

## Chapter 2

# Epidemiology of Overweight/Obesity and Cancer Risk

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**Abstract** Increased body adiposity is an established risk factor for cancer development. In a large standardized meta-analysis of prospective observational studies, the author and collaborators quantified the risk associated with body mass index (BMI) in 20 cancer types and demonstrated that associations are often sex- and site-specific; exist for a wider range of malignancies than previously thought; and are broadly consistent across geographic populations. Given the biological plausibility, the consistency of associations, the sufficiently long latency times between BMI measurement and cancer occurrence and the recent observations of apparent cancer risk protection in grossly obese patients following bariatric surgery, these associations are probably causal. Further analyses are now revealing that other major cancer risk factors may effect associations between BMI and cancer risk in a site-specific manner – for example hormonal replacement therapy usage and risk of breast and endometrial cancers. These observations point to a diversity of potential processes operating for different cancer types, such that it is unlikely that there is a ‘one system fits all’ mechanism. As the obesity epidemic continues, incidences of obesity-related cancers may rise. There is a need to better understand the biological and molecular mechanisms underpinning the link between obesity and different cancers, so that targeted-based strategies are developed to integrate with population-based weight control policies.

## 1 Introduction

Increased adiposity has long been recognized as an important risk factor for cardiovascular disease and type 2 diabetes. While a link between obesity and cancer risk had been postulated in the nutritional literature dating back to the classical animal

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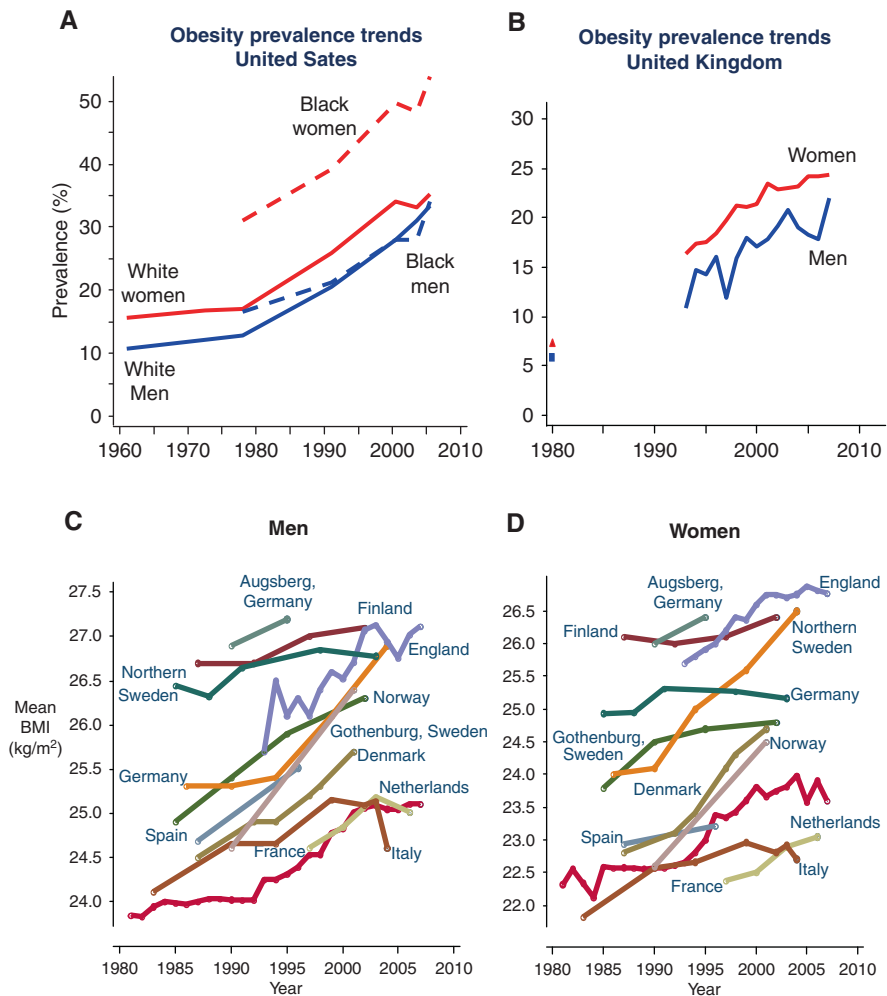
experiments in the 1940s from Tennenbaum [1], this association has only recently been highlighted in the epidemiology literature.

