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Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe

Running title: Obesity, body fat distribution, cancer risk

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ABSTRACT

Background: We evaluated the associations of anthropometric indicators of general obesity (body mass index, BMI), an established risk factor of various cancer, and body fat distribution (waist circumference, WC; hip circumference, HC; and waist-to-hip ratio, WHR), which may better reflect metabolic complications of obesity, with total obesity-related and site-specific (colorectal and postmenopausal breast) cancer incidence.

Methods: This is a meta-analysis of seven prospective cohort studies participating in the CHANCES consortium including 18,668 men and 24,751 women with a mean age of 62 and 63 years respectively. Harmonized individual participant data from all seven cohorts were analysed separately and alternatively for each anthropometric indicator using multivariable Cox proportional hazards models.

Results: After a median follow-up period of 12 years, 1,656 first incident obesity-related cancers [defined as postmenopausal female breast, colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney] had occurred in men and women. In the meta-analysis of all studies, associations between indicators of adiposity, per standard deviation (SD) increment, and risk for all obesity-related cancers combined yielded the following summary hazard ratios: 1.11 (95 % CI 1.02-1.21) for BMI, 1.13 (95 % CI 1.04-1.23) for WC, 1.09 (95 % CI 0.98-1.21) for HC, and 1.15 (95 % CI 1.00-1.32) for WHR. Increases in risk for colorectal cancer were 16%, 21%, 15%, and 20%, respectively per SD of BMI, WC, HC, and WHR. Effect modification by hormone therapy (HT) use was observed for postmenopausal breast cancer ($P_{interaction}$<0.001), where never HT users showed an approximately 20% increased risk per SD of BMI, WC, and HC compared to ever users.

Conclusions: BMI, WC, HC, and WHR show comparable positive associations with obesity-related cancers combined and with colorectal cancer in older adults. For postmenopausal breast cancer we report evidence for effect modification by HT use.

Keywords: CHANCES consortium; Ageing; Cohort; Obesity; Body fat distribution, Cancer; Prevention
INTRODUCTION

The proportion of overweight (body mass index, BMI>25 kg/m²) or obese (BMI>30 kg/m²) adults worldwide increased substantially between 1980 and 2013 (NCD Risk Factor Collaboration, 2016), with parallel increases in children and adolescents (Ng et al, 2014). Obesity prevalence reaches its peak between age 55 and 60 years in men with ~25% being obese in high-income countries and about 5 years later in women with ~30% being obese (Ng et al, 2014). This may have substantial implications for risk of subsequent cancer development, particularly in older adults (60+ years) considering that they are the fastest growing demographic group in most high-income countries.

It is well established that a high BMI is associated with an increased risk of a large number of non-communicable diseases, including cancer. Excess body fatness, as defined by high BMI, has been convincingly linked to an increased risk of eleven different cancer types, including cancer of the oesophagus (adenocarcinoma), gastric cardia, colorectum (CRC, colorectal cancer), gallbladder, pancreas, liver, breast (postmenopausal), ovary, endometrium, kidney and prostate (advanced stage) (World Cancer Research Fund / American Institute for Cancer Research, 2007; Renehan et al, 2008; Bhaskaran et al, 2014). An up-dated IARC consensus review also judged the strength of evidence sufficient for thyroid, meningioma, and multiple myeloma (Lauby-Secretan et al, 2016). These cancers alone comprise about 50% of the total global burden of cancer (based on GLOBOCAN 2012 data) (Arnold et al, 2016b).

However, there are uncertainties with regard to how well BMI captures the complex biology underlying associations between adiposity and cancer risk (Renehan et al, 2015). This is relevant to the development of cancer prevention strategies because it is increasingly recognized that a proportion of overweight or obese individuals – as defined by a high BMI – might not be at an increased risk for metabolic complications of obesity and its consequences such as cancer (Renehan et al, 2015). Waist circumference (WC) and waist-to-hip ratio (WHR) are therefore often used in epidemiological and clinical settings as a means of quantifying body fat distribution indicating central adiposity (National Heart, Lung, 1998; Hu, 2008), and they are thought to be superior predictors of risk of cancer development, at least for the colon and postmenopausal breast (Moore et al, 2004; Pischon et al, 2006;
White et al, 2015). Moreover, a greater hip circumference (HC), after controlling for WC and/or BMI, may be associated with reduced risks of coronary heart disease, type 2 diabetes, and mortality (Heitmann & Lissner, 2011; Cameron et al, 2013), but its relation to cancer risk has been fully explored in only a few recent studies (Keimling et al, 2013; Steffen et al, 2015), where either no association was found for risk of colon cancer with and without adjustment for BMI (Keimling et al, 2013) or inverse associations with risk of oesophageal adenocarcinoma after adjustment for WC (Steffen et al, 2015). Strictly speaking, HC is not a measure of central adiposity, but of fat accumulated in the lower part of the body (such as the hips and thighs) (Hu, 2008). Together, the evidence that measures of body fat distribution or central adiposity are better predictors of cancer risk than BMI is inconsistent. Also, only a few prospective studies comparing different measures of adiposity were carried out in adults aged 60 years and above.

Our primary objective was to derive standardized risk estimates for anthropometric measures of general adiposity (BMI) and body fat distribution (WC, HC, and WHR) and their association with ‘obesity-related’ cancers combined (i.e. cancer sites with convincing evidence of a positive association with greater body fatness) as well as CRC and (postmenopausal) breast cancer in a large population of older adults from Europe. Secondary objectives were to examine the shape of the dose–response relationships and to evaluate potential effect modification by sex, smoking status, use of hormone therapy (HT), and interaction between measures of body fat distribution and general adiposity.

METHODS

Study population. The Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES) project (www.chancesfp7.eu) is a multi-country study which aims to harmonize data from ongoing prospective cohort studies in Europe and North-America (Boffetta et al, 2014).

The following CHANCES cohorts provided data for the current analysis: the study centers in Denmark, Greece, the Netherlands, and Spain of EPIC-Elderly, which is a subset of the European Prospective Investigation into Cancer and Nutrition (EPIC) project that consists of participants aged 60
years or older at recruitment; the Epidemiological Study on Chances for Prevention, Early Detection, and Optimized THERapy of Chronic Diseases at Old Age (ESTHER), a population-based cohort covering the entire federal state of Saarland in Germany, aged 50 or older at recruitment; the PRIME Belfast study, which is a cohort of male residents aged 50-60 years of Belfast and the surrounding area in the United Kingdom; and the Tromsø study, which recruited men and women in Norway between 1994 and 1995 (4th wave) aged 50-84 years. Other CHANCES cohorts either decided not to participate in this analysis or could not provide cancer incidence data. The participating cohorts’ key characteristics are summarized in Table 1. Additional information on the individual cohorts has been given previously (Boffetta et al, 2014). We followed similar inclusion and exclusion criteria, which are displayed in Figure 1, as in a companion paper on overweight duration and risk of cancer (Arnold et al, 2016a). Further to the exclusions shown in Figure 1, we excluded participants with an implausible BMI below 15 or above 45 kg/m² from the analysis.

All CHANCES cohort studies are conducted in accordance with the Declaration of Helsinki. For each study, investigators satisfied the local requirements for ethical research, including obtaining informed consent from participants.

Outcomes. Incident cancer cases were identified through linkage to cancer registries (EPIC Netherlands, EPIC Denmark, Tromsø) or through self-reports that were confirmed by medical records and/or pathology reports (ESTHER, PRIME Belfast) or both (EPIC Spain, EPIC Greece). All analyses were conducted for cancer sites with convincing evidence of a positive association with greater body fatness (World Cancer Research Fund / American Institute for Cancer Research, 2007; Renehan et al, 2008; Lauby-Secretan et al, 2016). We examined first invasive breast cancer (ICD-O-3 C50) at postmenopausal ages, CRC (C18-21), and the combination of the two in conjunction with ‘other obesity-related cancers’ that included cancer of the lower oesophagus (C15.5, as a proxy for oesophageal adenocarcinoma in the absence of histological data), gastric cardia (C16.0), liver (C22), gallbladder (C23), pancreas (C25), endometrium (C54), ovary (C56) and kidney (C64), together labeled as ‘obesity-
related cancers’. Advanced prostate cancer was not included because we lacked information on tumor stage. Also, thyroid, meningioma, and multiple myeloma (Lauby-Secretan et al, 2016) were not included due to very small numbers of incident cases and inconsistencies in the available data across cohorts. Small numbers precluded the possibility of performing separate analyses of each obesity-related cancer site.

**Anthropometric assessment.** In all cohorts except ESTHER, height and weight were measured by trained personnel at baseline. In the ESTHER cohort, height and weight were self-reported by the study participants.

