Five cohort studies (four publications) [5, 10, 12, 36] were included in the analysis of waist circumference and pancreatic cancer risk and included 949 cases among 787 356 participants. Three studies were from Europe and two from the United States (supplemental Table S1, available at *Annals of Oncology* online). The summary RR for a 10-cm increase in waist circumference was 1.11 (95% CI 1.05–1.18) with no evidence of heterogeneity, $I^2 = 0\%$, $P = 0.74$ (Figure 5a). The summary RR ranged from 1.11 (95% CI 1.04–1.17) when the Cohort of Swedish Men was excluded to 1.14 (95% CI 1.06–1.22) when the Women's Health Initiative was excluded. The summary estimate was similar among men (summary RR = 1.13, 95% CI 0.89–1.44, $I^2 = 61\%$, $P_{heterogeneity} = 0.11$) and women (summary RR = 1.14, 95% CI 1.02–1.28, $I^2 = 29\%$, $P_{heterogeneity} = 0.24$), *P* for heterogeneity = 0.59 (results not shown). There was no evidence of small study effects with Egger's test, $P = 0.11$, or with Begg's test, $P = 0.22$. There was no evidence of a non-linear association between waist circumference and pancreatic cancer risk, $P_{\text{non-linearity}} = 0.28$ (Figure 3c).

## waist-to-hip ratio

Four cohort studies [5, 10, 12, 37] were included in the analysis of waist-to-hip ratio and pancreatic cancer risk and included 1047 cases among 878 137 participants. Three were from the United States and one from Europe (supplemental Table S1, available at *Annals of Oncology* online). The summary RR for a 0.1-unit increment in waist-to-hip ratio was 1.19 (95% CI 1.09–1.31) with no significant heterogeneity, $I^2 = 11\%$, $P = 0.34$ (Figure 5b). The summary RR ranged from 1.15 (95% CI 1.04–1.27) when the Women's Health Initiative was excluded to 1.24 (95% CI 1.12–1.37) when the Iowa Women's Health Study was excluded. The summary estimate was similar among men (summary RR = 1.20, 95% CI 0.96–1.50, $I^2$ = not calculable, $n = 1$) and women (summary RR = 1.17, 95% CI 1.00–1.36, $I^2 = 41\%$, $P_{heterogeneity} = 0.18$), *P* for heterogeneity by gender = 0.89 (results not shown). There was no evidence of small study effects with Egger's test, $P = 0.50$, or with Begg's test, $P = 0.73$. There was no evidence of a non-linear association between waist circumference and pancreatic cancer risk, $P_{\text{non-linearity}} = 0.29$ (Figure 3d).

# discussion

In this meta-analysis, we found evidence of an increased risk of pancreatic cancer with higher BMI and a similar association with measures of abdominal obesity, such as waist circumference and waist-to-hip ratio.

However, to our knowledge, for the first time in a meta-analysis of BMI and pancreatic cancer, we have found a potential non-linear association between BMI and pancreatic cancer risk. The most pronounced increase in risk