The amount of body adiposity may be approximated by a number of anthropometric measures, including body mass index (BMI: expressed in  $\text{kg/m}^2$ ), waist circumference (expressed in cm) and waist–hip ratio. By far the most commonly reported index in the literature is BMI, and this will be the main focus of this review. Using this metric, there is a well-established World Health Organization classification of four broad categories as follows: underweight, BMI  $<18.5 \text{ kg/m}^2$ ; normal weight, BMI  $18.5\text{--}24.9 \text{ kg/m}^2$ ; overweight, BMI  $25.0\text{--}29.9 \text{ kg/m}^2$ ; and obese, BMI  $\geq 30 \text{ kg/m}^2$ . Combining overweight and obesity may be expressed as excess body weight. Limitations of using BMI to express risk are recognized in the context of diseases such as cardiovascular disease – for example, central obesity determined by waist circumference or waist–hip ratio may be a most sensitive disease predictor – but it is unclear whether this is the case in the context of cancer risk.

This review updates the epidemiology of excess body weight and cancer risk focusing mainly of the large volume of association data linking BMI with several cancer types. The smaller volume of data linking waist circumference or waist–hip ratio and cancer risk will also be discussed. In support of these associations, the review also includes sections on ecological observations, biological mechanisms, causal associations (critiqued against the Bradford-Hill criteria) and attributable risk. Additionally, it has emerged that associations between excess body weight and cancer risk at specific sites may be considerably modified in the presence of other risk factors – and examples will be discussed. As a prelude to these discussions, some key aspects of the epidemiology of excess body weight are summarized.

## 2 Epidemiology of Excess Body Weight

To estimate the global prevalence of overweight and obesity in the world (2005), Kelly and colleagues [2] pooled sex- and age-specific prevalences in representative population samples from 106 countries and found the following: overall, 23.2% of the world's adult population was overweight (24.0% in men:22.4% in women) and 9.8% was obese (7.7% in men:11.9% in women). The estimated total numbers of overweight and obese adults were 937 million and 396 million, respectively. These values have been adopted by the World Health Organization. In many westernized countries, over a fifth of adult populations are obese – for example, 24.2% in men and 23.5% in women in the United States (2005) [3] and 21.9% in men and 24.4% in women in the United Kingdom (2007) [4] – but obesity is also prevalent in developing world countries. There are complex inter-relationships between socio-educational stratifications and excess body weight prevalence; but in general, outside the context of very low-income populations, obesity is more prevalent among lower socio-educational classes [5].



**Fig. 2.1** Epidemiology of overweight and obesity (a) Trends in sex-specific obesity prevalences for Whites and Blacks in the United States (*Source*: National Health and Nutrition Examination Surveys). (b) Trends in sex-specific obesity prevalences in the United Kingdom (taken as equivalent to England and Wales) (*Source*: Office of National Statistics Health Survey for England). (c and d) Trends for means of BMI distributions for 12 populations across 10 European countries. References for studies are cited in the supplemental material of ref. [42] or available from author. Trends are all increasing and generally linear, with some countries demonstrating plateau effects. Note: different y-axis ranges for men and women

In countries where there have been robust nationally representative historical data, trends in BMI distributions have been increasing since the 1980s, though from different starting points and at different rates as shown in Fig. 2.1a–d. Trend increases have generally been linear, but there are signals from some countries (England, Netherlands, Italy) of ‘tail off’ in the past 5 years.

### 3 Associations Between Adiposity and Cancer Risk

#### 3.1 Body Mass Index (BMI)

Epidemiological studies in the last three decades of the twentieth century often focused on associations between cancer risk and dietary macro- and micro-constituents and food processing, with less emphasis on the composite endpoints of nutrition, such as anthropometric measures and physical activity [6]. In 2002, the International Agency for Research into Cancer (IACR) [7] concluded, from a semi-quantitative review of the literature, that excess body weight is associated with increased risk of developing cancers of the post-menopausal breast, colorectum, endometrium, kidney and oesophageal adenocarcinoma. In 2007, the World Cancer Research Fund [8] used a more standardized approach to review the literature and reported that the evidence that body fatness is associated with increased risk of oesophageal adenocarcinoma, and with cancers of the pancreas, colorectum, post-menopausal breast, endometrium and kidney is ‘convincing’ and that a ‘probable’ association exists between body fatness and risk of gall bladder cancer.