Waist and hip circumference were measured by trained personnel in all cohorts except ESTHER, where these measures were not assessed; the narrowest torso circumference (natural waist) or midway between the lowest rib and iliac crest was used for the waist measurement, while the widest circumference or maximum circumference over the buttocks was used for the hip measurement. The majority of cohorts reported that participants were asked to remove any heavy outer garments (light clothing or underwear only allowed) for the anthropometric measurements. In ESTHER, data on WC or HC were not collected at baseline.

**Covariate assessment.** Age, sex, smoking status, physical activity, alcohol consumption, and HT use in women were collected in all cohorts following standardized procedures and *a posteriori* harmonized within the CHANCES project (Boffetta et al, 2014). All covariates except alcohol consumption (continuous, g/day) were modelled categorically: (daily) smoking status (never daily smoker; former daily smoker; current daily smoker; unknown), (vigorous) physical activity (yes; no; unknown) defined according to the CHANCES harmonization rules as ‘performing intense exercise at least once a week’, level of education attained (primary or less; more than primary but less than college or university; college or university; unknown), current use (or history) of HT in women (ever; never; unknown).
**Statistical analysis.** Cox proportional hazard models with age as the time metric were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the relation between four obesity indicators and the risk of developing (1) ‘obesity-related cancers’, (2) CRC, (3) postmenopausal breast cancer, and (4) ‘other obesity-related cancers’ in each of the included cohorts. All obesity indicators were treated as continuous covariates; BMI was examined as a measure of overall adiposity, whereas WC, HC, and WHR were examined as measures of body fat distribution. For comparability between the four obesity indicators, we calculated the HR and their CI per 1-standard deviation (SD) increment of each indicator (Keimling et al, 2013). The relationships between anthropometric measures were evaluated using Pearson correlation coefficients (Supplementary Table S1).

Subjects were censored at age of study exit (death, lost to follow-up, any cancer diagnosis other than cancers considered as outcomes in this study, and end of follow-up), whichever occurred first.

For all outcomes, three models with different sets of adjustments were fitted. Model 1 included each of the anthropometric measures alternatively, stratified by age (1-y categories) and sex, and adjusted for height (except the model for BMI). Model 2 (main model) extended Model 1 by further adjusting for smoking status, alcohol consumption, level of educational attainment, physical activity, and recruitment year. Missing values in any of the categorical covariates were included as a separate category. Model 3 was based as model 2, but with mutual adjustment for all anthropometric measures using residuals of WC, HC, and WHR (Roswall et al, 2014).

All Cox models were fitted for each study separately (EPIC-Elderly was sub-divided into study-centers/countries) giving a study-level risk per 1-SD increment and the results of models 2 and 3 were then combined using DerSimonian and Laird random-effect meta-analysis (Harris et al, 2008). The heterogeneity of associations across studies was expressed by $I^2$ (Higgins & Thompson, 2002).

The proportional hazard assumptions in the study-specific analysis were assessed by visual inspection of log-log plots and by statistical tests using Schoenfeld residuals. Because the proportional hazards were unlikely for sex and age, we stratified Cox models by sex and age (in 1-y categories).
Exclusion of individuals with missing data on smoking, education or physical activity gave virtually the same results.

To directly compare cancer risk discrimination between the four obesity indicators, we used respective predictions from Cox models (model 2, pooling all cohorts) to assess discrimination by Harrell’s C-index (Collaboration TFS, 2009).

For analyses addressing the impact of effect modification, we pooled all cohorts into one dataset, and additionally stratified all Cox models by study. To investigate potential non-linear dose-response associations between the four obesity indicators and cancer risks, we used three-knot restricted cubic spline models at Harrell’s default percentiles (i.e. 10th, 50th, and 90th) in combination with a Wald-type test to evaluate the linearity hypothesis (Orsini & Greenland, 2011).

We tested a priori for potential interactions between the four adiposity indicators and for effect modification of the studied associations by smoking status and HT use using likelihood ratio tests. Since Cox-models were stratified by sex and age, no formal tests for interaction by sex or age were performed.

All statistical tests were two-sided and P-values were considered statistically significant at the 0.05 level. All statistical analyses were performed using Stata 12.1 (College Station, Texas, USA).

RESULTS

In total, 43,419 participants were included in this study, with 1,656 obesity-related cancer cases occurring during a median follow-up time of 12 years, which ranged between 10.4 years in Germany (ESTHER) and 18.0 years in Northern Ireland (PRIME Belfast) (Table 1). Study participants were recruited between 1991 and 2003, with a mean age at study entry ranging from 54 years in Northern Ireland to 67 years in Greece (EPIC-Greece). The prevalence of obesity (BMI>30 kg/m²) at recruitment was lowest in Northern Ireland with 11% and highest in participants from Spain with 42%.

Meta-analysis of adiposity measures and risk of cancer. In the meta-analysis of all studies, BMI, WC, and WHR were significantly associated with an increased risk of ‘obesity-related cancers’; the HRs
per 1-SD increment in BMI, WC, and WHR were 1.11 (95% CI: 1.02-1.21), 1.13 (95% CI: 1.04-1.23), and 1.15 (95% CI: 1.00-1.32), respectively. For BMI, the risk was most pronounced in the PRIME Belfast study (HR=1.50, 95% CI: 1.08-2.07) and a statistically non-significant inverse association was observed in the EPIC-Spain cohort (HR=0.88, 95% CI: 0.74-1.04) (Figure 2). After adjusting for HC and WC (Model 3 – Supplementary Figure S1), the HR for EPIC-Spain per 1-SD increase in BMI changed to 1.14 (95% CI: 0.82-1.60) and heterogeneity across studies for BMI decreased from 59% ($P_{\text{heterogeneity}}=0.02$) to <1% ($P_{\text{heterogeneity}}=0.58$). Omitting EPIC-Spain from the meta-analysis also reduced heterogeneity for BMI (to 25%, $P_{\text{heterogeneity}}=0.25$) and for HC (61% to 7%, $P_{\text{heterogeneity}}=0.369$). HC was positively associated with risk of ‘obesity-related cancers’ with a comparable effect size (HR1-SD increase=1.09, 95% CI: 0.98-1.21) but did not reach formal statistical significance (Figure 2). Mutual adjustment for adiposity measures attenuated risk estimates for all measures of body fat distribution, i.e. WC, WHR, and HC. In contrast, the HR for BMI increased to 1.15 per 1-SD increment and remained statistically significant (95% CI: 1.09-1.22) (Model 3 – Figure S1).

For CRC, findings were more consistent across the four adiposity measures with little evidence for heterogeneity across studies (all $I^2<36\%$, all $P_{\text{heterogeneity}}>0.17$), although the risk estimates for EPIC-Spain followed a similar pattern as for ‘obesity-related cancers’ (Figure 3) including reduced heterogeneity after omitting EPIC-Spain (data not shown). Effect sizes for CRC were in general higher with strongest associations observed for WC (HR1-SD increase=1.21, 95% CI: 1.08-1.35) and the weakest for HC (HR1-SD increase=1.15, 95% CI: 1.01-1.32). After mutual adjustment for adiposity measures, only BMI remained a significant risk factor of CRC (HR1-SD increase=1.19, 95% CI: 1.08-1.31) (Figure S1).

For postmenopausal breast cancer, a significant positive association was observed with BMI but only after additional adjustment for HC and WC (model 3) with a HR per 1-SD increase in BMI of 1.15 (95% CI: 1.03-1.27) (Figure S1). Associations with other measures of adiposity were non-significant although effect sizes were comparable, except for WHR (Figure 4). In addition, heterogeneity across studies was high for relative risks associated with WHR ($I^2 = 66\%, P_{\text{heterogeneity}}=0.02$) and did not change after excluding EPIC-Spain.
WHR was strongest and most consistently associated with ‘other obesity-related cancers’ (i.e. lower oesophagus, gastric cardia, liver, gallbladder, pancreas, endometrium, ovary, and kidney) with a HR per 1-SD increase of 1.20 (95% CI: 1.04-1.38) (Figure 5). All other obesity-measures were non-significant. After mutual adjustment for adiposity measures, WC was also independently associated with ‘other obesity-related cancers’ (HR_{1-SD increase}=1.15, 95% CI: 1.03-1.28) (Figure S1), while the association with WHR was marginally attenuated.

All estimates for the association between the four adiposity measures by cancer site and cohort, and the pooled estimates for the different models are presented in Supplementary Table S2.