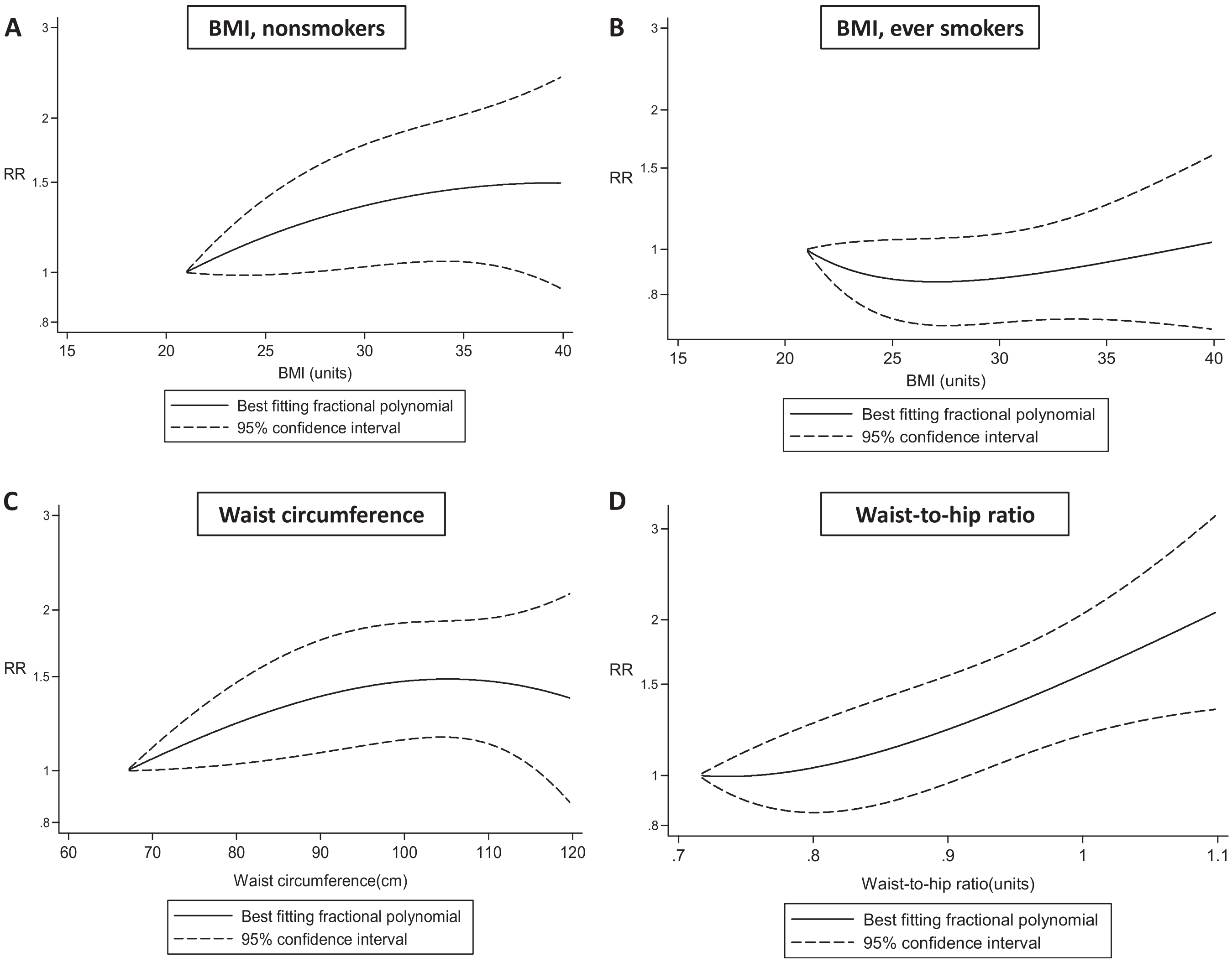

**Figure 3.** BMI stratified by smoking status, waist circumference and waist-to-hip ratio and pancreatic cancer incidence, nonlinear dose–response analysis. BMI, body mass index.