In parallel with the World Cancer Research Fund report, the author together with collaborators from the University of Bern, Switzerland, reported in the *Lancet* [9] a systematic review and standardized meta-analysis of prospective observational studies (221 datasets including 281,137 incident cases) quantifying associations with a 5 kg/m<sup>2</sup> BMI increase and risk of incident cancer for 20 cancer types. The summary of the risk estimates by gender is shown in Table 2.1. By using the standardized approach across a large number of cancer types and an updated literature search (to December 2007, capturing several studies from Asia-Pacific populations not included in previous meta-analyses), we were able to demonstrate that associations

- are sex- and site-specific – for example, associations are consistently stronger for colon versus rectal cancer; in turn, within these cancer types, associations are stronger for men than women;
- exist for a wider range of malignancies than previously thought – ‘new’ obesity-related cancers added to the list were thyroid cancer, malignant melanoma in men, multiple myeloma, leukaemia and non-Hodgkin lymphoma;
- are broadly consistent across geographic populations, namely North American, European and Australian and Asia-Pacific;
- may be ranked per given change in BMI across the cancer types by gender;
- with excess body weight are significant for several cancer types conventionally considered non-smoking-related malignancies.

In addition, we identified that for some cancer types, such as gastric cancer (based on reasonable study numbers), there are null associations, where earlier studies had raised possibilities that positive associations existed.

**Table 2.1** Gender-specific estimated risk ratios by cancer types

	Men			Women		
	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)	<i>I</i> <sup>2</sup> (%)	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)	<i>I</i> <sup>2</sup> (%)
Colorectal cancer						
Colon	22	1.24 (1.20, 1.28)	21	19	1.09 (1.05, 1.13)	39
Rectum	18	1.09 (1.06, 1.12)	3	14	1.02 (1.00, 1.05)	0
Gall bladder cancer		No association		2	1.59 (1.02, 2.47)	67
Leukaemia	7	1.08 (1.02, 1.14)	0	7	1.17 (1.04, 1.32)	80
Malignant melanoma	6	1.17 (1.05, 1.30)	44		No association	
Multiple myeloma	7	1.11 (1.05, 1.18)	7	6	1.11 (1.07, 1.15)	0
Non-Hodgkin lymphoma	6	1.06 (1.03, 1.09)	0	7	1.07 (1.00, 1.14)	47
Oesophageal adenocarcinoma	5	1.52 (1.33, 1.74)	24	3	1.51 (1.31, 1.74)	0
Pancreatic cancer		No association		11	1.12 (1.02, 1.22)	43
Renal cancer	11	1.24 (1.15, 1.34)	21	12	1.34 (1.25, 1.43)	45
Thyroid cancer	4	1.33 (1.04, 1.70)	77	3	1.14 (1.06, 1.23)	5
Prostate cancer	27	1.03 (1.00, 1.09)	0		NA	
Post-menopausal breast cancer		NA		31	1.12 (1.08, 1.16)	43
Endometrial cancer		NA		19	1.59 (1.50, 1.68)	77

Risk estimates are per increase in 5 kg/m<sup>2</sup> BMI (body mass index)  
All risk estimates are taken from meta-analyses of the previously published meta-analysis [9]  
Only risk estimates for cancer types with a significant positive association with BMI are shown  
<sup>a</sup>Number of studies  
NA Not applicable

3.2 Other Adiposity-Related Anthropometric Measures

Body adiposity is often sub-classified as subcutaneous adipose tissue and visceral adipose tissue (VAT) – waist–hip ratio and waist circumference measurements are thought to better reflect central adiposity or VAT, whereas BMI reflects total body fatness (combined subcutaneous adipose tissue and visceral adipose tissue). Waist–hip ratio or waist circumference might therefore be better measures of adiposity than BMI in terms of cancer risk, as is the case for cardiovascular risk [10], but the number of cohort studies relating these parameters to subsequent cancer development is small.

