Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies

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Summary

Background Excess bodyweight, expressed as increased body-mass index (BMI), is associated with the risk of some common adult cancers. We did a systematic review and meta-analysis to assess the strength of associations between BMI and different sites of cancer and to investigate differences in these associations between sex and ethnic groups.

Methods We did electronic searches on Medline and Embase (1966 to November 2007), and searched reports to identify prospective studies of incident cases of 20 cancer types. We did random-effects meta-analyses and meta-regressions of study-specific incremental estimates to determine the risk of cancer associated with a 5 kg/m² increase in BMI.

Findings We analysed 221 datasets (141 articles), including 282 137 incident cases. In men, a 5 kg/m² increase in BMI was strongly associated with oesophageal adenocarcinoma (RR 1·52, p<0·0001) and with thyroid (1·33, p=0·02), renal (1·24, p<0·0001), and colon (1·24, p<0·0001) cancers. In women, we recorded strong associations between a 5 kg/m² increase in BMI and endometrial (1·59, p<0·0001), gallbladder (1·59, p=0.04), oesophageal adenocarcinoma (1·51, p<0·0001), and renal (1·34, p<0·0001) cancers. We noted weaker positive associations (RR <1·20) between increased BMI and rectal cancer and malignant melanoma in men; postmenopausal breast, pancreatic, thyroid, and colon cancers in women; and leukaemia, multiple myeloma, and non-Hodgkin lymphoma in both sexes. Associations were stronger in men than in women for colon (p<0·0001) cancer. Associations were generally similar in studies from North America, Europe and Australia, and the Asia–Pacific region, but we recorded stronger associations in Asia–Pacific populations between increased BMI and premenopausal (p=0·009) and postmenopausal (p=0·06) breast cancers.

Interpretation Increased BMI is associated with increased risk of common and less common malignancies. For some cancer types, associations differ between sexes and populations of different ethnic origins. These epidemiological observations should inform the exploration of biological mechanisms that link obesity with cancer.

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Introduction

Excess bodyweight, whether in people who are overweight (defined as a body-mass index [BMI] of 25 to 29·9 kg/m²) or obese (BMI of 30 kg/m² or greater), is increasingly recognised as an important risk factor for some common cancers.[1,2] Several meta-analyses[3–19] have assessed whether BMI is associated with cancer risk; most have investigated cancer at a particular site in the body. Some have examined the risk of cancer for incremental increases in BMI;[3,5,8,10,11,13,15] others, the risk for overweight and obese categories in comparison with normal weight.[7,9,12,16,17] Some meta-analyses incorporated results from case-control and cohort studies;[3–5,7,9,10,12,13,15–17] others combined both incident cases and cancer deaths;[3,5,8–13,15,17] and others included studies that used diagnoses of obesity at discharge from hospital.[9,10,13,14,17] Comparison of associations across studies, populations, and cancer sites is therefore difficult.

In 2007, the World Cancer Research Fund (WCRF)[2] used a more standardised approach to review the evidence. This report concluded that the evidence that body fatness is associated with increased risk of oesophageal adenocarcinoma, and with cancers of the pancreas, colorectum, postmenopausal breast, endometrium, and kidney is convincing, and that a probably association exists between body fatness and risk of gallbladder cancer.[2] However, several unanswered questions remain, including whether associations hold for less common malignancies, and whether associations differ between sexes and populations of different ethnic backgrounds. Several large cohort studies that were not included in previous reviews, including the Million Women study,[20] studies from different continents,[21–23] and studies of less common malignancies, have been published. We aimed to compare associations across cancer sites, and between sexes and populations to quantify the risk of different cancers associated with an incremental increase in BMI. We used uniform methods and definitions to do a systematic review and meta-analysis of prospective observational studies.

Methods

Search strategy and selection criteria

We systematically searched Medline and Embase (from their commencements to November 2007), with no language restrictions, for studies in humans of the association between bodyweight and cancer incidence