was observed at a BMI > 35; however, when we further restricted the analyses to studies among nonsmokers and never smokers, the shape of the curve became initially steeper and there was evidence of an increased risk even within the high normal range of BMI. In contrast, there was no association between BMI and pancreatic cancer risk among ever smokers. Thus, residual confounding from smoking may have distorted the dose–response relationship between BMI and pancreatic cancer risk in the overall analysis. The positive associations between waist circumference and waist-to-hip ratio and pancreatic cancer risk appeared to be linear. We found little evidence of heterogeneity in the overall analyses of BMI, waist circumference and waist-to-hip ratio and pancreatic cancer incidence, while in the analysis of BMI and pancreatic cancer mortality, the moderate heterogeneity that was present was explained by a large American study [55]. Our analysis confirms the hypothesis that both overall body fatness and abdominal fatness are associated with increased risk of pancreatic cancer and provides further support for the findings from a recent meta-analysis [3] and the WCRF/AICR [2] report from 2007. However, with a larger number of studies, we also found significant associations among both men and women and among American, European and Asian studies and there was no evidence of a difference between the summary estimates for these subgroups, confirming the importance of body weight control for pancreatic cancer prevention in diverse populations and among both genders. Two pooled analyses [64, 65] and a meta-analysis [3] have previously reported somewhat stronger associations among women than among men, while our meta-analysis and another pooled analysis [66] showed similar results in men and women. The difference between our findings and the previous analyses may relate to the larger number of studies now available and therefore more statistical power to detect an association also among men. In addition, a higher percentage of men than women were current or former smokers in one of the pooled analyses [65]; thus, residual confounding from smoking may have to a larger degree obscured an existing association among men than among women. In another pooled analysis, the risk estimates for a BMI ≥ 35 were similar for men and women when excluding current and former smokers (RR = 1.65, 95% CI 0.96–2.84 for men versus RR =

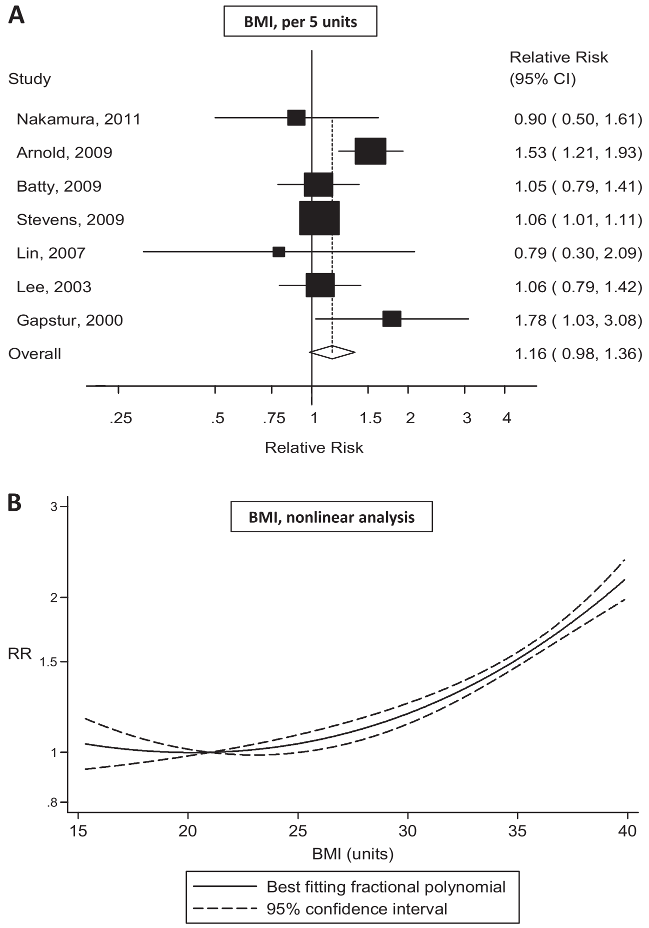

**Figure 4.** BMI and pancreatic cancer mortality, linear (per 5 units) and nonlinear dose–response analyses. BMI, body mass index.