Dose-response associations. After pooling all cohorts into one dataset, clear linear dose-response associations were found between all adiposity measures and ‘obesity-related cancers’, except for WHR ($P_{\text{non-linear}}=0.02$), where an increased cancer risk became apparent only at values >0.96 of the WHR (Supplementary Figure S2). For CRC, linear dose-response associations were observed for all four adiposity measures (Figure S2). For postmenopausal breast and ‘other obesity-related cancers’, dose-response relationships were inconsistent across the four obesity measures and linearity largely statistically insignificant (Supplementary Figure S3). These findings were confirmed when analyzing BMI and WC in pre-defined categories (Supplementary Table S6).

Direct comparisons between anthropometric indicators. C-indices for WC, HC, and WHR were marginally and non-significantly lower than for BMI in predicting risk of ‘obesity-related cancers’, CRC, postmenopausal breast cancer (range of C-index differences to BMI: -0.01 to -0.02) and vice versa for ‘other obesity-related cancers’ (range of C-index differences to BMI: 0.02 to 0.03) (Table 2). Compared to a null model including all confounding variables but none of the four anthropometric indicators, adding BMI, WC, HC, and WHR separately or jointly resulted in virtually similar model fit as evaluated by AIC (Table 2).
Effect modification by sex, smoking, HT use, and weight status. After stratification by sex, the risks for ‘obesity-related cancers’ associated with BMI and WC were comparable between men and women (Supplementary Table S3). However, HC yielded higher risk estimates in women for ‘obesity-related cancers’ and CRC. On the other hand, WHR yielded higher risk estimates in men compared to women for ‘obesity-related cancers’, CRC, and ‘other obesity-related cancers’. Some of these sex-specific differences became more pronounced or only apparent after mutual adjustment for adiposity measures (Model 3) (Table S3).

Some variability in risk estimates was observed across smoking categories (Supplementary Table S4). However, formal tests for effect modification were only significant for associations between HC and CRC \( (P_{\text{interaction}}=0.02) \) with a significantly increased risk observed in never smokers \( (HR_{1-SD \text{ increase}}=1.33, 95\% \text{ CI}: 1.16-1.54) \).

For postmenopausal breast cancer, significantly increased risks were observed in women who never used HT, with similar effect sizes of ~20% increased risk per 1-SD increase of BMI, WC, and HC \( (P_{\text{interaction}}<0.001) \) (Model 2, Supplementary Table S5).

No significant interactions between measures of body fat distribution (i.e. WC, HC, and WHR) and World Health Organizations’ BMI categories (normal weight: BMI <25 kg/m², overweight: BMI ≥25 to <30 kg/m², obesity: BMI ≥30 kg/m²) in relation to ‘obesity-related cancers’ and CRC or postmenopausal breast cancer were observed (data not shown). A borderline significant interaction for associations between WC and CRC across categories of BMI was observed \( (P_{\text{interaction}}=0.07) \) showing a significantly increased risk of CRC \( (HR_{1-SD \text{ increase}}=1.52, 95\% \text{ CI}: 1.20-1.92) \) in the overweight category.

**DISCUSSION**

In this pooled analysis of seven prospective cohort studies, we observed increased risks of ‘obesity-related cancers’, overall and of CRC and postmenopausal breast cancer associated with equivalent increments of general adiposity (BMI) and measures of body fat distribution (WC, HC, and WHR). Relative risk estimates were comparable across the different adiposity indices. For
postmenopausal breast cancer, there was indication that increased risks were confined to women who
never used HT. When mutually adjusting for all four anthropometric measures, which may be linked to
different underlying biological mechanisms, BMI appeared to be an independent risk factor of ‘obesity-
related cancers’, CRC, and postmenopausal breast cancer. In contrast, WC and WHR appeared to be
independent risk factors of ‘other obesity-related cancers’, which we could not analyse separately due to
low number of cases. To our knowledge, this is the first study of older adults to comprehensively compare
anthropometric measures of general adiposity and body fat distribution, to examine and quantify the
respective independent effects of these measures and to examine the shape of the dose–response
relationship for cancers known to be obesity-related.

Our analysis does not corroborate the hypothesis that central adiposity is a superior predictor of
CRC or postmenopausal breast cancer among older adults, as proposed by some previous studies (Pischon
et al, 2006; Stolzenberg-Solomon et al, 2013; White et al, 2015). In contrast, and in line with our results,
is an analysis of the NIH-AARP Diet and Health Study, where BMI, WC, and WHR were found to be
equally discriminatory for colon cancer risk (Keimling et al, 2013). HC was not associated with risk of
colon cancer in Keimling et al., while in our analysis HC virtually mirrored results for BMI, albeit effect
sizes were slightly lower as compared to BMI. HC in disease models that do not account for BMI and/or
WC is probably more indicative of general adiposity rather than an indicator of fat accumulation in the
lower extremities reflected by a high correlation between HC and BMI (Pearson correlation ~0.8 in our
data). Mutual adjustment of obesity indicators may reduce heterogeneity across studies as observed in our
data. This could indicate that BMI does not capture general adiposity equally well in all White Caucasians
and that holding WC and HC constant, improves the interpretation of BMI as a measure of general
adiposity.

Furthermore, in the Cancer Prevention Study-II Nutrition Cohort, positive associations between
WC and BMI and postmenopausal breast cancer risk were reported, but only the association with BMI
remained significant after mutual adjustment (Gaudet et al, 2014).
For postmenopausal breast cancer, early results from the Iowa Women Health Study suggested a statistically significant multiplicative interaction between BMI and WHR (Folsom et al., 2000). However, in subsequent reports that specifically tested interactions between BMI and indicators of central adiposity in relation to risk of CRC (Keimling et al., 2013) and breast cancer (Gaudet et al., 2015), no statistically significant associations were found. Our findings are in line with these more recent reports in that we did not find statistically significant multiplicative interactions between BMI and any of the three measures of body fat distribution.

For most of the cancer sites that we grouped into ‘other obesity-related cancers’ due to the small number of cases, previous studies reported somewhat stronger associations with regard to measures of central adiposity as compared to BMI, which is in line with our findings. For example, in the meta-analysis of Aune et al. on pancreatic cancer, WHR yielded an overall RR of 1.19 (95% CI: 1.09-1.31), while that for BMI was 1.10 (95% CI: 1.07-1.14) (Aune et al., 2012). Slightly stronger associations for WC and WHR, as compared to BMI, were also reported in the most recent WCRF/AICR pooled analyses for advanced prostate cancer (World Cancer Research Fund / American Institute for Cancer Research., 2014). We were not able to include prostate cancer in our analysis because of lack of data by stage.

In an analysis using data from the large EPIC prospective cohort, we reported previously that abdominal obesity, rather than general obesity, is a risk factor for the development of oesophageal adenocarcinoma and gastric cardia cancer (Steffen et al., 2015). In the prospective NIH-AARP cohort both overall adiposity (BMI) and abdominal adiposity (WC, WHR) were associated with a higher risk of oesophageal adenocarcinoma, but only BMI was associated with a higher risk of gastric cardia adenocarcinoma (O’Doherty et al., 2012). In an updated WCRF/AICR meta-analysis, BMI was more strongly associated with an increased risk of endometrial cancer compared to WC or WHR, although WC was also associated with an increased risk (Aune et al., 2015b). Similarly, an increased risk of ovarian cancer was reported with greater BMI and a marginally significant positive association with WC, but no association was found for HC or WHR (Aune et al., 2015a). We are not aware of studies investigating the role of body fat distribution and risk of cancers of the liver and gallbladder. The evidence with regard to
BMI was judged convincing for both of these cancer sites by the most recent WCRF/AICR pooled analyses (World Cancer Research Fund / American Institute for Cancer Research, 2015a, 2015b). For these last two cancer sites, further assessment of the impact of body fat distribution in future studies is warranted.

Although WC and WHR (and HC as noted above) have been interpreted as measures of body fat distribution, they may well also be markers of general adiposity (Anderson et al, 2014). In the current study, we saw that these measures have associations with cancer that are similar to those for BMI, but mostly when used in separate models. However, few studies have conducted mutual adjustments between BMI and measures of body fat distribution to try to clarify their independent roles. This is a limitation, which needs further assessment in future studies because it may provide insight into the biologic mechanisms underlying observed associations between adiposity and cancer risk (Keimling et al, 2013). Ideally, for mutual adjustment of BMI and measures of body fat distribution, residuals of measures of WC and/or HC should be used in order to retain the interpretability of BMI as an indicator of general adiposity and to avoid potential problems of multi-collinearity. Otherwise, BMI is not easily interpretable or becomes an indicator of muscularity rather than adiposity (Hu, 2008). It is also of note that WC, HC, and WHR have larger measurement errors compared with measurement of BMI, which may affect the reliability of respective risk estimates and calls for additional caution when comparing results between these indicators.

