Cancer incidence in relation to body fatness among 0.5 million men and women: findings from the China Kadoorie Biobank

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Abbreviations:

CKB: China Kadoorie Biobank; BMI: body-mass index; BFP: body fat percentage; WC: waist circumference; WHR: waist-to-hip ratio; HR: hazard ratio; MET: metabolic equivalent of task; HBV: hepatitis B virus; OSCC: oesophageal squamous cell carcinoma; OAC: oesophageal adenocarcinoma

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What's new

High BMI has been associated with an increased risk of several cancers. Evidence relating body fatness to risk of major cancers in China is lacking. In this large prospective cohort study in China, either high or low BMI contributes to the incidence of different types of cancers in China. The performance of different anthropometric measures was consistent with that of BMI, supporting measures of maintaining healthy body fatness to reduce cancer risk in Chinese population.

Abstract

High body-mass index (BMI) has been associated with an increased risk of several cancers. Evidence relating body fatness, especially based on different anthropometric measures, to risk of major cancers in China from prospective cohort studies is lacking. The prospective China Kadoorie Biobank (CKB) study recruited 0.5 million adults aged 30-79 years from 10 diverse areas across China during 2004-2008, recording 21,474 incident cancers during 8.95 years of follow-up. BMI, body fat percentage (BFP), waist circumference (WC), and waist-to-hip ratio (WHR) were measured at baseline. We assessed the associations of body fatness with 15 major cancers by calculating Cox regression yielded adjusted hazard ratios (HRs). Each 5 kg/m^2 increase in BMI was associated with an increased risk of endometrial (HR, 2.01; 95% CI, 1.72 to 2.35), postmenopausal breast (HR, 1.29; 95% CI, 1.18 to 1.40), colorectal (HR, 1.17; 95% CI, 1.10 to 1.25) and cervical (HR, 1.15; 95% CI, 1.03 to1.29) cancer, whereas it was associated with a reduced risk of oesophageal (HR, 0.73; 95% CI, 0.67 to 0.79), lung (HR, 0.78; 95% CI, 0.74 to 0.82), liver (HR, 0.85; 95% CI, 0.79 to 0.92), and gastric (HR, 0.88; 95% CI, 0.82 to 0.94) cancer. Significant linear trends of BMI-cancer associations were observed, excluding for lung, gastric and cervical cancer (both overall and non-linear $P<0.05$). The relation between BFP, WC and WHR and the above cancers was similar to that of BMI. Our study indicates that either high or low body fatness contributes to the incidence of different types of cancer in China.

Introduction

Excess body fatness is a major global health challenge. The prevalence of overweight and obesity has risen substantially worldwide over the past three decades [1]. During the same period, China has also experienced an increasing trend in the prevalence of overweight and obesity as a result of socioeconomic development and dramatic lifestyle changes; however, underweight remains prevalent in certain areas. Recent report showed that the prevalence of adult overweight and obesity in China were 22.8% and 7.1% in 2002, which increased to 30.1% and 11.9% respectively in 2012 [2]. The equivalent estimate of underweight decreased from 8.5 to 6.0%, but it was still higher than in most developed countries [2, 3]. It is important to evaluate the influence of body fatness on major diseases, including cancer, in China.

Previous studies have established associations between body-mass index (BMI, a measure of overall body fatness) and several cancers [4-6], but the evidence is mainly limited to Caucasians. BMI may vary in different populations [7], and lifestyles and cancer patterns are substantially different between populations, all of which can lead to different BMI-cancer associations. However, to date, the direction and magnitude of the association between BMI and cancer has rarely been evaluated in prospective studies of Chinese populations. The relationships between BMI and the risk of cancer incidence therefore remain largely unknown in China. Although BMI is a widely used measure of body fatness, it depends only on height and weight and has limitations in reflecting adipose tissue and muscle mass [8]. For a given BMI, East Asians generally have a 3-5% higher body fat percentage (BFP) than Europeans [9].

In this present study, we aimed to examine the relationship between body fatness, with different anthropometric measures, and cancer incidence for overall cancer and for 15 common cancer sites in a Chinese population with longitudinal data from the China Kadoorie Biobank (CKB).