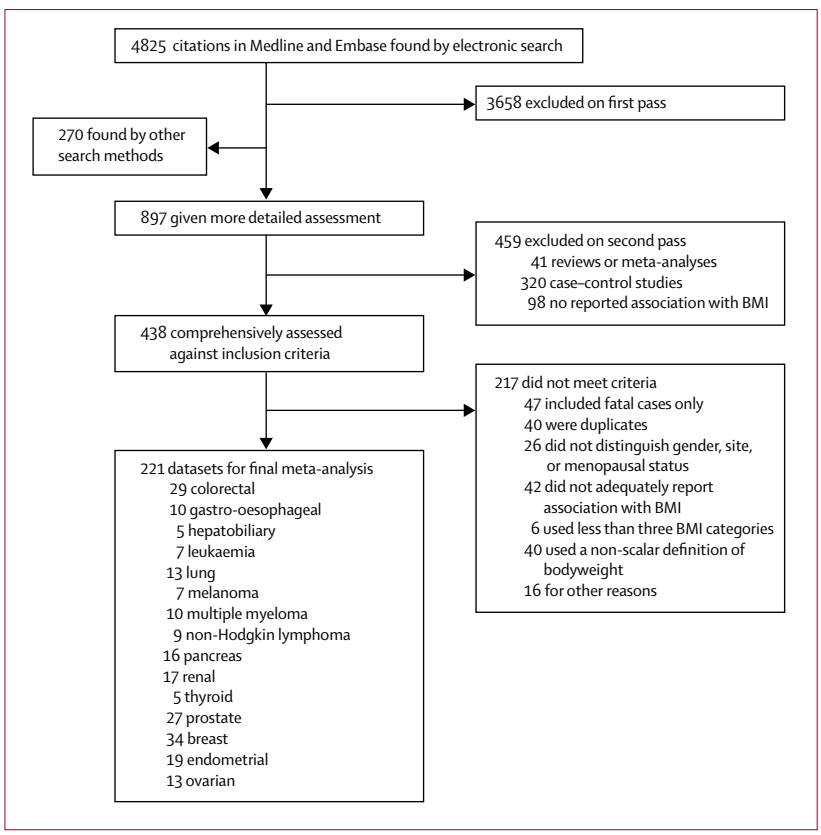

Figure 1: **Flow diagram of search strategy and study selection**
Numbers refer to datasets, rather than studies. NHL: non-Hodgkin lymphoma.

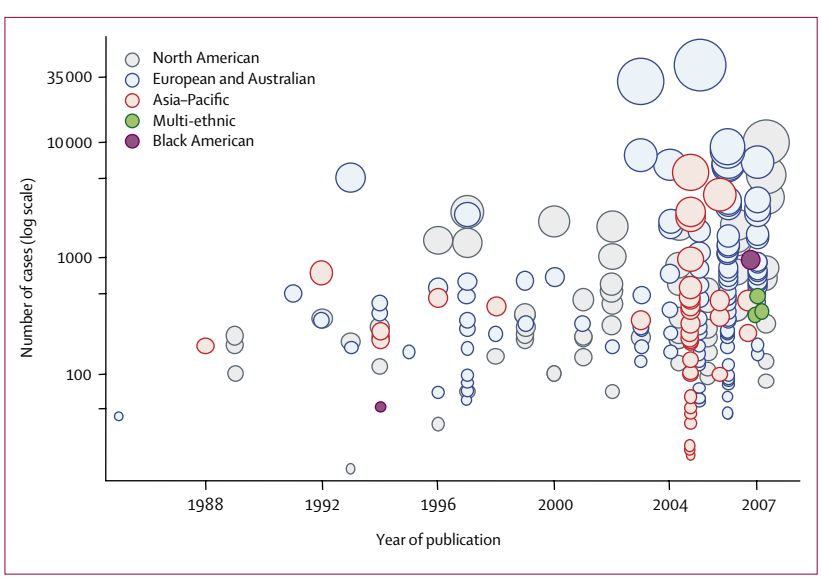

Figure 2: **Datasets by year and population group**
Size of circle is proportional to sample size.

See Online for webappendices 1 and 2

for 20 cancer types in 15 sites in the body: colorectal (colon and rectum); gastro-oesopheageal (gastric, oesophageal adenocarcinoma, and squamous cell carcinoma); hepatobiliary (gallbladder and liver); leukaemia; lung; malignant melanoma; multiple myeloma; non-Hodgkin lymphoma; pancreas; renal and thyroid for both genders; and prostate, breast (premenopausal and postmenopausal), endometrium, and ovary for single genders. Our core search consisted of terms related to bodyweight ("obesity", "adiposity", "body mass index", and "body size"), combined with specific terms for each cancer site (webappendix 1). If a site-specific dataset had been published more than once, we used the most recent publication. We scrutinised the reference lists of the identified reports,[1,2] reviews,[4,24–26] meta-analyses,[3,5–19] and other relevant publications to find additional pertinent studies. A research librarian who did an independent search for one site (endometrium) did not find any additional studies that met the inclusion criteria.

We included cohort studies if they determined BMI at baseline and then recorded incident cancer cases during follow–up. We specified that every cohort study must either report risk estimates (relative risks, odds ratios, or hazard ratios) with 95% CIs separately for men, women, or both across at least three categories of BMI or must report sufficient data to estimate these.[A: okay?] We also included case–control studies nested in such cohort studies and control arms from clinical trials. We included studies in which height and weight (to calculate BMI) had been self-reported, and those in which they had been directly measured.

The eligibility of each study was assessed independently by two investigators (AGR and MT). We excluded studies that were not published as full reports, such as conference abstracts and letters to editors, studies of cancer mortality (rather than incidence), studies of cancer precursors (for example colorectal adenoma), and studies that reported results only for "all breast" or "all colorectal" cancers.

Data extraction and quality assessment

One investigator (AGR) extracted data, which was checked by two others (MT and MZ). We used information about: study design and patient characteristics, and risk estimates and their 95% CIs (either with one BMI category as a referent group or expressed as a slope per incremental BMI increase [standardised to 5 kg/m² increments]). We collected data for both minimally adjusted and maximally adjusted risk estimates, if available. Populations were categorised into five groups: North American (greater than 80% White), European and Australian, Asia–Pacific (including Japanese populations based in Hawaii), Multi-ethnic, and Black American. We extracted the mean BMI (and its standard deviation) by sex for each study, or, if these data were missing, used sex-specific and population-specific values (webappendix 2).