Links between greater adiposity and increased risk of many cancers are biologically plausible considering that obesity is related to a vast array of metabolic and physiological dysfunctions (Park et al, 2014). A number of these altered processes have specifically been implicated in cancer development; notably (1) abnormalities of insulin resistance and the IGF-I system; described as the insulin-IGF-I-insulin pathway, which may promote tumor development at many anatomic sites (Park et al, 2014; Renehan et al, 2015); 2) the impact of adiposity on the biosynthesis and bioavailability of endogenous sex steroids (e.g., oestradiol) which applies predominantly, but not exclusively, to postmenopausal breast, endometrial and ovarian cancers (Park et al, 2014; Renehan et al, 2015); our findings that obesity-
associated risk of postmenopausal breast cancer was strongest in women, who never used HT support that
hypothesis 3) obesity induced low-grade chronic systemic inflammation; and 4) alterations in the levels of
adipocyte-derived factors, known as adipokines (Lee et al, 2015). All of these proposed pathways have
been extensively investigated in mechanistic studies and tested in epidemiological settings. For example,
adiponectin, one of the most abundant adipokines, has been shown to be a key mediator in the
development of several types of obesity-related cancers including endometrial, breast, advanced prostate,
CRC, renal, and pancreatic (Dalamaga et al, 2012). Unlike most of the other adipose tissue derived
adipokines, serum adiponectin is reduced in obesity and correlates inversely with BMI, WC, HC, and
WHR, independently of age and menopausal status (Dalamaga et al, 2012). Migrating adipose progenitor
cells, which can be found in high concentration in white adipose tissue and may acquire a tumor-
promoting function, and the gut microbiome are two emerging mechanistic hypotheses linking obesity
with cancer risk (Renehan et al, 2015).

Our study has some limitations that may affect the interpretation of the results. Despite the
pooling of seven cohorts, we were not able to compare adiposity measures across all anatomical cancer
sites with strong evidence of an association with obesity because of low numbers of cases. These cancer
sites were therefore combined in ‘other obesity-related cancers’. For this reason, we could not investigate
whether one or several of these cancers may have driven the observed associations with WC and WHR.
Also related to the low number of cases, we were not able to sub-divide CRC in its anatomical sub-sites –
knowing that effects sizes are more pronounced for cancers of the colon as compared to the rectum
(World Cancer Research Fund / American Institute for Cancer Research., 2011) – or to sub-divide breast
cancer by receptor status. However, associations with BMI appear to be unrelated to receptor status in
postmenopausal women who have never used HT (Renehan et al, 2015).

Further limitations of our study are related to differences in study design between cohorts,
including differences in length of follow-up and assessment of several covariates. In order to harmonize
the data and variable definitions across cohorts, some covariates such as physical activity were only
available in binary form (yes/no). Despite adjustment for the main confounding factors, namely smoking
and physical activity, we cannot rule out confounding by other unmeasured factors, most importantly reproductive factors and diet. As these were not consistently available from all cohorts, we were not able to take these into account in our analyses. However, we don’t expect risk estimates being noticeably confounded by diet as has been shown previously (Renehan et al., 2012). In the ESTHER study, BMI based on self-reported height and weight was the only adiposity indicator available. Although self-reported BMI may grossly under-estimate prevalence of adiposity at the population level, ranking of individuals according to their BMI is less affected (Hu, 2008). Furthermore, study-specific risk estimates for ESTHER were consistent with the other cohorts and the summary estimates; excluding ESTHER from the meta-analysis had virtually no effect on the summary estimates (data not shown). Keeping ESTHER in our analysis also facilitates comparison of results with our companion paper, where we investigated the impact of overweight duration on obesity-related cancers (Arnold et al., 2016a). Finally, we did not a priori stratify our analysis by sex, mainly due to sample size considerations. However, in secondary analysis, largely similarly increased risks among men and women were observed for the investigated adiposity indicators (Table S3).

Strengths of our study include the availability of harmonized individual-level data for the estimation of cohort-specific risk estimates. This allowed us to use the same exposure definitions, disease endpoints, and multivariate models in all included studies. Our investigation included only prospective cohort studies, which reduces the potential of biases that are often reason for concern in retrospective studies, e.g. recall and selection bias. Individuals within each of our cohorts were largely White Caucasian, which adds further validity to our results because the effects of a given WC in a White population may be very different to the same WC in an Asian or African-American population. However, these potential ethic differences need to be evaluated in future studies. Further, we explored and compared, to our knowledge for the first time in a pooled analysis of cohorts consisting of middle-aged and older adults, non-linear associations between BMI, WC, HC, and WHR for cancer-sites known to be adiposity-related.
Conclusions

General adiposity as measured by BMI and body fat distribution as measured by WC, HC or WHR show comparable positive associations with obesity-related cancers combined, with CRC, and with postmenopausal breast cancer. For postmenopausal breast cancer there was evidence for effect modification by HT use which needs further exploration in other cohorts and populations. Avoiding abdominal fatness may also be important for specific cancer sites, but requires further investigation. Overall, our results underscore the importance of avoiding excess body fatness for cancer prevention irrespective of age and gender.
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Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe
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Text S1. Residual models.

Table S1. Correlation matrix of anthropometric measures in the CHANCES cohorts.

Table S2. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures for men and women, by cohort and cancer site.

Table S3. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures, by sex and cancer site.

Table S4. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures, by smoking status and cancer site.

Table S5. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident breast cancer (postmenopausal) per 1 standard deviation (SD) increment of anthropometric measures, by hormone therapy (HT) use.

Table S6. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per categories of Body mass index (BMI) and waist circumference (WC), by sex.

Figure S1. Random-effects meta-analysis of the association of different obesity-indicators per 1 standard deviation (SD) increment with (A) ‘obesity-related cancers’, (B) colorectal cancer, (C) postmenopausal breast cancer, and (D) ‘other obesity-related cancers’ after mutual adjustment for each obesity-indicator.

Figure S2. Association of different obesity indicators with ‘obesity-related cancers’ and with colorectal cancer, allowing for non-linear effects.

Figure S3. Association of different obesity indicators with postmenopausal breast cancer and with ‘other obesity-related cancers’, allowing for non-linear effects.

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Residual models.

Residuals of waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR) were calculated with separate sex-specific linear regression models with body mass index (BMI) as the independent variable and WC, HC, and WHR as the dependent variables. These residuals are by definition independent of BMI and they facilitate model fitting and interpretation, where BMI and measures of central adiposity are included in the same model (Hu, 2008; Roswall et al, 2014). In such models, BMI retains its interpretation as a measure of overall adiposity, while the residuals of WC and WHR retain their interpretation as measures of central adiposity that are independent of overall adiposity. On the other hand, relative risk associated with higher HC adjusted for BMI, WC, or both can be interpreted as an indicator of the combination of the bone structure of the pelvis (which is mostly genetically determined), gluteofemoral muscle mass, and gluteofemoral fat accumulation (Hu, 2008).
Table S1. Correlation matrix of anthropometric measures in the CHANCES cohorts.

|                  | BMI   | WC    | HC    | WHR   | Height | WC-residuals | HC-residuals | WHR-residuals |
|------------------|-------|-------|-------|-------|--------|--------------|--------------|---------------|
| **Men and Women**|       |       |       |       |        |              |              |               |
| BMI              | 1.00  |       |       |       |        |              |              |               |
| WC               | 0.75  | 1.00  |       |       |        |              |              |               |
| HC               | 0.82  | 0.61  | 1.00  |       |        |              |              |               |
| WHR              | 0.30  | 0.78  | -0.02 | 1.00  |        |              |              |               |
| Height           | -0.19 | 0.18  | -0.15 | 0.34  | 1.00   |              |              |               |
| WC-residuals     | 0.00  | 0.48  | 0.13  | 0.49  | 0.20   | 1.00         |              |               |
| HC-residuals     | 0.00  | 0.12  | 0.51  | -0.26 | 0.29   | 0.25         | 1.00         |               |
| WHR-residuals    | 0.00  | 0.37  | -0.21 | 0.64  | 0.00   | 0.77         | -0.40        | 1.00          |
| **Men**          |       |       |       |       |        |              |              |               |
| BMI              | 1.00  |       |       |       |        |              |              |               |
| WC               | 0.85  | 1.00  |       |       |        |              |              |               |
| HC               | 0.76  | 0.79  | 1.00  |       |        |              |              |               |
| WHR              | 0.53  | 0.74  | 0.18  | 1.00  |        |              |              |               |
| Height           | -0.16 | 0.00  | 0.09  | -0.10 | 1.00   |              |              |               |
| WC-residuals     | 0.00  | 0.51  | 0.24  | 0.55  | 0.34   | 1.00         |              |               |
| HC-residuals     | 0.00  | 0.20  | 0.60  | -0.33 | 0.42   | 0.40         | 1.00         |               |
| WHR-residuals    | 0.00  | 0.34  | -0.24 | 0.82  | 0.01   | 0.68         | -0.40        | 1.00          |
| **Women**        |       |       |       |       |        |              |              |               |
| BMI              | 1.00  |       |       |       |        |              |              |               |
| WC               | 0.84  | 1.00  |       |       |        |              |              |               |
| HC               | 0.87  | 0.78  | 1.00  |       |        |              |              |               |
| WHR              | 0.41  | 0.75  | 0.17  | 1.00  |        |              |              |               |
| Height           | -0.29 | -0.21 | -0.09 | -0.23 | 1.00   |              |              |               |
| WC-residuals     | 0.00  | 0.53  | 0.08  | 0.74  | 0.21   | 1.00         |              |               |
| HC-residuals     | 0.00  | 0.09  | 0.48  | -0.37 | 0.36   | 0.17         | 1.00         |               |
| WHR-residuals    | 0.00  | 0.44  | -0.20 | 0.90  | -0.01  | 0.82         | -0.41        | 1.00          |