Two previous meta-analyses [11, 12], both including case–control and cohort studies, examined the cumulative evidence linking waist–hip ratio and breast cancer risk. For pre-menopausal breast cancer risk, both analyses arrived at the same conclusion: namely that adiposity determined by waist–hip ratio reverses the inverse association noted with BMI to either a null or positive association. For post-menopausal breast cancer risk, the findings were less straightforward: the analysis by Connolly and colleagues [11] suggested that waist–hip ratio may have a stronger

positive association than BMI, whereas the analysis by Harvie and colleagues [12], having adjusted for BMI, found a null association for waist–hip ratio.

For colorectal cancer, two meta-analyses [13, 14] addressed associations with waist–hip ratio and/or waist circumference, both limiting their inclusions to cohort studies. Dai and colleagues [13] concluded that indices of abdominal obesity are more sensitive than BMI for predicting cancer risk, but this conclusion was based on analyses of uppermost categories versus lowermost categories of distributions for BMI, waist–hip ratio and waist circumference – however, these may not be directly comparable categories. The analysis reported by Moghaddam and colleagues [14] used a dose–response approach and arrived at a more cautious conclusion – namely that for a 2 kg/m<sup>2</sup> increase in BMI, the risk of colorectal cancer increased by 7%, and for a 2 cm increase in waist circumference, the risk increased by 4%. Here again, however, it is unclear whether a 2 kg/m<sup>2</sup> increase in BMI and a 2 cm increase in waist circumference equate to equivalent quantities of adipose tissue.

The European Prospective Investigation into Cancer and Nutrition have recently examined this question for oesophageal cancer recognizing that two main histological types exist – oesophageal adenocarcinoma and oesophageal squamous cell carcinoma – and that associations with BMI are positive for oesophageal adenocarcinoma, yet negative for oesophageal squamous cell carcinoma [15]. The European Prospective Investigation into Cancer and Nutrition analysis found that where waist–hip ratio was the anthropometric measure of adiposity, the negative associations with oesophageal squamous cell carcinoma disappeared.

In summary, in at least two examples where BMI is inversely associated with cancer risk (pre-menopausal breast and oesophageal squamous cell carcinoma), indices of central adiposity probably provide a more appropriate measure, i.e. the true relationship with adiposity is probably a null association. However, where indices of central adiposity are ‘more sensitive’, measures of risk association is far from conclusive. In all of these analyses, one needs to be cautious in the interpretation of risk estimates derived from multivariate models due to potential problems of overfitting and collinearity between covariates.

## 4 Ecological Observations

If the associations between BMI and risk of several cancer types were causal (and the likelihood is that they are – see later), and given the rising trends of obesity in many populations, one may expect to observe parallel temporal trends in some obesity-related certain cancers. For example, in the United Kingdom, the incidence of endometrial cancer was relatively stable for two-and-half decades after the commencement of national cancer registrations in the early 1970s. However, after 1996, there have been clear increases – these may be attributable to the parallel increases in obesity in the United Kingdom population (Fig. 2.2a), but equally may reflect changes in other major risk factors, such as hormonal replacement therapy usage. By contrast, the incidence of endometrial cancer is little changed in White women in the United States (despite the increasing prevalence of obesity in this population

over the time period 1975–2006), though there have been modest increases among Black women (Fig. 2.2b).

In a similar manner, there are well-documented increases in the incidences of oesophageal adenocarcinoma in countries such as the United Kingdom over the past decades (Fig. 2.2c) [16]. These may in part be attributable to the parallel rises in levels of obesity in that country. However, on deeper examination, it is clear that the rises in incidence of oesophageal adenocarcinoma predated the rises in obesity prevalence. Furthermore, for this cancer type, the incidence rates are considerably higher in men compared with women, despite the near identical risk estimates per 5 kg/m<sup>2</sup> increment in BMI for each gender. Taken together, increased prevalence of obesity in a population is likely to be only one of several ‘drivers’ of cancer incidence for that population. This contrasts with cigarette smoking prevalence in a population that does ‘track’ incidences of lung cancer-related mortality (albeit with a lag period of 30–40 years) [17]. For the exposure of excess body weight and cancer risk, associations are more modest (1.2–1.6 per shift from one World Health Organization BMI category to the next) compared with those of smoking and lung cancer (risk estimates from 12- to 20-fold for ever versus never smokers) [18], and there are several other factors determining rates of incident obesity-related cancers (e.g. mammographic, colorectal and prostate-specific antigen screening, hormone replacement therapy usage).