Methodological quality was assessed according to three study components which might affect the strength of the association between BMI and cancer risk: length

	Number of datasets*	Population group			Number of cases in men	Number of cases in women	Total sample size	Number that measured BMI directly	Median number of potential cancer-specific confounders in analysis	Geometric mean duration of follow-up (years)
		North America	Europe and Australia	Asia–Pacific						
Colorectal cancer†	29	11	12	6			4833139	16	2 (0 to 6)	11·0 (9·1–13·3)
Colon					22440	20975				
Rectum					14894	9052				
Gastro-oesophageal cancers†	10	0	8	2			4673213	8	2 (1 to 3)	10·8 (7·4–16·0)
Gastric					817	325				
Oesophageal adenocarcinoma					1315	735				
Oesophageal squamous cell carcinoma					6201	1114				
Hepatobiliary cancers†	5	0	3	2			3319024	4	1 (1 to 1)	12·7 (7·0–23·1)
Gallbladder					928	1111				
Liver					2039	31				
Leukaemia	7	1	5	1	3371	5317	4757649	4	1 (1 to 3)	13·7 (7·7–24·5)
Lung cancer	13	1	8	4	7426	4273	2649345	10	3 (1 to 4)	11·9 (8·5–16·6)
Malignant melanoma	7	1	5	1	3492	4786	3966859	5	1 (1 to 1)	10·6 (7·1–15·7)
Multiple myeloma	10§	4	4	1	4273	3664	5171374	3	1 (1 to 2)	14·6 (10·7–20·0)
Non-Hodgkin lymphoma	9	2	6	1	7041	6248	5043747	3	1 (1 to 2)	12·4 (8·6–17·8)
Pancreatic cancer	16‡	4	8	3	2390	2053	3338001	6	3 (2 to 5)	9·4 (7·7–11·4)
Renal cancer	17‡	7	7	2	6073	4614	5473638	10	2 (1 to 5)	10·6 (8·5–13·3)
Thyroid cancer	5	0	4	1	1212	2375	3303073	5	1 (1 to 2)	14·4 (7·2–28·8)
Prostate cancer	27	12	10	5	70421		3029338	14	2 (1 to 3)	10·6 (8·6–13·1)
Breast cancer	34§	12	16	5			2559829	15	5·5 (1 to 11)	8·4 (7·1–10·0)
Premenopausal						7930				
Postmenopausal						23909				
Endometrial cancer	19‡	5	12	1		17084	3044538	12	2 (1 to 6)	10·6 (8·2–13·8)
Ovarian cancer	13	4	7	2		12208	2703734	5	3 (1 to 4)	12·2 (8·8–16·9)

Data are number, median (range), or geometric mean (95% CI). BMI=body-mass index. * Dataset refers to a site-specific cohort per paper. Several papers reported multiple sites. If a paper reported two separate cohorts (e.g. one each for men and women) for the same site, these were counted as two datasets. †These sites were grouped together in the literature search, since site-specific estimates were frequently reported in the same article. ‡Totals do not equal sum of population groups since they include multiethnic populations: one each for pancreatic, renal, and endometrial cancers. §Totals do not equal sum of populations groups since they include Black American population: one each for multiple myeloma and breast cancer.

Table 1: **Baseline characteristics for studies included in meta-analysis**

of follow-up; whether BMI was self-reported or measured; and the extent of adjustments for potential confounding factors (webappendix 2).

Statistical analysis

We transformed category-specific risk estimates into estimates of the risk ratio (RR) associated with every 5 kg/m² increase in BMI by use of the method of generalised least-squares for trend estimation.[27] These estimates were calculated from the assumption of a linear relation between the natural logarithm of risk ratio and increasing BMI. The value assigned to each BMI category was the mid-point for closed categories, and the median for open categories (assuming a normal distribution for BMI).[28] We combined the risk ratios for each 5 kg/m² increase in BMI by use of random-effect meta-analysis.[29] Unless otherwise stated, we used the most adjusted risk estimate from each study. We assessed heterogeneity between studies with the I^2 statistic[30] as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity.

We did meta-regression analyses for each site to identify study-level factors that modify the association between increased BMI and cancer risk, and contribute to heterogeneity between studies.[31] For sensitivity analyses, we repeated our analyses with a fixed-effects model, used minimally adjusted risk ratios, and estimated the median for open BMI categories with different methods.[32] We also did influence-analyses to assess the effect of each study on the summary risk estimates.[32] Furthermore, we explored threshold effects across BMI ranges using splines within the generalised least-squares for trend estimation models.[27] Publication bias was examined in funnel plots and with a regression

asymmetry test.[33] We used STATA version 9.0 (College Station, TX, USA) to analyse data.