All values are Pearson correlation coefficients.

Residuals of WC, HC, and WHR were calculated with separate sex-specific linear regression models with BMI as the independent variable and WC, HC, and WHR as the dependent variables in each of the three models; all models were adjusted for cohort.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.
Model 2: stratified for age (1-y categories), and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; in the pooled analysis, models were additionally stratified by cohort.

Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.

Note: Results of Model 1 are not shown due to space limitations, but results were similar to Model 2.

Abbreviations: BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio.

**Table S2.** Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures for men and women, by cohort and cancer site

|                | Obesity-related cancers* | Breast cancer | Colorectal cancer | Other obesity-related cancer5 |
|----------------|--------------------------|---------------|-----------------|-----------------------------|
|                | Model 2 | Model 3 | Model 2 | Model 3 | Model 2 | Model 3 | Model 2 | Model 3 | Model 2 | Model 3 | Model 2 | Model 3 |
| **Body mass index** |               |               |           |           |           |           |           |           |           |           |           |           |
| EPIC_DK        | 1.06 (0.96, 1.16) | 1.06 (0.96, 1.16) | 1.08 (0.99, 1.17) | 1.08 (0.99, 1.17) | 1.10 (0.97, 1.24) | 1.10 (0.97, 1.24) | 1.10 (0.97, 1.24) | 1.10 (0.97, 1.24) | 1.10 (0.97, 1.24) | 1.10 (0.97, 1.24) |
| **Waist circumference** |               |               |           |           |           |           |           |           |           |           |           |           |
| EPIC_DK        | 1.05 (0.95, 1.16) | 1.05 (0.95, 1.16) | 1.07 (0.98, 1.18) | 1.07 (0.98, 1.18) | 1.09 (0.99, 1.21) | 1.09 (0.99, 1.21) | 1.09 (0.99, 1.21) | 1.09 (0.99, 1.21) | 1.09 (0.99, 1.21) | 1.09 (0.99, 1.21) |
| **Hip circumference** |               |               |           |           |           |           |           |           |           |           |           |           |
| EPIC_DK        | 1.04 (0.94, 1.14) | 1.04 (0.94, 1.14) | 1.06 (0.97, 1.17) | 1.06 (0.97, 1.17) | 1.08 (0.98, 1.19) | 1.08 (0.98, 1.19) | 1.08 (0.98, 1.19) | 1.08 (0.98, 1.19) | 1.08 (0.98, 1.19) | 1.08 (0.98, 1.19) |
| **Waist-to-hip ratio** |               |               |           |           |           |           |           |           |           |           |           |           |
| EPIC_DK        | 1.11 (1.05, 1.17) | 1.11 (1.05, 1.17) | 1.13 (1.09, 1.17) | 1.13 (1.09, 1.17) | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) | 1.14 (1.10, 1.18) |

* First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardiomyopathy, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

* Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum. 

* No data available on WC, HC, and WHR. 

* No breast cancer cases because men only.

Model 2: stratified for age (1-y categories), and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; in the pooled analysis, models were additionally stratified by cohort.

Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.

Note: Results of Model 1 are not shown due to space limitations, but results were similar to Model 2.
| Table S3. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1-standard deviation (SD) increment of anthropometric measures, by sex and cancer site |
| --- | --- | --- | --- | --- | --- | --- |
| | Model 1 | Model 2 | Model 3 |
| Cases | HR | 95% CI | Cases | HR | 95% CI | Cases | HR | 95% CI |
| MEN | | | | | | | | | |
| **Body mass index (1 SD=3.6 kg/m²)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 524 | 1.13 | 1.04 | 1.24 | 524 | 1.14 | 1.05 | 1.25 | 389 | 1.17 | 1.00 | 1.38 |
| Colorectal cancer | 318 | 1.13 | 1.01 | 1.26 | 318 | 1.16 | 1.01 | 1.33 | 243 | 1.15 | 0.98 | 1.34 |
| Other obesity-related cancers<sup>b</sup> | 206 | 1.14 | 0.99 | 1.31 | 206 | 1.15 | 1.01 | 1.33 | 146 | 1.10 | 0.85 | 1.43 |
| **Waist circumference (1 SD=10.1 cm)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 389 | 1.15 | 1.03 | 1.28 | 389 | 1.15 | 1.03 | 1.28 | 389 | 1.14 | 1.01 | 1.27 |
| Colorectal cancer | 243 | 1.13 | 0.98 | 1.29 | 243 | 1.15 | 0.98 | 1.36 | 243 | 1.06 | 0.90 | 1.25 |
| Other obesity-related cancers<sup>b</sup> | 146 | 1.20 | 1.01 | 1.42 | 146 | 1.19 | 1.00 | 1.42 | 146 | 1.31 | 1.09 | 1.56 |
| **Hip circumference (1 SD=7.2 cm)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 389 | 1.02 | 0.91 | 1.14 | 389 | 1.04 | 0.93 | 1.17 | 389 | 0.90 | 0.80 | 1.02 |
| Colorectal cancer | 243 | 1.04 | 0.90 | 1.20 | 243 | 1.07 | 0.89 | 1.28 | 243 | 0.91 | 0.78 | 1.06 |
| Other obesity-related cancers<sup>b</sup> | 146 | 1.01 | 0.84 | 1.21 | 146 | 1.03 | 0.85 | 1.24 | 146 | 0.90 | 0.74 | 1.09 |
| **Waist-to-hip ratio (1 SD=0.06)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 389 | 1.20 | 1.09 | 1.33 | 389 | 1.19 | 1.07 | 1.31 | 389 | 1.15 | 1.04 | 1.27 |
| Colorectal cancer | 243 | 1.18 | 1.03 | 1.35 | 243 | 1.21 | 0.99 | 1.47 | 243 | 1.09 | 0.94 | 1.27 |
| Other obesity-related cancers<sup>b</sup> | 146 | 1.28 | 1.10 | 1.50 | 146 | 1.26 | 1.07 | 1.48 | 146 | 1.25 | 1.08 | 1.45 |
| WOMEN | | | | | | | | | |
| **Body mass index (1 SD=4.6 kg/m²)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 1132 | 1.08 | 1.01 | 1.15 | 1132 | 1.10 | 1.03 | 1.17 | 867 | 1.07 | 1.00 | 1.16 |
| Colorectal cancer | 273 | 1.17 | 1.03 | 1.32 | 273 | 1.17 | 1.04 | 1.32 | 222 | 1.15 | 1.00 | 1.31 |
| Breast cancer | 555 | 1.09 | 0.99 | 1.19 | 555 | 1.12 | 1.02 | 1.22 | 499 | 1.10 | 0.99 | 1.23 |
| Other obesity-related cancers<sup>b</sup> | 304 | 0.99 | 0.87 | 1.12 | 304 | 1.00 | 0.88 | 1.13 | 236 | 1.16 | 0.89 | 1.50 |
| **Waist circumference (1 SD=11.6 cm)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 867 | 1.08 | 1.01 | 1.16 | 867 | 1.09 | 1.01 | 1.17 | 867 | 1.04 | 0.96 | 1.12 |
| Colorectal cancer | 222 | 1.23 | 1.07 | 1.42 | 222 | 1.24 | 1.07 | 1.44 | 222 | 1.13 | 0.98 | 1.29 |
| Breast cancer | 409 | 1.05 | 0.95 | 1.17 | 409 | 1.07 | 0.96 | 1.19 | 409 | 0.96 | 0.86 | 1.08 |
| Other obesity-related cancers<sup>b</sup> | 236 | 1.01 | 0.87 | 1.16 | 236 | 1.00 | 0.87 | 1.16 | 236 | 1.07 | 0.93 | 1.23 |
| **Hip circumference (1 SD=9.3 cm)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 867 | 1.08 | 1.00 | 1.16 | 867 | 1.09 | 1.01 | 1.17 | 867 | 1.04 | 0.96 | 1.13 |
| Colorectal cancer | 222 | 1.20 | 1.04 | 1.38 | 222 | 1.18 | 1.04 | 1.34 | 222 | 1.08 | 0.93 | 1.25 |
| Breast cancer | 409 | 1.09 | 0.99 | 1.21 | 409 | 1.11 | 1.00 | 1.24 | 409 | 1.05 | 0.94 | 1.18 |
| Other obesity-related cancers<sup>b</sup> | 236 | 0.95 | 0.82 | 1.09 | 236 | 0.96 | 0.83 | 1.10 | 236 | 0.98 | 0.84 | 1.13 |
| **Waist-to-hip ratio (1 SD=0.07)** | | | | | | | | | |
| Obesity-related cancers<sup>a</sup> | 867 | 1.04 | 0.97 | 1.12 | 867 | 1.04 | 0.97 | 1.12 | 867 | 1.01 | 0.94 | 1.09 |
| Colorectal cancer | 222 | 1.16 | 1.00 | 1.35 | 222 | 1.17 | 0.98 | 1.40 | 222 | 1.06 | 0.94 | 1.20 |
| Breast cancer | 409 | 0.98 | 0.89 | 1.09 | 409 | 0.98 | 0.89 | 1.1 | 409 | 0.95 | 0.85 | 1.05 |
| Other obesity-related cancers<sup>b</sup> | 236 | 1.08 | 0.94 | 1.23 | 236 | 1.06 | 0.9 | 1.2 | 236 | 1.07 | 0.94 | 1.22 |