Methods

Study population

The CKB is a large, prospective cohort study, and the study design, methods, and ethics have been described elsewhere [10, 11]. In brief, a total of 512,891 adults aged 30-79 years were recruited from 10 geographically diverse areas in China between June 2004 and July 2008 at baseline. The study areas (5 urban and 5 rural) were chosen to cover a range of socioeconomic statuses, risk exposures and disease

patterns. Of the 512,891 participants, 4,529 were excluded because of (i) cancers diagnosed at baseline (n=2,577), (ii) incident cancers diagnosed during the first 12 months of follow-up (n=1,945), and (iii) missing information or extreme values on anthropometric measures of body fatness (n=7). As a result, 508,362 participants (208,247 men and 300,115 women) were included in the subsequent analysis. In addition, women who had had a hysterectomy (n=11,623) were excluded from analyses for cervical and endometrial cancer, and women who had had an oophorectomy (n=4,431) were excluded for analyses for ovarian cancer. All participants provided their written informed consent and consented to follow-up.

Assessment of anthropometric measurements

At recruitment, standing height, weight, waist circumference (WC), hip circumference and BFP were measured in local study clinics by trained health workers with the participants wearing light clothes and no shoes. Standing height was measured to the nearest 1 mm using a manufactured instrument. WC was measured to the nearest 1 mm at the narrowest part between the lowest ribs and the highest point of the iliac crest and hip circumference at the maximum width of the buttocks, using a soft non-stretchable tape. Weight and BFP were measured using a BMI composition analyzer (TANITA TBF-300GS). BMI was calculated as weight in kilograms divided by standing height in meters squared (kg/m^2), and waist-to-hip ratio (WHR) was calculated as WC divided by hip circumference.

Assessment of covariates

The participants were interviewed using laptop-based questionnaires at baseline to collect data on demographic and socioeconomic statuses, smoking and alcohol consumption, physical activity, self-reported medical history and reproductive history (in women). For the present study, participants who reported to have smoked at least one cigarette daily or their equivalent for at least six months were defined as current regular smokers, and those who drank alcohol at least once a week were defined as current regular drinkers. Physical activity was quantified with metabolic equivalent tasks (METs) based on the type, duration and intensity of self-reported physical activity and on the time spent on sedentary activity.

Ascertainment of outcomes

We ascertained vital status by means of linkage with the Disease Surveillance Points (DSP) system of the China CDC [12]. Information about incident cancers was collected through established chronic disease registries (for cancer, stroke, ischemic heart disease, and diabetes) in the study areas and the national health insurance (HI) claim databases. The HI databases recorded details of all hospitalized

events, coded examination and treatment procedures. About 95% of the study participants had been successfully linked to the HI databases in 2013. Linkage to the HI database was renewed annually [10, 13]. Suspicious diagnoses were further confirmed via active follow-up by visiting local committees or directly contacting the participants. The main outcomes were all cancer combined (International Classification of Diseases, Tenth Revision, (ICD-10): C00–C97) and 15 most common cancers in China (supplementary **Table S1**).

Based on previous evidence on different effects of BMI on breast cancer patients with menopausal status [5, 14], we conducted separate analyses with respect to female breast cancer, and we defined postmenopausal women as time-updated aged 50 years or older. For the overall cancer analysis, the first cancer event was counted. For the site-specific cancer analysis, participants first diagnosed with any cancer other than the cancer of interest during the follow-up period were censored at the date of diagnosis. Participants who were diagnosed at more than one cancer site (including sites not investigated here) at the same time were censored for any cancer site but were included in overall cancer analysis.

Statistical analysis

To relate anthropometric measures of body fatness with the risk of overall cancer and each cancer site of interest, a Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (95%CIs), with age as the underlying time scale. HRs were fitted with adjustment for education level, marital status, annual household income, alcohol consumption, smoking status and physical activity, and with stratification according to age at risk (in 5 year intervals), sex, and region (10 study sites). Test and graph on Schoenfeld residuals showed that the proportional hazards assumption was satisfied.

We initially considered BMI, BFP, WC and WHR in categories. BMI was classified into five categories: less than 18.5 kg/m^2, 18.5-21.9, 22.0-24.9, 25.0-29.9, and 30.0 or more. In the analysis, we chose the BMI category of 22.0-24.9 as the reference group. We defined participants with a BMI of 25.0-29.9 as “overweight” and participants with a BMI of 30.0 or more as “obesity”, in accordance with the WHO’s criteria. BFP, WC and WHR were classified into two categories as normal weight and the obesity, respectively [15-17]. The sex-specific cutoff points were 25% in men and 35% in women for BFP, 85cm in men and 80cm in women for WC, and 0.90 in men and 0.85 in women for WHR, respectively. The normal weight group was used as a reference category. Then, we fitted adjusted Cox

models, with four anthropometric measures as continuous linear terms separately, to evaluate the average effects per 5 kg/m^2 increase in BMI and per 1 standard deviation (SD) increase in BFP, WC and WHR on cancer risk. We also repeated the analyses separately for nonsmokers to control potential confounding.