Role of the funding source

See Online for webappendices 3–5 and webtable

The sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

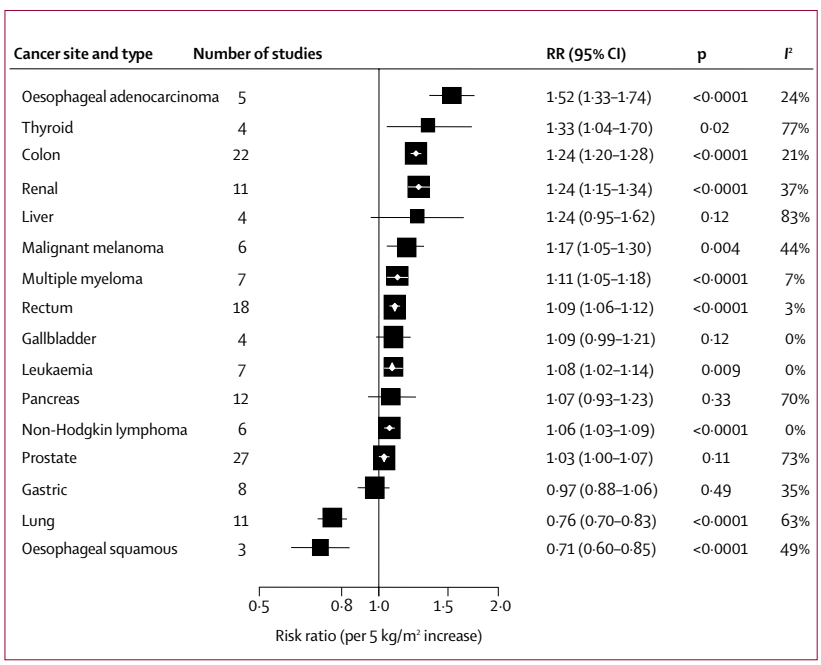

Figure 3: **Summary risk estimates by cancer sites in men**

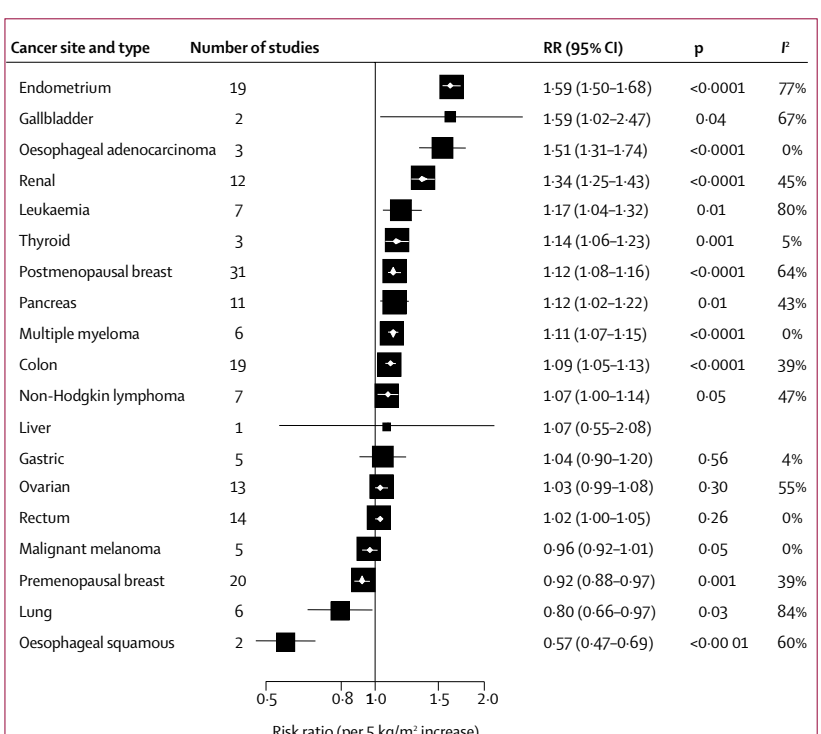

Figure 4: **Summary risk estimates by cancer sites in women**

Results

Of 4285 citations, we identified 221 datasets from 141 articles which met the inclusion criteria (see webappendix 3). Figure 1 shows our search and selection process, and webappendix 4 lists excluded articles with reasons for their exclusion. Agreement between observers on which studies to include was good (Cohen's unweighted κ=0·86). All papers used in our analysis were published in English, except for one that was written in Chinese.[34] Figure 2 shows that more than half the papers (73/141) were published since 2004, that many of the larger datasets were from recent publications, and that only a few studies from Asia–Pacific regions, and most with small numbers, were before 2004. The 141 papers reported on 76 studies (67 cohort studies, six nested case–control studies, and three randomised trials). 28 studies were from North America, 35 from Europe and Australia, and 11 from Asia–Pacific. One cohort was multi-ethnic (three papers),[35–37] and two cohorts (one as a subcohort within one article) analysed black American populations.[38,39]

Table 1 summarises the characteristics of included studies; the webtable has more details. The analysis included 282 137 incident cases (154 333 men and 127 804 women), over more than 133 000 000 person-years of follow-up. The geometric mean follow-up per cancer site varied from 8·4 years (breast cancer) to 14·4 years (multiple myeloma). Notably, no North American population data contributed to the summaries for gallbladder, gastric, liver, oesophageal, or thyroid cancers. The proportion of studies in which BMI was measured directly varied by cancer site, as did the median number of potential confounders that were included in adjusted analyses.