<sup>a</sup> First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

<sup>b</sup> Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 1: stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for height.
Model 2: as model 1 and further adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/dl), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), and recruitment year.
Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the model for WHR was further adjusted for BMI using WHR-residuals.

Notes: no formal test for interaction by sex was performed because Cox models were stratified by sex to meet the proportionality of hazards assumption; SDs for anthropometric measure shown within brackets are the pooled average across all 7 cohorts by sex.
Table S4. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per 1 standard deviation (SD) increment of anthropometric measures, by smoking status and cancer site

|                          | Obesity-related cancers* | Breast cancer | Colorectal cancer | Other obesity-related cancersb |
|--------------------------|--------------------------|---------------|-------------------|-------------------------------|
|                          | Model 2                  | Model 3       | Model 2           | Model 3                       | Model 2 | Model 3 | Model 2 | Model 3 | Model 2 | Model 3 | Model 2 | Model 3 |
|                          | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     | HR           | 95% CI     |
| **Body mass index (1 SD=4.2 kg/m²)** |              |             |              |             |              |             |              |             |              |              |             |              |             |              |             |              |              |             |              |             |              |             |              |             |              |             |             |
| Current daily smoker     | 1.09 | 0.98 - 1.21 | 1.06 | 0.94 - 1.19 | 1.26 | 1.03 - 1.55 | 1.28 | 1.00 - 1.63 | 1.11 | 0.93 - 1.32 | 1.03 | 0.85 - 1.25 | 0.92 | 0.75 - 1.13 | 0.93 | 0.76 - 1.14 |
| Former daily smoker      | 1.10 | 1.00 - 1.20 | 1.08 | 0.97 - 1.21 | 1.02 | 0.85 - 1.22 | 1.05 | 0.85 - 1.28 | 1.17 | 1.01 - 1.35 | 1.16 | 0.97 - 1.38 | 1.13 | 0.94 - 1.37 | 1.08 | 0.87 - 1.33 |
| Never daily smoker       | 1.12 | 1.04 - 1.20 | 1.08 | 1.00 - 1.18 | 1.11 | 0.99 - 1.25 | 1.08 | 0.93 - 1.25 | 1.20 | 1.05 - 1.37 | 1.23 | 1.06 - 1.43 | 1.10 | 0.95 - 1.28 | 0.98 | 0.84 - 1.16 |
| **Waist circumference (1 SD=12.1 cm)** |              |             |              |             |              |             |              |             |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Current daily smoker     | 1.14 | 1.02 - 1.28 | 1.07 | 0.95 - 1.20 | 1.13 | 0.89 - 1.44 | 0.88 | 0.68 - 1.13 | 1.19 | 0.99 - 1.43 | 1.19 | 0.97 - 1.44 | 1.05 | 0.86 - 1.27 | 1.12 | 0.91 - 1.37 |
| Former daily smoker      | 1.09 | 0.98 - 1.22 | 1.00 | 0.89 - 1.11 | 0.97 | 0.79 - 1.19 | 0.87 | 0.72 - 1.07 | 1.14 | 0.96 - 1.35 | 0.94 | 0.79 - 1.12 | 1.23 | 1.01 - 1.50 | 1.25 | 1.03 - 1.53 |
| Never daily smoker       | 1.11 | 1.02 - 1.22 | 1.10 | 1.01 - 1.19 | 1.10 | 0.95 - 1.27 | 1.05 | 0.90 - 1.21 | 1.27 | 1.08 - 1.49 | 1.16 | 1.00 - 1.35 | 1.02 | 0.86 - 1.21 | 1.10 | 0.94 - 1.28 |
| **Hip circumference (1 SD=8.6 cm)** |              |             |              |             |              |             |              |             |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Current daily smoker     | 0.99 | 0.87 - 1.12 | 0.93 | 0.83 - 1.04 | 1.26 | 0.99 - 1.60 | 1.07 | 0.84 - 1.36 | 0.91 | 0.74 - 1.12 | 0.88 | 0.73 - 1.05 | 0.89 | 0.72 - 1.10 | 0.89 | 0.73 - 1.08 |
| Former daily smoker      | 1.04 | 0.93 - 1.16 | 0.95 | 0.86 - 1.06 | 1.02 | 0.84 - 1.24 | 0.97 | 0.80 - 1.17 | 1.08 | 0.90 - 1.29 | 0.92 | 0.78 - 1.09 | 1.03 | 0.84 - 1.28 | 0.95 | 0.78 - 1.16 |
| Never daily smoker       | 1.14 | 1.05 - 1.24 | 1.09 | 0.99 - 1.19 | 1.12 | 0.97 - 1.29 | 1.10 | 0.95 - 1.27 | 1.33 | 1.16 - 1.54 | 1.14 | 0.97 - 1.33 | 1.00 | 0.85 - 1.17 | 1.00 | 0.85 - 1.18 |
| **Waist-to-hip ratio (1 SD=0.1)** |              |             |              |             |              |             |              |             |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |              |
| Current daily smoker     | 1.22 | 1.08 - 1.37 | 1.09 | 0.99 - 1.21 | 0.96 | 0.76 - 1.21 | 0.87 | 0.68 - 1.10 | 1.36 | 1.13 - 1.64 | 1.22 | 1.04 - 1.42 | 1.19 | 0.98 - 1.46 | 1.14 | 0.96 - 1.35 |
| Former daily smoker      | 1.11 | 0.99 - 1.25 | 1.03 | 0.93 - 1.14 | 0.94 | 0.77 - 1.13 | 0.91 | 0.76 - 1.10 | 1.15 | 0.95 - 1.38 | 0.98 | 0.83 - 1.17 | 1.36 | 1.10 - 1.68 | 1.25 | 1.04 - 1.50 |
| Never daily smoker       | 1.04 | 0.94 - 1.16 | 1.04 | 0.96 - 1.13 | 1.03 | 0.89 - 1.19 | 1.00 | 0.87 - 1.16 | 1.08 | 0.89 - 1.29 | 1.05 | 0.90 - 1.22 | 1.08 | 0.89 - 1.32 | 1.07 | 0.92 - 1.25 |

*First primary cancers of the breast (postmenopausal), colorectum, lower esophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

**Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 2: stratified for age (1-y categories), sex, and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Model 3: as model 2, but models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.

All P-values for interaction (LRT test) > 0.10, except for HC vs. CRC in model 2 (P=0.02).