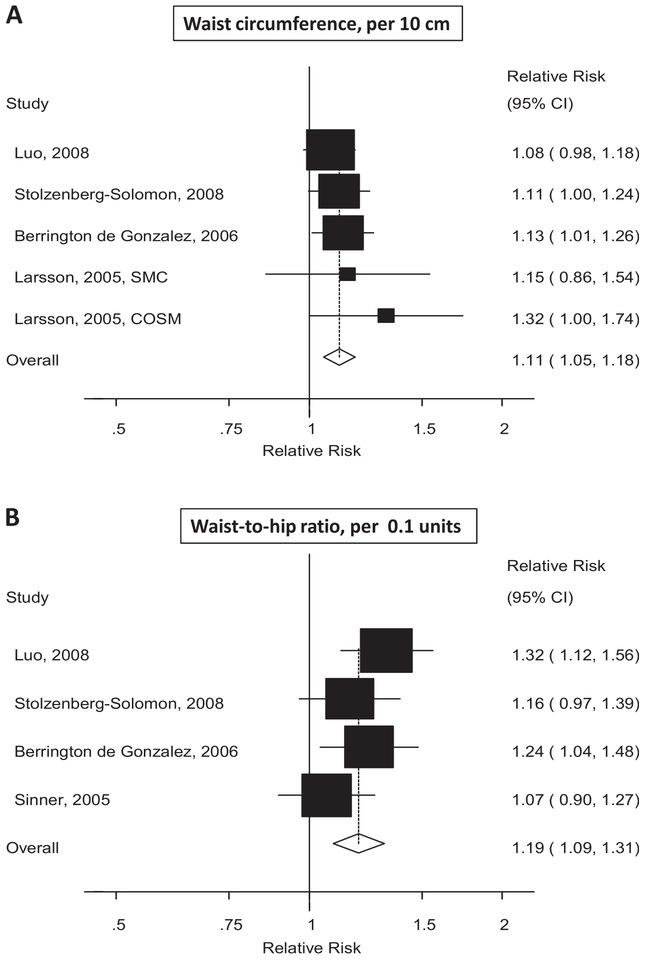

**Figure 5.** Waist circumference and waist-to-hip ratio and pancreatic cancer incidence, linear dose–response analysis.

1.65, 95% CI 1.13–2.40 for women) [64]. In most of the studies, data on smoking were collected only at baseline and it is possible that residual confounding from changes in smoking over time still may be present in the analysis of nonsmokers; however, this would most likely result in the underestimation of the association between BMI and pancreatic cancer risk.

Our meta-analysis has some limitations that may affect the interpretation of the results. The main limitation is the low number of cohort studies available reporting on waist circumference and waist-to-hip ratio, which limited our possibility to conduct subgroup and sensitivity analyses of these measures (including stratification by smoking status). In addition, we were not able to investigate whether the association between abdominal fatness and pancreatic cancer risk was independent of BMI because of the few studies that had explored this question. It is possible that the positive association between BMI or abdominal fatness and pancreatic cancer risk could be due to unmeasured or residual confounding by other lifestyle factors, such as lower physical activity or dietary factors. The results persisted when stratified by adjustment for physical activity, diabetes and smoking and also when restricted to never smokers. Diabetes may, however, also be considered an intermediate variable since BMI partly could increase pancreatic cancer risk through an effect on diabetes, but from our subgroup analyses, it seems that there is still an association between higher BMI and increased pancreatic cancer risk that is independent of diabetes. Overweight and obesity are typically associated with unhealthy diets but very few studies adjusted for intake of alcohol, red meat, fruit and vegetables and energy intake; thus, these subgroup analyses are difficult to interpret. Measurement errors in the assessment of height and weight may have influenced our results. Most of the studies relied on self-reported height and weight, and although there may be some underreporting of weight and overreporting of height, most studies have found a high correlation between self-reported and measured height and weight [67, 68]. In addition, the results were very similar when studies were stratified by whether weight and height were measured or self-reported, lending further credibility to self-reported anthropometric measures. Weight was collected at baseline and not during follow-up in most of the studies; thus, it is possible that these measures may not reflect usual adult weight and so there may be some misclassification of long-term exposure. Pancreatic cancer is usually diagnosed in the later stages and is frequently associated with profound weight loss; thus, it is also possible that the use of baseline data in this case may provide more valid results than if the data were updated through follow-up because of less influence of pre-diagnostic weight loss. The subgroup analyses of BMI and pancreatic cancer among nonsmokers and never and ever smokers were based on a limited number of studies and we can therefore not rule out the possibility that some degree of reporting bias may be present (e.g. more studies that found a difference between smokers and nonsmokers reported stratified results than studies that did not find a difference) and may have led to exaggerated findings in this subgroup. Nevertheless, a pooled analysis also reported stronger results among never smokers than among smokers [64]; thus, reporting bias is not likely to be the sole explanation for this finding. Although meta-analyses of published literature may be susceptible to small study effects, we found no evidence of small study effects with either Egger's test or Begg's test or when visually inspecting the funnel plots.