5 Biological Mechanisms

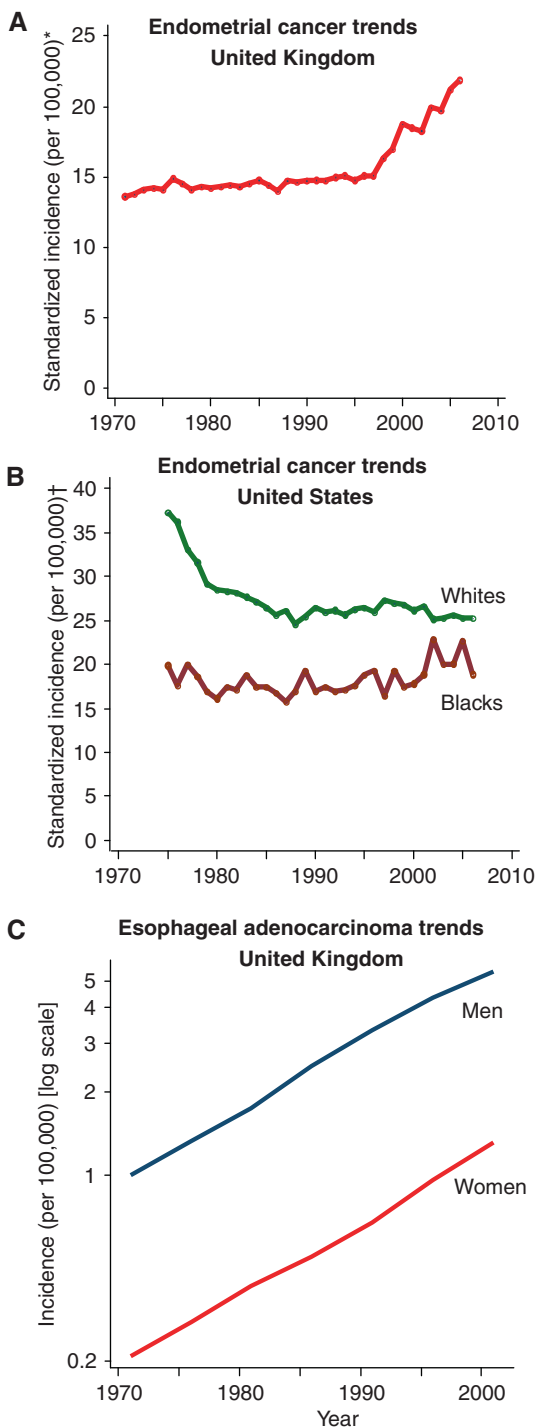
The mechanisms linking excess body weight and cancer risk are not fully understood (Table 2.2), though three hormonal systems – insulin and insulin-like growth factor (IGF) axis, sex steroids and adipokines – are the most studied candidates. Extensive reviews may be found elsewhere [19–22]. While all three systems are interlinked through insulin, their roles may vary between cancer sites. The

Table 2.2 Candidate mechanisms linking obesity and cancer risk

Most studied biological mechanisms	Insulin and insulin-like growth factors (IGFs) Sex steroids and sex steroid binding globulin Adipokines (e.g. adiponectin and leptin)
Hypoxia and angiogenesis	
Shared genetic susceptibility	
Migrating adipose stromal cells	
Other biological mechanisms	Obesity-related inflammatory cytokines Nuclear factor κβ system Altered immune response
Mechanical mechanisms	Hypertension and renal cancer Acid reflux and oesophageal adenocarcinoma Increased iodine uptake and thyroid cancer

Source: See ref. [20] for full details

**Fig. 2.2** Ecological observations: trends in obesity and cancer risk. **(a)** Trends for endometrial cancer incidence in the United Kingdom (UK: for these purposes taken as equivalent to England and Wales). Endometrial cancer is an obesity-related malignancy ranked highest BMI–cancer association among women ([9]). For the United Kingdom, secular trends increased in the past decade consistent with the corresponding increasing trends in prevalence of obesity. **(b)** By contrast, secular trends for endometrial cancer incidence in the United States have remained essentially constant in Whites and risen only slightly among Blacks (source: SEER 9 areas <http://seer.cancer.gov/>). **(c)** Sex-specific secular trends for oesophageal adenocarcinoma incidences in the United Kingdom (Source: Ref. [16]).  
 \*Standardized against European standard population. †Standardized against US standard population