Note: SDs for anthropometric measure shown within brackets are the pooled average across all 7 cohorts and men and women combined.
Table S5. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident breast cancer (postmenopausal) per 1 standard deviation (SD) increment of anthropometric measures, by hormone therapy (HT) use.

| Cases | Model 2 | Model 3 |
|-------|---------|---------|
|       | HR  | 95% CI  | HR  | 95% CI |
| **Body mass index** (1 SD=4.6 kg/m²) |     |         |     |         |
| never HT user | 263 | 1.22    | 1.08 - 1.38 | 1.28 | 1.11 - 1.47 |
| ever HT user  | 245 | 0.99    | 0.86 - 1.14 | 0.91 | 0.76 - 1.10 |
| unknown      | 47  | 1.26    | 0.95 - 1.67 | 1.02 | 0.73 - 1.43 |
| **Waist circumference** (1 SD=11.6 cm) |     |         |     |         |
| never HT user | 205 | 1.21    | 1.05 - 1.40 | 0.95 | 0.81 - 1.11 |
| ever HT user  | 167 | 0.93    | 0.78 - 1.11 | 0.99 | 0.83 - 1.18 |
| unknown      | 37  | 1.00    | 0.71 - 1.41 | 1.01 | 0.75 - 1.35 |
| **Hip circumference** (1 SD=9.3 cm) |     |         |     |         |
| never HT user | 205 | 1.24    | 1.08 - 1.42 | 1.00 | 0.86 - 1.16 |
| ever HT user  | 167 | 0.96    | 0.80 - 1.14 | 1.08 | 0.91 - 1.28 |
| unknown      | 37  | 1.13    | 0.82 - 1.55 | 1.25 | 0.92 - 1.68 |
| **Waist-to-hip ratio** (1 SD=0.07) |     |         |     |         |
| never HT user | 205 | 1.06    | 0.91 - 1.23 | 0.96 | 0.83 - 1.12 |
| ever HT user  | 167 | 0.94    | 0.80 - 1.11 | 0.95 | 0.81 - 1.11 |
| unknown      | 37  | 0.89    | 0.64 - 1.24 | 0.91 | 0.67 - 1.24 |

Model 2: stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Model 3: as model 2, but models for BMI, WC, and HC mutually adjusted using WC- and HC-residuals; the models for WHR were further adjusted for BMI using WHR-residuals.

All P-values for interaction (LR test) <0.001.

Note: SDs for anthropometric measure shown within brackets are the pooled average across all cohorts in women.
Table S6. Hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of incident cancer per categories of Body mass index (BMI) and waist circumference (WC), by sex

| BMI categories | Obesity-related cancers | Breast cancer | Colorectal cancer | Other obesity-related cancers |
|---------------|-------------------------|---------------|-------------------|----------------------------|
| n | Cases | HR | 95 % CI | p-trend | Cases | HR | 95 % CI | p-trend | Cases | HR | 95 % CI | p-trend |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| MEN | | | | | | | | | | | | |
| <25 kg/m² | 5,192 | 127 | 1 (ref.) | 81 | 1 (ref.) | 46 | 1 (ref.) | | | | | |
| 25-29.9 kg/m² | 9,733 | 285 | 1.25 | 1.01 - 1.55 | 173 | 1.23 | 0.94 - 1.62 | 112 | 1.29 | 0.91 - 1.83 | | |
| >30 kg/m² | 3,743 | 112 | 1.36 | 1.04 - 1.78 | 64 | 1.33 | 0.94 - 1.88 | 11 | 1.44 | 0.94 - 1.88 | 0.095 |
| WC categories | | | | | | | | | | | | |
| <102 cm | 9,677 | 254 | 1 (ref.) | 170 | 1 (ref.) | 84 | 1 (ref.) | | | | | |
| >102 cm | 4,348 | 135 | 1.25 | 1.00 - 1.57 | 73 | 1.07 | 0.80 - 1.44 | 62 | 1.60 | 1.13 - 2.28 | | |

| WOMEN | | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| <25 kg/m² | 8,422 | 418 | 1 (ref.) | 207 | 1 (ref.) | 116 | 1 (ref.) | | | | | |
| 25-29.9 kg/m² | 9,888 | 442 | 1.02 | 0.89 - 1.17 | 224 | 1.11 | 0.92 - 1.35 | 116 | 1.02 | 0.77 - 1.36 | 116 | 0.86 | 0.66 - 1.13 | |
| >30 kg/m² | 6,441 | 272 | 1.17 | 1.00 - 1.39 | 124 | 1.22 | 0.96 - 1.55 | 76 | 1.44 | 1.04 - 2.00 | 72 | 0.90 | 0.65 - 1.24 | 0.517 |
| WC categories | | | | | | | | | | | | |
| <88 cm | 10,482 | 502 | 1 (ref.) | 249 | 1 (ref.) | 134 | 1 (ref.) | | | | | |
| >88 cm | 8,566 | 365 | 1.14 | 0.99 - 1.32 | 160 | 1.13 | 0.91 - 1.39 | 103 | 1.33 | 1.00 - 1.76 | 102 | 1.01 | 0.77 - 1.34 | |

*a* First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

*b* Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 2: stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Notes: BMI categories according to World Health Organization; category <25 kg/m² includes 47 men and 169 women with a BMI <18.5 kg/m², respectively; WC categories according to American Heart Association/National Heart, Lung and Blood Institute.
Figure S1. Random-effects meta-analysis of the association of different obesity-indicators per 1 standard deviation (SD) increment with (A) ‘obesity-related cancers’\(^a\), (B) colorectal cancer, (C) postmenopausal breast cancer, and (D) ‘other obesity-related cancers’\(^b\) after mutual adjustment for each obesity-indicator.

\(^a\) First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

\(^b\) Same as all obesity-related cancers but excluding first primary cancers of the breast and colorectum.

Model 3: stratified for age (1-y categories) and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; and models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; and the models for WHR were further adjusted for BMI using WHR-residuals.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.
Figure S1 continued. Random-effects meta-analysis of the association of different obesity-indicators per 1 standard deviation (SD) increment with (A) ‘obesity-related cancers’\textsuperscript{a}, (B) colorectal cancer, (C) postmenopausal breast cancer, and (D) ‘other obesity-related cancers’\textsuperscript{b} after mutual adjustment for each obesity-indicator.

\textsuperscript{a} First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

\textsuperscript{b} Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Model 3: stratified for age (1-y categories) and sex, and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height; and models for BMI, WC, and HC were mutually adjusted using WC- and HC-residuals; and the models for WHR were further adjusted for BMI using WHR-residuals.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.
Figure S2. Association of different obesity indicators with 'obesity-related cancers' and with colorectal cancer, allowing for non-linear effects.

First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

The figures show a 3-knot restricted cubic spline model at Harrell’s default percentiles (i.e. 10th [reference point], 50th, and 90th) allowing for non-linear effects and are stratified for age (3-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height. P-values are from Wald-test evaluating the linearity hypothesis.
Figure S3. Association of different obesity indicators with postmenopausal breast cancer and with ‘other obesity-related cancers’\(^a\), allowing for non-linear effects.

\(^a\) First primary cancers of the lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

The figures show a 3-knot restricted cubic spline model at Harrell’s default percentiles (i.e. 10\(^{th}\) [reference point], 50\(^{th}\), and 90\(^{th}\)) allowing for non-linear effects and are stratified for age (1-y categories) and cohort (pooled analysis), and adjusted for daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height. \(P\)-values are from Wald-test evaluating the linearity hypothesis.
N=40,663 available from EPIC-Elderly
N=9,949 available from ESTHER
N=2,745 available from PRIME Belfast
N=10,262 available from the Tromsø Study

N=63,619 Total available study participants

N=1,215 Excluded because of missing contact age or age at recontact

N=62,404 left for analysis

N=17,838 Excluded because of less than two valid BMI measurements during follow-up

N=44,566 left for analysis

N=1,147 Excluded because of cancer history/prevalent cancer

N=43,419 (68%) Included in main analysis

N=26,985 included from EPIC-Elderly
N=8,577 included from ESTHER
N=1,944 included from PRIME Belfast
N=5,913 included from the Tromsø Study

N=62,404 left for analysis

N=17,838 Excluded because of less than two valid BMI measurements during follow-up

N=44,566 left for analysis

N=1,147 Excluded because of cancer history/prevalent cancer

N=43,419 (68%) Included in main analysis

N=26,985 included from EPIC-Elderly
N=8,577 included from ESTHER
N=1,944 included from PRIME Belfast
N=5,913 included from the Tromsø Study

N=62,404 left for analysis

N=17,838 Excluded because of less than two valid BMI measurements during follow-up