Figures 3 and 4 show the results of meta-analyses of risk ratios (per 5 kg/m² increase in BMI) in men and in women. Separate meta-analyses for each site are in webappendix 5. In men, increased BMI was strongly associated with oesophageal adenocarcinoma (RR 1·52, p<0·0001) and thyroid (1·33, p=0·02), renal (1·24, p<0·0001), and colon (1·24, p<0·0001) cancers. We noted a weaker positive association between increased BMI and malignant melanoma (1·17, p=0·004), multiple myeloma (1·11, p<0·0001), rectal cancer (1·09, p<0·0001), leukaemia (1·08, p=0·009), and non-Hodgkin lymphoma (1·06, p<0·0001). Between-study heterogeneity was high for thyroid and liver cancers, and moderate or low for the other sites (figure 3).

In women, a 5 kg/m² increase in BMI was strongly associated with endometrial (1·59, p<0·0001), gallbladder (1·59, p=0·04), and renal (1·34, p<0·0001) cancers and with oesophageal adenocarcinoma (1·51, p<0·0001). Weaker positive associations were seen for

	Studies		Cases		Risk ratio in men*	Risk ratio in women*	p value†	p value‡
	Men	Women	Men	Women				
Colon cancer								
All studies	22	19	22 440	20 975	1·24 (1·21–1·28)	1·09 (1·05–1·14)	<0·0001	<0·0001
Studies with both sexes	13	13	17 495	19 256	1·24 (1·18–1·31)	1·08 (1·02–1·34)	0·001	<0·0001
All but one study[46]	21	18	8635	4337	1·26 (1·21–1·30)	1·10 (1·06–1·15)	<0·0001	<0·0001
Rectal cancer								
All studies	18	14	14 894	9052	1·09 (1·06–1·12)	1·02 (0·99–1·04)	0·001	0·002
Studies with both sexes	11	11	11 035	8644	1·08 (1·05–1·11)	1·01 (0·98–1·04)	0·003	0·003
All but one study[46]	17	13	5712	1560	1·09 (1·05–1·15)	1·05 (0·99–1·12)	0·32	0·34
Pancreatic cancer								
All studies	12	11	2390	2053	1·07 (0·93–1·23)	1·12 (1·03–1·23)	0·54	0·84
Studies with both sexes	7	7	839	778	1·07 (0·83–1·39)	1·12 (0·95–1·33)	0·78	0·78
Renal cancer								
All studies	11	12	6941	4614	1·24 (1·15–1·34)	1·34 (1·25–1·42)	0·17	0·08
Studies with both sexes	6	6	4525	3089	1·18 (1·08–1·29)	1·35 (1·29–1·42)	0·003	0·004
All but one study[45]	10	11	3011	1977	1·26 (1·15–1·39)	1·34 (1·24–1·46)	0·36	0·19

*Risk ratio per 5 kg/m² increase in BMI (95% CI). †Meta-regression analysis with univariable model of sex. ‡Meta-regression analysis with multivariable models including the method of BMI determination (measured or self-reported)–the extent of cancer-site specific risk factor adjustment–and geographic region. We analysed only cancer sites with more than 10 studies that included both sexes.

Table 2: **Comparisons of risk ratios in men and women**

increased BMI and leukaemia (1·17, p=0·01), and cancers of the thyroid (1·14, p=0·0001), postmenopausal breast cancer (1·12, p<0·0001), pancreas (1·12, p=0·01), colon (1·09 p<0·0001), and non-Hodgkin's lymphoma (1·07, p=0·05). Heterogeneity between studies was high for endometrial and lung cancers and leukaemia, and moderate or low for the other sites (figure 4).

Increased BMI was negatively associated with the risk of lung cancer (0·76, p<0·0001 in men and 0·80, p=0·03 in women), with much heterogeneity between studies (figures 3 and 4). Smoking is a powerful confounder for lung cancer: smokers tend to have lower BMIs than non-smokers of the same age and sex,[40] and smoking is a major risk factor for lung cancer. Five prospective studies[20,41–44] reported associations between BMI and lung-cancer risk separately by smoking status; the summary risk ratio was 0·76 (95% CI 0·67–0·85) in smokers, with no association (RR 0·91 95% CI 0·76–1·10) in non-smokers. When we plotted the study-specific risk ratios for men and women combined against the proportion of those in each cohort who had ever smoked, inverse associations became stronger as the proportion of smokers per study increased (see webfigure). We did not analyse lung cancer further.

We used random-effects meta-regression analyses to examine whether patterns differed between the sexes. We included all cancer sites for which more than ten datasets were available, to compare estimates between men and women (colon, rectal, pancreatic, and renal cancer). Table 2 shows results from univariable and multivariable modelling for all studies, and studies in which estimates for both sexes were reported. Associations with increased BMI were stronger in men than in women for colon (p<0·0001) and rectal (p=0·003) cancers, and were stronger in women than in men for renal cancer (p=0·004). These differences were robust for colon cancer, whereas for other sites, they were largely driven by a large Norwegian study.[45,46] We found little evidence for a difference between men and women for the association of increased BMI with pancreatic cancer.