*insulin-IGF* hypothesis postulates that chronic hyperinsulinaemia decreases concentrations of IGF binding proteins-1 and -2, leading to increased bio-available or free IGF-I with concomitant changes in the cellular environment (IGF-I increases mitosis; is anti-apoptotic, pro-angiogenic; and increases cell motility) favouring tumour formation [23]. Circulating total IGF-I, a major determinant of free IGF-I concentrations, is also consistently associated with increased risk of prostate, colorectal and pre-menopausal breast cancers [24], and in some studies of post-menopausal breast cancer [25, 26]. Mean circulating concentrations of total IGF-I are higher in men than women [27], which may in part explain some observed differences, for instance, in colorectal cancer risk are greater in men compared with women. However, the insulin-IGF hypothesis has two fundamental inconsistencies – first, levels of total IGF-I increase linearly with increasing BMI but only to a pivotal point around 27 kg/m<sup>2</sup>, thereafter declining with increasing weight [23]; second, in overweight/obese individuals who intentionally lose weight (a presumed cancer-protective behaviour), total IGF-I concentrations tend to increase (a conceptually ‘bad’ environment for cancer risk) [28].

For post-menopausal 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. In endometrial cancer, there may be more than one system involved: Increased oestradiol levels not only increase endometrial cell proliferation and inhibit apoptosis but might also stimulate the local synthesis of IGF-I in endometrial tissue [21]. Furthermore, chronic hyperinsulinaemia may promote tumourigenesis in oestrogen-sensitive tissues by reducing blood concentrations of sex hormone binding globulin, which in turn increases bio-available oestrogen [21]. Adiposity is inversely related to testosterone concentrations in men [29], but positively related in women [30], which may be relevant to gender differences in the relationship of BMI and cancer risk.

Adiponectin is the most abundant adipokine, secreted mainly from VAT, and is inversely correlated with BMI. In terms of tumour development, this insulin-sensitizing agent is anti-inflammatory, anti-angiogenic and inhibits tumour growth in animal models [31]. Beyond these mechanisms, other candidate systems include mutual genetic susceptibility, obesity-related inflammatory cytokines, altered immune response, oxidative stresses, obesity-related hypoxia, adipocyte-secreted pro-angiogenic factors, the nuclear factor  $\kappa$ B system [23], hypertension and lipid peroxidation for renal cancer [32] and acid reflux for oesophageal adenocarcinoma [33, 34]. The mechanisms linking adiposity and less common malignancies are speculative.

## 6 Causal Association and Attributable Risk

While the syntheses from others [8] and our review [9] demonstrated associations between BMI and cancer risks, a key question (not least for the development of cancer prevention strategies) is whether these associations are causally related. We recently addressed this in a review testing the data from our systematic review

against the nine Bradford-Hill criteria [35, 36] for judging causal association. The review [37] argued that the available data support strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence and probably analogy, suggesting that many of the observed associations are probably causal. Additionally, recent studies with long-term follow-up of patients undergoing bariatric surgery for morbid obesity point to a reduction in cancer incidence (albeit this reduction seems limited to women) associated with sustained weight loss [38, 39], and in turn, add further support to a causal association between obesity and cancer risk. Furthermore, investigators have argued that additional criteria for assessing causality should include adjustment for available confounding factors, evaluation of measurement error and study design and assessment of residual confounding [40] – these too were evaluated in our review [37] and we found lack of alternative explanations.

Given the likely causal association, it seems reasonable to ask the question, what proportion of cancers in a population are attributable to excess body weight, as this in turn relates to the potential number of avoidable incident cancers. The media often highlight that obesity is linked to 20% of all cancer deaths in women and 14% in men, quoting the large US Cancer Prevention Study II [41]. Using the risk estimates derived from our meta-analysis [9], we recently estimated more conservative population attributable risks for incident cancers of 3.2% in men and 8.6% in women [42]. Nonetheless, across 30 European countries, this amounts to over 124,000 avoidable cancer cases per year; and importantly, this analysis showed that as the prevalence of hormonal replacement therapy usage declines (hormonal replacement therapy tends to attenuate the relative effect of BMI – see later) and BMI distributions in populations are ‘skewed to the right’, these numbers may climb considerably in the future.