N=44,566 left for analysis

N=1,147 Excluded because of cancer history/prevalent cancer

N=43,419 (68%) Included in main analysis

N=26,985 included from EPIC-Elderly
N=8,577 included from ESTHER
N=1,944 included from PRIME Belfast
N=5,913 included from the Tromsø Study
NOTE: Weights are from random effects analysis
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NOTE: Weights are from random effects analysis
### Table 1. Study and participants characteristics by cohort in the CHANCES consortium of middle-aged and older adults

| Characteristic                      | EPIC Elderly | Germany (ESTHER) | Northern Ireland (PRIME Belfast) | Norway (Tromsø) |
|-------------------------------------|--------------|------------------|----------------------------------|-----------------|
|                                    | Denmark      | Greece           | Netherlands                      | Spain           |
| Recruitment year, range             | 1993-1997    | 1994-1999        | 1993-1997                        | 1992-1996       |
| Age at entry, years (SD)            | 62.5 ± 1.5   | 66.9 ± 4.4       | 64.3 ± 2.7                       | 62.5 ± 1.7      |
| Sex                                 |              |                  |                                  |                 |
| Men, n (%)                          | 5072         | 2882             | 210                              | 1949            |
| Women, n (%)                        | 5853         | 4299             | 4085                             | 2635            |
| Education                           |              |                  |                                  |                 |
| Low, n (%)                          | 4193         | 6539             | 1303                             | 3927            |
| Medium, n (%)                       | 4889         | 3980             | 2451                             | 320             |
| High, n (%)                         | 1827         | 220              | 521                              | 287             |
| Unknown, n (%)                      | 16           | 24               | 20                               | 208             |
| BMI at baseline, kg/m² (SD)         | 26.2 ± 3.9   | 29.3 ± 4.3       | 25.8 ± 3.9                       | 29.5 ± 4.0      |
| Underweight, n (%)                  | 62           | 19               | 46                               | 4              |
| Normal weight, n (%)                | 4421         | 1114             | 1947                             | 493             |
| Overweight, n (%)                   | 4861         | 3125             | 1745                             | 2167            |
| Obese, n (%)                        | 1581         | 2923             | 557                              | 1920            |
| WC at baseline, cm (SD)             | 89.1 ± 12.4  | 95.9 ± 11.4      | 84.2 ± 10.3                      | 97.1 ± 10.7     |
| HC at baseline, cm (SD)             | 101.2 ± 7.8  | 106.3 ± 9.1      | 103.8 ± 8.3                      | 107.9 ± 8.5     |
| WHR at baseline, ratio (SD)         | 0.88 ± 0.10  | 0.90 ± 0.09      | 0.81 ± 0.07                      | 0.90 ± 0.08     |
| Height at baseline, cm (SD)         | 168.8 ± 8.8  | 158.2 ± 8.7      | 163.8 ± 6.5                      | 159.5 ± 8.6     |
| Vigorous physical activity          |              |                  |                                  |                 |
| No, n (%)                           | 1752         | 16.0 ± 5566      | 77.5 ± 1669                      | 38.9 ± 4311     |
| Yes, n (%)                          | 5135         | 47.0 ± 1506      | 21.0 ± 2480                      | 57.7 ± 2422     |
| Unknown, n (%)                      | 4038         | 37.0 ± 109       | 1.5 ± 146                        | 3.4 ± 31        |
| Alcohol intake, grams/d (SD)        | 19.0 ± 19.8  | 7.5 ± 15.4       | 7.8 ± 11.9                       | 13.0 ± 13.0     |
| Smoking status                      |              |                  |                                  |                 |
| Never daily smoker, n (%)           | 3625         | 33.2 ± 4891      | 68.1 ± 2052                      | 47.8 ± 3109     |
| Former daily smoker, n (%)          | 4078         | 37.3 ± 1285      | 17.9 ± 1532                      | 35.7 ± 732      |
| Current daily smoker, n (%)         | 3201         | 29.3 ± 805       | 11.2 ± 694                       | 16.2 ± 740      |
| Unknown, n (%)                      | 21           | 0.2 ± 200        | 2.8 ± 17                         | 0.4 ± 3         |
| Median follow-up time, years        | 11.9 ± 1.3   | 13.2 ± 1.3       | 13.2 ± 1.3                       | 13.4 ± 1.3      |
| N cancers cases                     |              |                  |                                  |                 |
| N all obesity-relateda              | 465          | 127              | 250                              | 164             |
| N breast cancer (age>50, women only)| 193          | 22               | 109                              | 42              |
| N colorectal cancer                 | 141          | 39               | 80                               | 66              |
| N other obesity-relatedb            | 131          | 66               | 61                               | 56              |

a First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.
Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Note: All values are means, except when stated otherwise.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.

### Table 2. Changes in risk discrimination for the risk of incident cancer in men and women combined after addition of anthropometric indicators to the null model

|                         | Null model | BMI                      | WC                      | HC                      | WHR                      | BMI + WC + HC |
|-------------------------|------------|--------------------------|-------------------------|-------------------------|--------------------------|---------------|
|                         | Estimate   | 95% CI                   | Estimate                | 95% CI                  | Estimate                  | 95% CI        | Estimate     | 95% CI                  | Estimate                  | 95% CI        | Estimate     | 95% CI        | Estimate                  | 95% CI        |
| **Obesity-related cancers** |            |                          |                         |                         |                          |                |              |                          |                          |                |              |                          |                          |                |
| AIC                     | 15826.6    | 15823.6                  | 15820.6                 | 15823.7                 | 15823.4                  | 15823.1       |                |                          |                          |                |              |                          |                          |                |
| C-index                 | 0.688      | 0.675 - 0.699            | 0.663                   | 0.649 - 0.677           | 0.663                    | 0.650 - 0.677 | 0.664        | 0.651 - 0.678           | 0.663                    | 0.650 - 0.677 |                |                          |                          |                |
| **Colorectal cancer**   |            |                          |                         |                         |                          |                |              |                          |                          |                |              |                          |                          |                |
| AIC                     | 5678.8     | 5672.8                   | 5670.2                  | 5674.8                  | 5674.0                   | 5673.5        |                |                          |                          |                |              |                          |                          |                |
| C-index                 | 0.688      | 0.667 - 0.709            | 0.689                   | 0.668 - 0.711           | 0.680                    | 0.655 - 0.704 | 0.681        | 0.657 - 0.706           | 0.681                    | 0.656 - 0.705 |                |                          |                          |                |
| **Breast cancer**b      |            |                          |                         |                         |                          |                |              |                          |                          |                |              |                          |                          |                |
| AIC                     | 5031.2     | 5030.3                   | 5031.9                  | 5032.0                  | 5033.1                   | 5032.9        |                |                          |                          |                |              |                          |                          |                |
| C-index                 | 0.824      | 0.813 - 0.836            | 0.823                   | 0.812 - 0.835           | 0.801                    | 0.787 - 0.815 | 0.803        | 0.789 - 0.817           | 0.801                    | 0.787 - 0.815 |                |                          |                          |                |
| **Other obesity-related cancers**c | |                          |                         |                         |                          |                |              |                          |                          |                |              |                          |                          |                |
| AIC                     | 4780.7     | 4782.7                   | 4781.4                  | 4782.2                  | 4777.0                   | 4780.6        |                |                          |                          |                |              |                          |                          |                |
| C-index                 | 0.588      | 0.561 - 0.615            | 0.587                   | 0.559 - 0.614           | 0.605                    | 0.573 - 0.637 | 0.612        | 0.581 - 0.643           | 0.618                    | 0.587 - 0.648 |                |                          |                          |                |

a First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

b Same as all obesity-related cancers but excluding first primary cancers of the breast and of the colorectum.

Note: Null model included sex, age, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: AIC, Akaike Information Criterion; BMI, body mass index; CI, confidence interval; HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio.
**Figure 1.** Flowchart of participant inclusion.

**Figure 2.** Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with "obesity-related cancers".

First primary cancers of the breast (postmenopausal), colorectum, lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

**Figure 3.** Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with colorectal cancer.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

**Figure 4.** Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with postmenopausal breast cancer.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.

**Figure 5.** Random-effects meta-analysis of the association of different obesity indicators per 1 standard deviation (SD) increment with "other obesity-related cancers".

First primary cancers of the lower oesophagus, cardia stomach, liver, gallbladder, pancreas, endometrium, ovary, and kidney.

Adjustments were made for sex, age at entry, daily smoking (never, former, current, missing), average alcohol consumption (g/d), education (primary or less, more than primary but less than college, college or university, missing), vigorous physical activity (yes, no, missing), recruitment year, and height.

Abbreviations: BMI, body mass index; DK, Denmark; GR, Greece; HC, hip circumference; NL, the Netherlands; SP, Spain; WC, waist circumference; WHR, waist-to-hip ratio.