Our meta-analysis also has several strengths. Because we based our analysis on prospective studies, recall bias and selection bias are not likely to explain our findings. In addition, prospective studies avoid the reliance on use of proxy respondents, which have been used extensively in case–control studies of pancreatic cancer due to the poor survival rates. Our meta-analysis included a large number of cohort studies with relatively long follow-up and included 9504 cases among 5 037 555 participants in the BMI analysis, so we had statistical power to detect moderate or weak associations. We also had statistical power to detect significant associations in various subgroups of populations including men and women, Asian, American and European studies, by duration of follow-up and number of cases. The results were generally robust to the influence of single studies. In addition, we investigated whether reverse causation (e.g. pre-diagnostic disease might have influenced BMI) could have biased the results by restricting the analyses to studies that excluded early follow-up; however, the risk estimates were similar in these analyses. Further, we explored, to our knowledge for the first time in a meta-analysis, a non-linear association between BMI, waist circumference and waist-to-hip ratio and pancreatic cancer. Our results underscore the importance of body weight control in pancreatic cancer prevention in diverse populations and irrespective of gender, but they suggest that avoiding abdominal fatness also may be important. In addition, with decreasing prevalence of smoking in several populations, it is important that future epidemiological studies report more detailed results (e.g. stratified by smoking status), both to avoid selective reporting of results and to avoid residual confounding that can result in underestimation of the impact of body fatness on pancreatic cancer risk.

In summary, our meta-analysis, which is the most up-to-date review of the evidence, confirms the hypothesis that increased BMI and abdominal obesity are associated with increased pancreatic cancer risk. The association between elevated BMI and increased pancreatic cancer risk is observed in both men and women and in North American, European and Asian studies. A non-linear association is observed in the overall analysis with increased risk above a BMI of 25 but most pronounced above a BMI of 35; however, in analyses restricted to nonsmokers, there is evidence of increased risk even among persons in the normal range of BMI (21<25). Thus, our results provide further support for previous recommendations to be as lean as possible within the normal range of BMI but also suggest that avoiding abdominal obesity is likely to be important in the prevention of pancreatic cancer.

## acknowledgements

We thank the systematic literature review team at the University of Leeds for their contributions to the pancreatic cancer database. Contributors—VJB, JEC and the systematic literature review team at the University of Leeds conducted the search, data selection and data extraction up to December 2005. RV was responsible for developing and managing the database for the Continuous Update Project. DA did the updated literature search, data extraction, study selection, statistical analyses and wrote the first draft of the original manuscript. DCG was expert statistical advisor and contributed towards the statistical analyses. All authors contributed to the revision of the manuscript. TN is the principal investigator of the Continuous Update Project. The views expressed in this review are the opinions of the authors. They may not represent the views of WCRF/AICR and may differ from those in future updates of the evidence related to food, nutrition, physical activity and cancer risk. All authors had full access to all the data in the study. DA takes responsibility for the integrity of the data and the accuracy of the data analysis.

## funding

This work was funded by the World Cancer Research Fund (2007/SP01) as part of the Continuous Update Project.

## disclosure

The authors declare no conflict of interest.