## 7 Confounding and Effect Modifications

### *7.1 Hormonal Replacement Therapy and Breast Cancer*

Evidence from randomized controlled trials [43] and observational studies [44] have shown that women taking hormonal replacement therapy for menopause are at increased risk of breast cancer, a risk that is greater with the use of combined oestrogen–progesterone than oestrogen-only preparations. As hyperoestrogenaemia secondary to increased aromatase activity in peripheral adipose tissue is relevant to the development of obesity-related post-menopausal breast cancer, it is reasonable to hypothesize that the use of hormonal replacement therapy may effect the association between BMI and breast cancer risk. This hypothesis has been tested in at least five cohort studies [45–49] where risk estimates were reported stratified by hormonal replacement therapy status. Table 2.3 summarizes these studies and demonstrates that hormonal replacement therapy is an effect modifier for the associations between BMI and post-menopausal breast cancer, namely risk estimates per 5 kg/m<sup>2</sup> increase in BMI are higher among never users compared with ever users.

**Table 2.3** Associations between BMI and post-menopausal breast cancer risk stratified by HRT usage

	Total cohort		Never users		Ever users		
	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)	HRT type	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)
Morimoto et al. [45]	1030	1.11 (0.83, 1.50)	319	1.34 (1.18, 1.52)	HRT, NOS	711	1.00 (0.91, 1.10)
Feigelson et al. [46]	1934	1.08 (0.98, 1.19)	1182	1.22 (1.14, 1.30)	EO and EP combined <sup>b</sup>	752	0.94 (0.85, 1.03)
Lahmann et al. [47]	1402	1.05 (0.86, 1.28)	911	1.14 (1.04, 1.26)	HRT, NOS	494	0.88 (0.77, 1.01)
Mellemkjaer et al. [48]	633	1.02 (0.93, 1.12)	217	1.08 (0.93, 1.24)	HRT, NOS	416	0.98 (0.86, 1.11)
Ahn et al. [49]	2087	1.10 (0.95, 1.28) <sup>c</sup>	925	1.19 (1.13, 1.27)	HRT, NOS	1162	1.02 (0.95, 1.09)

Risk estimates are per increase in 5 kg/m<sup>2</sup> BMI (body mass index) as per methods used in ref. [9]  
CI confidence intervals, HRT hormonal replacement therapy, NOS not otherwise specified

<sup>a</sup>Number of cases

<sup>b</sup>EO (oestrogen only) and EP (oestrogen and progesterone) reported together as 'risk ratio estimates were similar in the two groups'

<sup>c</sup>This risk estimate is not reported directly in the paper – instead this has been calculated combining the estimates for never and ever HRT (random-effects)

Indeed, associations in ever users are generally null: The mechanistic implication is that the ‘excess’ oestrogen environment associated with hormonal replacement therapy (of the order of a 10-fold increase compared with normal physiological ranges) dilutes the association seen between BMI and post-menopausal breast cancer risk. These observations are consistent with the findings of the Million Women Study [50] and other studies (seven studies cited in ref. [48]) where the increase risk associated with use of oestrogen-only or combined oestrogen–progesterone is attenuated with increasing BMI category. The observations are also consistent with the findings from the pooled analysis of the Hormonal Breast Collaborative that the increase in breast cancer risk associated with BMI is largely accounted for by circulating oestrogen levels [30].

A further dimension to the association between BMI and breast cancer risk is mammographic density, the latter being negatively correlated with BMI. Where there is adjustment of mammographic density, BMI–cancer risk estimates increase [51].