Moreover, we assessed a potential non-linear relationship between BMI and site-specific cancers using a restricted cubic spline (RCS) analysis[18]. The number of knots, from 3 to 7, was determined according to Akaike's information criterion (AIC) to balance best fit and over fitting[19]. In this study, the knots were located at equal percentiles of BMI, BFP, WC and WHR. For each cancer type, we retained the same number of knots in the overall RCS models and subsequently models of modification effects of stratified variables. Subgroup analyses for selected cancer sites were performed to estimate the consistency of the relationship when appropriate, according to sex, area, age at risk, menopause status, smoking status, alcohol drinking status, infection with hepatitis B virus (HBV) or total physical activity. Modification effects of the stratified variables were evaluated, respectively, by the interaction terms with BMI spline variables, which were further examined using the likelihood test compared to the model without interaction terms.

We did several sensitivity analyses: extending the exclusion of incident cancers to the first three years of follow-up; additionally adjusting for occupation and family cancer history; additionally adjusting for histories of chronic hepatitis or cirrhosis, emphysema or bronchitis, tuberculosis and peptic ulcer; additionally defining menopause status using self-reported premenopausal at recruitment. All analyses were performed in SAS (version 9.4), and Fig.s were plotted in R (version 3.2.1).

Results

Baseline characteristics

A total of 508,362 participants in CKB were eligible for the present analysis, of whom the mean age at recruitment was 51.47 years; 59.04% of the participants were women, and 55.95% were from rural areas. Overall, the mean BMI was 23.66 (SD 3.38) kg/m^2; 31.11% of men and 34.24% of women were overweight or obesity (BMI≥25.0), in comparison, 4.41% of men and 4.26% of women were underweight (BMI<18.5). **Table 1** presents the means and percentages of baseline variates by BMI categories after adjustment for age, sex and region when appropriate. Participants with higher BMI were more likely to be women and live in urban areas, and urban men and women had higher BMIs than rural men and women. Compared to women, men had a higher WC and WHR, but had a lower

BFP both in rural and urban areas (supplementary **Table S2**). BMI, BFP, WC and WHR were positively correlated with one another with r values ranging from 0.26 to 0.83 (supplementary **Table S3**), but the distribution patterns based on sex and area were substantially different as the age increased (supplementary **Fig. S1**).

BMI and cancer incidence

During 4,554,445 person-years of follow-up (median: 8.95 years), there were 21,474 (4.22%) incident cancer patients, of whom 17,198 (3.38%) developed one of the 15 cancers of interest. **Fig. 1** shows the effect of BMI increase (per 5 kg/m^2) on cancer incidence after adjusting for potential confounders. There was a slightly inverse association of BMI with overall cancer incidence (adjust HR 0.97, 95% CI 0.94-0.99), but the association disappeared in nonsmokers.

A significant positive association with site-specific cancer incidence was observed for endometrial (adjust HR 2.01, 95% CI 1.72-2.35), postmenopausal breast (1.29, 1.18-1.40), colorectal (1.17, 1.10-1.25), and cervical cancer (1.15, 1.03-1.29), and there was an inverse association for oesophageal (0.73, 0.67-0.79), lung (0.78, 0.74-0.82), liver (0.85, 0.79-0.92) and gastric cancer (0.88, 0.82-0.94). No clear associations were found for the other seven cancer sites of interest, i.e., oral cavity, pancreatic, bladder, lymphoma, leukaemia, prostate, and ovarian.

As compared with participants with the reference group (BMI: 22.0-24.9kg/m^2), significant associations were observed for overweight (25.0-29.9kg/m^2) and obesity (≥30.0kg/m^2) participants with risk of endometrial (1.48, 1.10-1.98 for overweight and 3.54, 2.41-5.20 for obesity, respectively), postmenopausal breast (1.15, 1.00-1.32 and 1.60, 1.29-1.99) and colorectal cancer (1.13, 1.02-1.26 and 1.28, 1.06-1.55). Significant associations were observed for lower BMI (18.5-21.9 kg/m^2) and underweight (<18.5kg/m^2) participants with risk of oesophageal (1.14, 1.01-1.28 for lower BMI and 1.62, 1.31-1.99 for underweight, respectively), lung (1.11, 1.02-1.20 and 1.53, 1.35-1.74) and liver cancer (1.18, 1.05-1.32 and 1.33, 1.08-1.62). Also, an increased risk of gastric cancer (1.47, 1.22-1.77) was observed in underweight participants (**Table 2**).