## references

1. Ferlay J, Shin HR, Bray F et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893–2917.
2. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR 2007.
3. Renehan AG, Tyson M, Egger M et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008; 371: 569–578.
4. Abate N. Insulin resistance and obesity. The role of fat distribution pattern. Diabetes Care 1996; 19: 292–294.
5. Berrington de Gonzalez A, Bueno-de-Mesquita HB, Roddam A 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: 879–885.
6. Samanic C, Chow WH, Gridley G et al. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control 2006; 17: 901–909.
7. Nothlings U, Wilkens LR, Murphy SP et al. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. Cancer Causes Control 2007; 18: 165–175.
8. Luo J, Iwasaki M, Inoue M et al. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: a large-scale population-based cohort study in Japan—the JPHC study. Cancer Causes Control 2007; 18: 603–612.

9. Verhage BA, Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry and pancreatic cancer risk: an illustration of the importance of microscopic verification. Cancer Epidemiol Biomarkers Prev 2007; 16: 1449–1454.
10. Stolzenberg-Solomon RZ, Adams K, Leitzmann M et al. Adiposity, physical activity, and pancreatic cancer in the National Institutes of Health-AARP Diet and Health Cohort. Am J Epidemiol 2008; 167: 586–597.
11. Jee SH, Yun JE, Park EJ et al. Body mass index and cancer risk in Korean men and women. Int J Cancer 2008; 123: 1892–1896.
12. Luo J, Margolis KL, Adami HO et al. Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). Br J Cancer 2008; 99: 527–531.
13. de Martel C, Llosa AE, Friedman GD et al. Helicobacter pylori infection and development of pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2008; 17: 1188–1194.
14. Meinhold CL, Berrington de Gonzalez A, Albanes D et al. Predictors of fasting serum insulin and glucose and the risk of pancreatic cancer in smokers. Cancer Causes Control 2009; 20: 681–690.
15. Johansen D, Borgstrom A, Lindkvist B, Manjer J. Different markers of alcohol consumption, smoking and body mass index in relation to risk of pancreatic cancer. A prospective cohort study within the Malmo Preventive Project. Pancreatology 2009; 9: 677–686.
16. Stevens RJ, Roddam AW, Spencer EA et al. Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. Int J Cancer 2009; 124: 2400–2405.
17. Andreotti G, Hou L, Beane Freeman LE et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. Cancer Causes Control 2010; 21: 1759–1775.
18. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012.
19. Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 2003; 89: 519–523.
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: 1993–1998.
21. Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. Int J Epidemiol 1993; 22: 30–37.
22. Shibata A, Mack TM, Paganini-Hill A et al. A prospective study of pancreatic cancer in the elderly. Int J Cancer 1994; 58: 46–49.
23. Zheng W, Doyle TJ, Kushi LH et al. Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. Am J Epidemiol 1996; 144: 175–182.
24. Tulinius H, Sigfusson N, Sigvaldason H et al. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev 1997; 6: 863–873.
25. Stolzenberg-Solomon RZ, Albanes D, Nieto FJ et al. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. J Natl Cancer Inst 1999; 91: 535–541.
26. Robsahm TE, Tretli S. Height, weight and gastrointestinal cancer: a follow-up study in Norway. Eur J Cancer Prev 1999; 8: 105–113.
27. Nilsen TI, Vatten LJ. A prospective study of lifestyle factors and the risk of pancreatic cancer in Nord-Trondelag, Norway. Cancer Causes Control 2000; 11: 645–652.
28. Michaud DS, Giovannucci E, Willett WC et al. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001; 286: 921–929.
29. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR et al. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Causes Control 2002; 13: 417–426.
30. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR et al. Prospective study of diet and pancreatic cancer in male smokers. Am J Epidemiol 2002; 155: 783–792.
31. 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: 480–482.
32. Anderson KE, Johnson TW, Lazovich D, Folsom AR. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. J Natl Cancer Inst 2002; 94: 1168–1171.
33. Stolzenberg-Solomon RZ, Limburg P, Pollak M et al. Insulin-like growth factor (IGF)-1, IGF-binding protein-3, and pancreatic cancer in male smokers. Cancer Epidemiol Biomarkers Prev 2004; 13: 438–444.