We also examined whether estimates varied between populations in cancer sites for which we had at least two datasets from the main geographic regions. For many cancers, associations between increased BMI and risk were consistent across populations (table 3). However, for some sites, differences in study populations might account for some of the observed heterogeneity recorded between studies; for example, we recorded a positive association between increased BMI and premenopausal breast cancer in Asia–Pacific populations, but an inverse association in the other regions (p=0·009). For postmenopausal breast cancer, the association tended to be stronger in studies from Asia–Pacific than in studies from North America, Europe, and Australia (p=0·06).

We also examined whether results for postmenopausal breast cancer differed according to whether menopause was defined clinically or based on age, and showed that point estimates were similar (webappendix 6). Risk estimates for postmenopausal breast cancer from studies of postmenopausal women only were also similar to those from cohorts of both premenopausal and postmenopausal women.

See Online for webfigure

See Online for webappendix 6

The method of BMI determination affected estimates of the association between BMI and cancer risk in women, but not in men (webappendix 7). The additional

See Online for webappendix 7

	Studies	Risk ratio*	p value (univariable model)†	p value (multivariable models)‡
Men				
Colon	22		0·20	0·35
North American¶	6	1·35 (1·21–1·50)		
European and Australian	10	1·21 (1·18–1·24)		
Asia–Pacific	6	1·32 (1·20–1·46)		
Rectum	18		0·54	0·18
North American¶	2	1·03 (0·94–1·13)		
European and Australian	10	1·09 (1·06–1·12)		
Asia–Pacific	6	1·05 (0·90–1·23)		
Pancreas	11		0·04	0·14
North American¶	2	1·43 (1·19–1·72)		
European and Australian	6	1·08 (0·93–1·24)		
Asia–Pacific	3	0·77 (0·54–1·11)		
Renal§	11		0·49	0·50
North American¶	3	1·24 (0·84–1·83)		
European and Australian	5	1·21 (1·12–1·32)		
Asia–Pacific	2	1·31 (1·18–1·62)		
Prostate	27		0·003	0·20
North American¶	12	1·00 (0·96–1·03)		
European and Australian	10	1·04 (1·01–1·07)		
Asia–Pacific	5	1·15 (0·95–1·39)		
Women				
Colon	19		0·04	0·09
North American¶	9	1·13 (1·06–1·19)		
European and Australian	7	1·04 (1·00–1·07)		
Asia–Pacific	3	1·13 (0·89–1·44)		
Rectum	14		0·82	0·82
North American¶	4	1·12 (1·03–1·22)		
European and Australian	7	1·00 (0·98–1·03)		
Asia–Pacific	3	1·08 (0·82–1·43)		
Pancreas	10		0·62	0·76
North American¶	3	1·16 (1·03–1·31)		
European and Australian	5	1·14 (1·05–1·23)		
Asia–Pacific	2	1·34 (0·98–1·83)		
Premenopausal breast	19		0·01	0·009
North American¶	5	0·91 (0·85–0·98)		
European and Australian	9	0·89 (0·84–0·94)		
Asia–Pacific	5	1·16 (1·01–1·32)		
Postmenopausal breast	30		0·04	0·06
North American¶	11	1·15 (1·08–1·23)		
European and Australian	14	1·09 (1·04–1·14)		
Asia–Pacific	5	1·31 (1·15–1·48)		
Ovarian	13		0·40	0·29
North American¶	4	0·97 (0·85–1·11)		
European and Australia	7	1·03 (0·98–1·07)		
Asia–Pacific	2	1·39 (0·66–2·89)		

Data are number or RR (95% CI), unless otherwise specified. *Risk ratios per 5 kg/m² increase in BMI. †Meta-regression regression analyses with region but no other variables. ‡Meta-regression regression analyses with the method of BMI determination (measured or self-reported), and the extent of adjustment for risk factors specific to cancer sites. §Data for renal cancer in women not analysed since only one Asia–Pacific dataset. ¶Denotes North American White populations since too few studies of Black Americans for subanalysis.

Table 3: **Comparison of risk ratios for different cancer sites between main population groups**

effect size (across all sites) between studies in which women self-reported their measurements and those in which weight and height were directly measured was 1·06 (95% CI 1·02–1·09). In men, the additional effect size was 1·02 (0·98–1·05). Other study-level variables, such as the year of publication, mean age at baseline, mean BMI at baseline, and the duration of follow-up, had little effect on the association between increased BMI and cancer.