Fig. 2 shows the estimated non-linear relationship between BMI and all site-specific cancers. Linear trends were obvious for the positive associations with endometrium, postmenopausal breast and colorectal cancer, and for the inverse associations with oesophageal and liver cancer (overall $P<0.05$ and non-linear $P>0.05$). However, a non-linear association was observed for lung, gastric and cervical cancer (both overall and non-linear $P<0.05$). A peaked pattern was observed for cervical cancer with a

peak risk at BMI 24 kg/m^2 (1.48, 1.11-1.99 for BMI<24, and 0.94, 0.73-1.21 for BMI >24), which appears unstable considering the association results in BMI categories (**Table 2**). A similar pattern was also identified for premenopausal breast cancer.

Subgroups and sensitivity analyses

To exclude the potentially confounding effect from smoking, we restricted the analysis in nonsmokers assuming a linear effect of per 5 kg/m^2 in BMI (**Fig. 1**), and found consistently positive associations for endometrial, postmenopausal breast, colorectal and cervical cancer, and inverse associations for oesophageal, lung, liver and gastric cancer. For the above eight cancers, the potential effect modification for each BMI-cancer association was further assessed by refitting non-linear models stratified by sex, area, age at risk, smoking status, alcohol drinking status, total physical activity and menopausal status (supplementary **Fig. S2 through S9**). BMI was inversely associated with oesophageal and lung cancer risk regardless of stratified variables, although the effect was both attenuated in women (0.80, 0.71-0.91 and 0.83, 0.77-0.89, respectively), which may suggest an effect modification driven by smoking because 97.64% women were nonsmokers. The inverse association with liver cancer was significant in rural areas (0.77, 0.70-0.85) rather than urban areas. Moreover, BMI was inversely associated with liver cancer risk in participants without chronic HBV infection (0.88, 0.80-0.96) (**Fig. 3**), which could also exclude potential confounders due to prevalent HBV infection in China. For female cancers, the difference of association effect was also evaluated by menopausal status (supplementary **Fig. S10**). In addition to the expected positive association for postmenopausal breast cancer, positive associations were also observed for postmenopausal cervical (1.21, 1.05-1.38) and premenopausal ovarian cancer (1.70, 1.19 to 2.42). There was no obvious evidence regarding effect modification for the associations of gastric and colorectal cancer risk with BMI (supplementary **Fig. S3 and S4**).

In the sensitivity analyses, the association of BMI with the risk of cancer incidence did not change appreciably with additional adjustment for occupation and cancer family history; or additionally adjusting for histories of chronic hepatitis or cirrhosis, emphysema or bronchitis, tuberculosis and peptic ulcer; or using self-reported menopause status at recruitment instead of time-updated age≥50y (data not shown). Nor did the results change materially when we extended the exclusion to the first three years of follow up (supplementary **Table S4**).

Other anthropometric measures and cancer incidence

The linear effects of per SD increases in BFP, WC and WHR on cancer incidence were further assessed. BFP, WC and WHR showed consistent positive associations with endometrial, postmenopausal breast, colorectal and cervical cancer, and inverse associations with oesophageal, lung, liver and gastric cancer, although the WHR were not significantly associated with decreased risk of lung, liver and gastric cancer. These associations remained stable in nonsmokers (**Fig. 1**). After divided into two groups, as compared with participants with low levels of BFP, WC or WHR, those with high levels showed increased risk of endometrial, postmenopausal breast and colorectal cancer. High levels of BFP and WC rather than WHR were significantly associated with decreased risk of oesophageal, gastric, liver and lung cancer, whereas high levels of WHR did with cervical cancer (supplementary **Table S5**).

Discussion

In this large prospective cohort study of 21,474 incident cancers among 508,362 participants in a Chinese population, we found that body fatness was associated with eight of the 15 examined site-specific cancers, after adjusting for potential confounders. Higher BMI was associated with an increased risk of endometrial, postmenopausal breast, colorectal and cervical cancer, and with a reduced risk of oesophageal, lung, liver and gastric cancer. The results from other anthropometric measures were largely in line with the reports from BMI. To our knowledge, this is the largest prospective study to provide a systematic, accurate association between body fatness and the risk of major cancers in a Chinese population.