34. 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: 1062–1067.
35. Kuriyama S, Tsubono Y, Hozawa A et al. Obesity and risk of cancer in Japan. Int J Cancer 2005; 113: 148–157.
36. Larsson SC, Permert J, Hakansson N et al. Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer 2005; 93: 1310–1315.
37. Sinner PJ, Schmitz KH, Anderson KE, Folsom AR. Lack of association of physical activity and obesity with incident pancreatic cancer in elderly women. Cancer Epidemiol Biomarkers Prev 2005; 14: 1571–1573.
38. Patel AV, Rodriguez C, Bernstein L et al. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. Cancer Epidemiol Biomarkers Prev 2005; 14: 459–466.
39. Navarro Silvera SA, Miller AB, Rohan TE. Hormonal and reproductive factors and pancreatic cancer risk: a prospective cohort study. Pancreas 2005; 30: 369–374.
40. Nothlings U, Wilkens LR, Murphy SP et al. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. J Natl Cancer Inst 2005; 97: 1458–1465.
41. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005; 23: 4742–4754.
42. Lukanova A, Bjor O, Kaaks R et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. Int J Cancer 2006; 118: 458–466.
43. Yun JE, Jo I, Park J et al. Cigarette smoking, elevated fasting serum glucose, and risk of pancreatic cancer in Korean men. Int J Cancer 2006; 119: 208–212.
44. Reeves GK, Pirie K, Beral V et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007; 335: 1134.
45. Berrington de Gonzalez A, Yun JE, Lee SY et al. Pancreatic cancer and factors associated with the insulin resistance syndrome in the Korean cancer prevention study. Cancer Epidemiol Biomarkers Prev 2008; 17: 359–64.
46. Jiao L, Mitrou PN, Reedy J et al. A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. Arch Intern Med 2009; 169: 764–770.
47. Andreotti G, Freeman LE, Hou L et al. Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. Int J Cancer 2009; 124: 2495–2500.
48. Gapstur SM, Gann PH, Lowe W et al. Abnormal glucose metabolism and pancreatic cancer mortality. JAMA 2000; 283: 2552–2558.
49. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000; 11: 915–923.
50. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS Jr. Physical activity, body weight, and pancreatic cancer mortality. Br J Cancer 2003; 88: 679–683.
51. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348: 1625–1638.
52. Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. Cancer Causes Control 2004; 15: 873–881.
53. Lin Y, Kikuchi S, Tamakoshi A et al. Obesity, physical activity and the risk of pancreatic cancer in a large Japanese cohort. Int J Cancer 2007; 120: 2665–2671.
54. Batty GD, Kivimaki M, Morrison D et al. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. Cancer Epidemiol Biomarkers Prev 2009; 18: 673–675.
55. Arnold LD, Patel AV, Yan Y et al. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? Cancer Epidemiol Biomarkers Prev 2009; 18: 2397–2405.

56. Nakamura K, Nagata C, Wada K et al. Cigarette smoking and other lifestyle factors in relation to the risk of pancreatic cancer death: a prospective cohort study in Japan. Jpn J Clin Oncol 2011; 41: 225–231.
57. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188.
58. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992; 135: 1301–1309.
59. Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am J Epidemiol 1996; 144: 610–621.
60. Bagnardi V, Zambon A, Quatto P, Corrao G. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. Am J Epidemiol 2004; 159: 1077–1086.
61. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–1558.
62. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–634.
63. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–1101.
64. Arslan AA, Helzlsouer KJ, Kooperberg C et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med 2010; 170: 791–802.
65. Jiao L, Berrington de Gonzalez A, Hartge P et al. Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts. Cancer Causes Control 2010; 21: 1305–1314.
66. Genkinger JM, Spiegelman D, Anderson KE et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer 2011; 129: 1708–1717.
67. Rimm EB, Stampfer MJ, Colditz GA et al. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990; 1: 466–473.
68. Weaver TW, Kushi LH, McGovern PG et al. Validation study of self-reported measures of fat distribution. Int J Obes Relat Metab Disord 1996; 20: 644–650.