Results were generally consistent when we repeated analyses with a fixed-effects model rather than a random-effects model (webappendix 8). Risk ratios were somewhat attenuated for liver (1·12, 1·05–1·19) and thyroid (1·19, 1·08–1·30) cancers in men, and for gallbladder (1·37, 1·26–1·48) cancer in women. Repetition of analyses with minimally adjusted risk ratios rather than maximally adjusted estimates did not produce different results. We examined to what extent results were affected by the way we assigned midpoints to open upper BMI categories (webappendix 8). Results based on our assigned midpoints did not differ from those based on midpoints reported in individual studies (p=0·98, based on 12 datasets). We repeated analyses with a gamma distribution to estimate the median for open upper BMI categories: results were similar to those from analyses with a normal distribution. We explored the possibility of threshold effects across BMI ranges by use of splines in generalised-least-squares for trend estimation models. When we adjusted models for population group, method of BMI determination, and extent of cancer-specific risk-factor adjustment, the association between increased BMI and the risk of endometrial cancer was non-linear: the increase in risk associated with each 5 kg/m² increase in BMI was greater above 28 kg/m² (RR 3·04, 2·31–4·01).

Influence analyses showed that, for most of sites, no single studies affected the sex-specific summary estimates (webappendix 9). Finally, we noted funnel plot asymmetry for colon cancer in men and women: increased BMI had large effects on cancer risk in small studies (p=0·002 and 0·006, respectively) but little evidence for other sites. To test whether this could have affected results, we repeated analyses excluding studies with less than 150 cases (seven in men and eight in women). These analyses produced similar summary estimates and did not affect the strength of evidence for differences between men and women in the BMI–cancer risk association for colon cancer (webappendix 10).

Discussion

Our large standardised meta-analysis shows that increased BMI is associated with an increased risk of several cancers in adults. Our findings extend the results of previous reports,[1,2] to show associations between increased BMI and cancer risk for less common malignancies, and evidence that associations might differ between men and women for some sites, in

particular for colon cancer. The magnitudes of associations between increased BMI and cancer were similar across populations for most cancer sites. However, the association was particularly strong for breast cancer in Asia–Pacific populations, which needs confirmation from further studies.

Meta-analyses of observational studies are prone to biases and confounding factors that are inherent in these studies.[47] We restricted our analyses to prospective studies and the case–control studies nested within them, and excluded traditional case–control studies, which are prone to recall and interviewer bias.[48] Furthermore, we assessed the methodological quality of component studies and explored sources of heterogeneity with meta-regression models. We showed that the method by which BMI is determined was a source of heterogeneity in results for cancer risk at several sites, which is consistent with the finding that self-reported weight is lower than true bodyweight. In turn, underestimation of weight varies with age (increases in older individuals), and with relative baseline BMI (increases with higher BMI).[49] Our results indicate that this affected associations in female populations. Extensive sensitivity analyses indicated that results were robust to changes in model assumptions.

Increased BMI was associated with some cancers, but not others: the specificity of these associations argues against confounding and bias, and for a possible causal link between increased BMI and the risk of developing some cancers. Summary estimates from maximally and minimally adjusted analyses were similar, indicating that for the cancers we studied, the effect of BMI on cancer risk is not confounded by other included factors Alternatively, important confounding factors might not have been measured with sufficient precision, or not have been measured at all in these studies. For some cancer types, smoking seemed to be a major confounder in the association of increased BMI with risk. This was exemplified in the case of lung cancer, for which increased BMI was not associated with cancer risk in those who have never smoked, but was inversely associated in smokers. Similarly, increased BMI had a strong inverse association with squamous cell carcinoma of the oesophagus, which is more strongly associated with smoking than is oesophageal adenocarcinoma.[50] However, we could not determine the effect of smoking on risk of squamous cell carcinoma of the oesophagus, since too few studies were stratified by smoking status. For postmenopausal risk of breast cancer, studies of postmenopausal women only had similar results to those from cohorts with both premenopausal and postmenopausal women, suggesting that excess bodyweight is relevant to risk both before and after menopause. However, the use of hormone replacement therapy[51,52] and mammographic density[53] could be additional confounders. This needs further study.

Anthropometric measures other than increased BMI, for example waist-to-hip ratio or waist circumference, might be better measures of adiposity in terms of cancer risk, as is the case for cardiovascular risk.[54] Two previous meta-analyses (mixed case–control and cohort studies)[55,56] reported positive associations between waist-to-hip ratio and premenopausal breast cancer. In our review, too few studies determined waist-to-hip ratio or waist circumference to permit comprehensive analyses of such associations across several sites.

Several meta-analyses have quantified associations between BMI and cancer risk at specific sites. Some have quantified associations separately for men and women;[3,5,8–12,15–19] others for men and women combined.[4,14,57] Since our analysis raised the probability of differences between sexes at several sites, future studies should report BMI–cancer risk associations separately by sex. Inclusion criteria for studies differed and several reviews included both conventional case–control studies and cohort studies.[3–5,9,10,12,15–18] Furthermore, several meta-analyses[3,5,8,9,11,15,17,18] combined cohort studies of cancer deaths with studies of cancer incidence.