Comparison with other studies and potential mechanism

In the current study, BMI was positively associated with endometrial, postmenopausal breast, colorectal and cervical cancer in a Chinese population, which was roughly consistent with previous findings in Caucasians [5, 14, 20, 21]. Similar effect sizes (per 5 kg/m^2 increase in BMI) between populations were observed for colorectal and cervical cancer, but a stronger effect was reported for endometrial (2.01, 1.72-2.35) and postmenopausal breast cancer (1.29, 1.18-1.40) in our study than the results from a recent review that concluded 19 cohort studies of endometrial cancer (1.59, 1.50-1.68) and 34 cohort studies of postmenopausal breast cancer (1.12, 1.08-1.16) [21]. In our study, a higher BMI was associated with an increased risk of cervical cancer in postmenopausal women, rather than premenopausal women. This evidence, in combination with the association difference between premenopausal and postmenopausal breast cancer, further supported the notion that altered sex hormone metabolism might account for the association between BMI and female cancers [21].

We found inverse associations of BMI with the risk of oesophageal, lung, liver and gastric cancer. Potential confounders, such as smoking and chronic diseases, may result in lower BMI and drive an inverse association of BMI with cancer risk. However, the above inverse associations persisted in the absence of smoking and after controlling other potential confounders, or considering the other anthropometric measures in our study, or after excluding the first three years of follow up. For lung cancer, our finding of inverse association is consistent with the majority reports in Western or Asian populations [5, 14, 22]. This was interpreted as confounding or residual confounding by cigarette smoking, but our data did not support this explanation. We repeated the analyses in non-smokers, and found that the effect of BMI did not materially change after exclusion of smokers. However, the potential for residual confounding could not be fully excluded as the smoking status was self-reported. There was also the possibility of cofounding by the amount smoked and the degree of inhalation. Of particular interest, for cancer on sites of oesophagus, liver and gastric, our study provided roughly contrary associations as compared with results from Western populations. The IARC has reported that there is sufficient evidence that the absence of excess body fatness lowers the risk of oesophageal adenocarcinoma (OAC), gastric cardia and liver cancer [4]. In China, oesophageal squamous cell carcinoma (OSCC) is the predominant subtype, in contrast to OAC that is overwhelmingly found in Western populations. The former is mainly due to poor nutrition, excessive alcohol consumption, and smoking, and the latter is often affected by antecedent Barrett oesophagus [23, 24]. Similarly, instead of cardia adenocarcinoma with an increasing incidence in Western populations, most gastric cancers are of the non-cardia type in China, for which helicobacter pylori infection, smoking and salted foods are main risk factors [25]. HBV infection is a predominant risk factor in China, which is a high-risk area containing approximately 50% of new liver cancers and deaths around the world; however, in developed countries, obesity, type 2 diabetes, heavy alcohol consumption, and smoking are the main risk factors, resulting in an increasing incidence of liver cancer in the past decades [26]. Given that a higher BMI was also associated with reduced liver cancer in subjects without HBV infection, the inverse association could not be driven by HBV infection. Nevertheless, evidence of non-linearity was found between BMI and cancers of lung and gastric, although there was no significant threshold effect. Few studies reported nonlinear relationship and effect modifications between BMI and different cancer sites, which means our results were incomparable to other studies to some extent. Further studies are

needed to clarify whether the observed inverse associations are truly presented or misleading due to limited statistical power.

In this study, there were roughly no associations with BMI for seven cancer sites of interest, i.e., oral cavity, pancreatic, bladder, lymphoma, leukaemia, prostate and ovarian cancer. However, we found borderline positive associations for pancreatic (1.16, 1.00-1.36), premenopausal breast cancer (1.14, 1.00-1.31) and oral cavity cancer (0.82, 0.67-1.00) in the absence of smoking, in addition to a significant positive association for premenopausal ovarian cancer (1.70, 1.19-2.42).The IARC has concluded an increase in the risk of pancreatic and ovarian cancer in obese people compared with normal weight people [4]. Bhaskaran and colleagues reported an inverse association between BMI and oral cavity cancer, but the effect disappeared in never smokers [5]. Because the number of incident cancers from these sites was relatively small, our study might not have enough statistical power to find a reliable relationship between BMI and certain cancer sites.