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The WRCF review[2] also examined associations for several cancer types. However, by contrast with that review, we reported our results as sex-specific estimates; addressed differences across populations; and calculated risk estimates for several additional cancer types: leukaemia, malignant melanoma, multiple myeloma, non-Hodgkin lymphoma, and thyroid cancer. Moreover, despite attempts to standardise methodological processes across different centres, selection of studies for the WCRF review was inconsistent. For example, studies of cancer mortality were included in the analyses of cancers of the pancreas, endometrium, and gallbladder, but not for oesophageal adenocarcinoma, kidney, colon, or breast cancers. Because obesity has been associated with poor prognosis in, for example breast,[58] colon,[59,60] endometrium,[61] ovary,[62] and prostate[63] cancers (and with a favourable prognosis in renal call carcinoma[64]), we restricted our analyses to studies of incident cancers. Our combined risk estimates were generally more conservative than estimates from previous reviews, and provided only weak evidence for the association of increased BMI with the risk of gallbladder,[9] pancreatic,[5,8] and prostate[15] cancers in men, and for ovarian cancer[16,17] in women.

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Mechanisms that link excess weight and cancer risk are not fully understood, though three hormonal systems—the insulin and insulin-like growth factor (IGF) axis, sex steroids, and adipokines—are the most studied candidates. All three systems are interlinked through insulin; however, their roles might vary between cancer sites. The insulin–cancer hypothesis postulates that chronic hyperinsulinaemia decreases concentrations of IGF binding protein-1 and IGF binding protein-2, which increases bioavailable or free IGF-I with concomitant changes in the cellular

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environment (mitogenesis and anti-apoptosis) that favour tumour formation.[65] Circulating total IGF-I, which is a major determinant of free IGF-I concentrations, is also associated with an increased risk of colorectal and prostate cancers, and with premenopausal rather than postmenopausal breast cancer.[66] Mean circulating concentrations of total IGF-I are higher in men than in women,[67] which could partly explain the differences between sexes—eg, in colorectal cancer risk.

For postmenopausal breast cancer, the increase in risk might be explained by the higher rates of conversion of androgenic precursors to oestradiol through increased aromatase enzyme activity in adipose tissue. More than one system might affect the risk of endometrial cancer: increased oestradiol not only increases endometrial cell proliferation and inhibits apoptosis, but might also stimulate the local synthesis of IGF-I in endometrial tissue.[25] Furthermore, chronic hyperinsulinaemia might promote tumorigenesis in oestrogen-sensitive tissues, since it reduces blood concentrations of sex-hormone-binding globulin, and in turn, increases bioavailable oestrogen.[25] Adiposity is inversely related to testosterone concentrations in men,[68] but positively related in women;[69] which could be relevant to sex differences in the association between BMI and cancer risk.

Adiponectin is the most abundant adipokine. It is secreted mainly from visceral fat adipocytes, and is inversely correlated with BMI. Mean circulating concentrations are higher in women than men. In terms of tumour development, this insulin-sensitising agent is antiangiogenic and anti-inflammatory, and inhibits tumour growth in animals.[70] Inverse associations between adiponectin concentrations and cancer risk have been reported in some studies in people.[70] Beyond these mechanisms, other candidate systems include obesity-related inflammatory cytokines, altered immune response, oxidative stresses, the nuclear factor κB system,[65] hypertension and lipid peroxidation for renal cancer,[71] and acid-reflux for oesophageal adenocarcinoma. We do not yet know what mechanisms might link the less common malignancies with obesity.

In US adults, 71% of men and 62% of women are overweight or obese (with a BMI of more than 25 kg/m²);[72] in the UK, 65% of men and 56% of women are overweight or obese.[73] Moreover, these prevalences are expected to increase, in the UK, for example, to 75% of men and 58% of women by 2010.[73] Excess bodyweight could therefore contribute to a substantially larger burden of cancer in such populations. We have modelled a 5 kg/m² increase in BMI, which corresponds to weight gains of about 15 kg in men and 13 kg in women who have an average BMI of 23 kg/m². Many of the observed associations between increased BMI and cancer risk are for cancers that are not related to smoking. Conceivably, as cigarette smoking (which is the largest cause of cancers in developed countries) decreases, excess bodyweight could become the dominant lifestyle factor that contributes to cancer occurrence in such countries.

Important questions remain about the cumulative effects of excess bodyweight over several decades, the effect of key weight-change periods in the life-course of individuals, and interactions with other risk factors.[74] Other unresolved questions relate to the most appropriate measure of adiposity in terms of cancer risk, the mechanisms that underpin sex differences, and differences across ethnicities. Finally, we need to know whether effective interventions to reduce BMI in adult populations will reduce cancer risks. This knowledge will allow the formulation of public-health strategies to prevent obesity-related cancers worldwide.

Contributors

AGR contributed to protocol design, data extraction, quality assessment, statistical analysis, and writing the report. MT contributed to protocol design, data extraction, and writing the report. ME contributed to protocol design, quality assessment, statistical analysis, and revision of the report. MZ contributed to data extraction, statistical analysis, and writing the report. RFH contributed to interpretation of data and revision of the report. All authors have seen and approved the final version.

Conflict of interest statement

AGR has received hospitality from Diagnostic Systems Laboratories and from several pharmaceutical companies that make hormone replacements, and a lecture honorarium from Eli-Lilly.

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