BMI is widely used as an approximation of general adiposity, but it does not fully define body fat compartments at population levels. Given a BMI, individuals may have different body fat distributions and distinct metabolic and cardiovascular disease risks [27]. WC and WHR, which are anthropometric measures of central obesity, are stronger predictors than BMI for the risk of type 2 diabetes and cardiovascular disease [28, 29]. BFP is a direct measure of body fat composition and is associated with cardiovascular and metabolic diseases, independent of BMI [30-32]. Most studies have focused on the BMI-cancer association, but evidence of other anthropometric measures (particularly for BFP) of body fatness with cancer incidence is limited. In our study, WC, WHR and BFP showed generally similar association patterns to those of BMI in relation to the cancer risk at various sites, although the effect size varied with incremental changes in different measures. With the use of multiple anthropometric measures, our results may provide clues on different mechanisms of the adiposity-cancer association across different sites.

Strengths and limitations of this study

The main strengths of the present study are its prospective design and large sample size with 0.5 million participants from 10 geographically diverse areas across China, in which data on associations between body fatness and cancer risk remain limited. Through linkage to chronic disease registries and national HI claim databases, precise incident cancer cases could be collected. Although convincing evidence exists of an association between BMI and the risk of cancer incidence in Caucasians, few data

exist on the effect of other anthropometric measures of body fatness. In the present study, we examined the role of body fatness in the incidence of cancer with different anthropometric measures; the findings presented new evidence for certain cancer sites. Furthermore, we applied a restricted spline regression analysis to assess the non-linearity and effect modification, which makes another strength of our study.

Our study has certain limitations as well. First, because of the short follow-up period, there might be an inadequate sample size for some types of low-incidence cancer. Therefore, the association observed from certain cancers may be due to less statistical power. In this study, we were only able to left censor the data by one year, which might not be a sufficient length of time to exclude all underlying cancers, particularly those with a long latency period. However, the results changed little when we extended the exclusion to three years in the sensitivity analysis. Second, the anthropometric measures were recorded only at a single point during recruitment, without repeated measures during follow-up. Thus, no conclusions can be drawn regarding the changes in anthropometric measures over time. Third, given that the CKB is a population-based cohort, our analyses are insufficiently detailed to explore the potential difference among cancer subtypes.

Conclusion

In conclusion, in this large prospective study, we investigated the effect of body fatness on the cancer incidence in over half a million participants. In the Chinese population, high body fatness are associated with an increased risk of endometrial, postmenopausal breast, colorectal and cervical cancer, and low body fatness is associated with an increased risk of oesophageal, lung, liver and gastric cancer. Overall, either high or low body fatness may contribute to the cancer incidence in China. Heterogeneity in association with previous studies may suggest different patterns of body fatness and cancer incidence between Chinese and Caucasians. Further research is needed to determined the potential mechanism and verify our findings.

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Ethics statement
The CKB study was approved by the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK).

Conflict of interests
We declare that we have no conflict of interests.

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Figure Titles and Legends

Fig. 1. Adjusted hazard ratios for overall cancer and 15 site-specific cancers, from Cox models with BMI, BFP, WC and WHR fitted as linear effects

The hazard ratios (HRs) were presented per 5kg/m^2 increase in BMI and per 1 standard deviation (SD) increase in BFP, WC and WHR, with the size inversely propotional to the variance of the logarithm of HR. Horizontal lines represent 95% confidence intervals (CIs). Separate multivariable Cox regression models were fitted with the use of age as the underlying time scale for all study participants (n=508,362) and the nonsmokers (those not reaching the criteria of current regular smokers, n=373,783). Adjusted for level of education, marital status, household income, alcohol consumption, smoking status, physical activity, and stratified according to age at risk, sex, and region.

Fig. 2. Non-linear association between BMI and 15 site-specific cancers

The hazard ratios (HRs) were derived from restricted cubic spline regression with knots chosen by the Akaike information criterion, with adjustment for age at risk, sex, region, level of education, marital status, household income, alcohol consumption, smoking status, physical activity. The reference BMI for these plots (with HR fixed as 1.0) was 22 kg/m^2.

Fig. 3. Association between BMI and selected cancers with effect modification of potential confounders

Separate models were fitted for each cancer with a restricted cubic spline for BMI, adjusted for age at risk, sex, region, level of education, marital status, household income, alcohol consumption, smoking status, physical activity when appropriate. Modification effects of the stratified variables were evaluated, respectively, by the interaction terms with BMI spline variables. The *P* values for interaction were computed from likelihood tests compared to the model without interaction terms. The reference BMI for these plots (with HR fixed as 1.0) was 22kg/m^2. Estimated HRs per 5kg/m^2 were derived from linear Cox models.

P(int)= *P* values for interaction