## ***7.2 Hormonal Replacement Therapy and Endometrial Cancer***

Similar to breast cancer risk, evidence from randomized controlled trials [52] and observational studies [53] have shown that post-menopausal women taking hormonal replacement therapy are at increased risk of endometrial cancer, but in contrast, the risk is greater with the use of oestrogen-only compared with combined oestrogen–progesterone, as the inclusion of progesterone is thought to offer some protection. Here again, it is reasonable to hypothesize that the use of hormonal replacement therapy may effect the association between BMI and endometrial cancer risk. Three cohort studies [54–56] have reported risk estimates stratified by hormonal replacement therapy status, and similar findings to those for breast cancer emerge (Table 2.4); namely, the risk estimates per 5 kg/m<sup>2</sup> increase BMI are higher among never users compared with ever users. When these data are taken together with the findings from the Million Women Study [57] (which only reported on the interaction between BMI, hormonal replacement therapy and endometrial cancer risk among hormonal replacement therapy ever users), it appears that the risk estimates per 5 kg/m<sup>2</sup> for cyclical combined hormonal replacement therapy were similar to those for oestrogen-only (approximately 1.20) and only return a null association for continuous combined hormonal replacement therapy, suggesting that the effect of progesterone is dependent on the numbers of days per cycle exposure. Furthermore, in the example of endometrial cancer, obesity is predominantly a risk factor for type I endometrioid tumours (accounting for 70% of endometrial cancers), which is linked with hyperoestrogenic states [58].

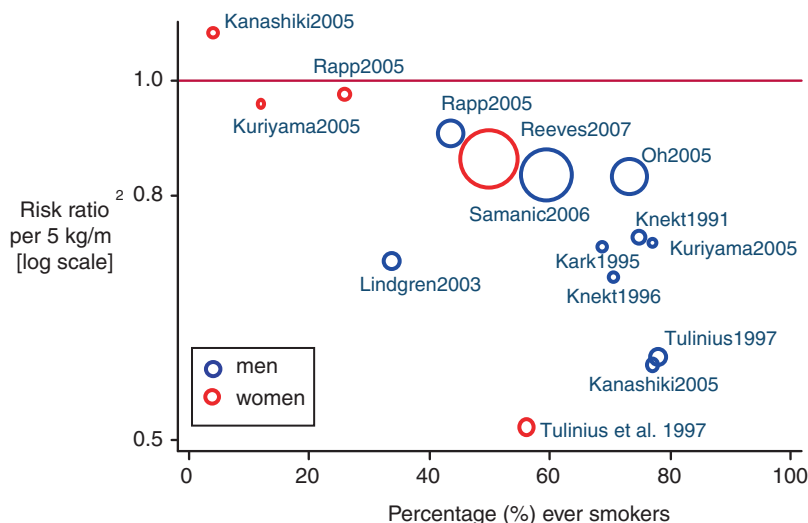
## ***7.3 BMI, Smoking and Cancer Risk***

In our meta-analysis [9], we noted three cancer types in which the association between BMI and risk was inverse, namely pre-menopausal breast cancer,

Table 2.4 Associations between BMI and endometrial cancer risk stratified by HRT usage

	Total cohort		Never users		Ever users		
	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)	HRT type	<i>n</i> <sup>a</sup>	Risk ratio (95% CIs)
Chang et al. [54]	677	1.40 (1.17, 1.67)	358	2.26 (1.87, 2.73)	EO	34	1.19 (0.93, 1.53)
Chang et al. [54]	NA		NA		EP, NOS	242	1.25 (1.05, 1.47)
Friedenreich et al. [55]	567	1.34 (1.22, 1.47)	151	1.61 (1.151, 1.85)	HRT, NOS	186	1.10 (0.88,1.38)
McCullough et al. [56]	318	1.89 (1.64, 2.17)	207	1.93 (1.64, 2.28)	EP, NOS	186	1.29 (0.82, 2.01)
Beral et al. [57]	NA		NA		EP continuous	73	1.02 (0.73, 1.42)
Beral et al. [57]	NA		NA		EP cyclic	242	1.25 (1.05, 1.47)

Risk estimates are per increase in 5 kg/m<sup>2</sup> BMI (body mass index) as per methods used in ref. [9]  
*CI* confidence intervals, *NA* not applicable, *EO* oestrogen only, *EP* oestrogen and progesterone combined, *HRT*, *NOS* hormonal replacement therapy, not otherwise specified  
<sup>a</sup>Number of cases



**Fig. 2.3** BMI, smoking and lung cancer risk. Plot of sex-specific risk ratios per 5 kg/m<sup>2</sup> increment increase in BMI (i.e. ‘slopes’) for cohort studies of lung cancer risk versus percentage ever smokers per study. The references for the studies are available from the supplemental file of ref. [9] and author. The size of each circle is proportional to the sample size of each cohort. The plot demonstrates that as the percentage of ever smokers increases, the ‘study-slope’ or BMI–cancer association becomes more negative

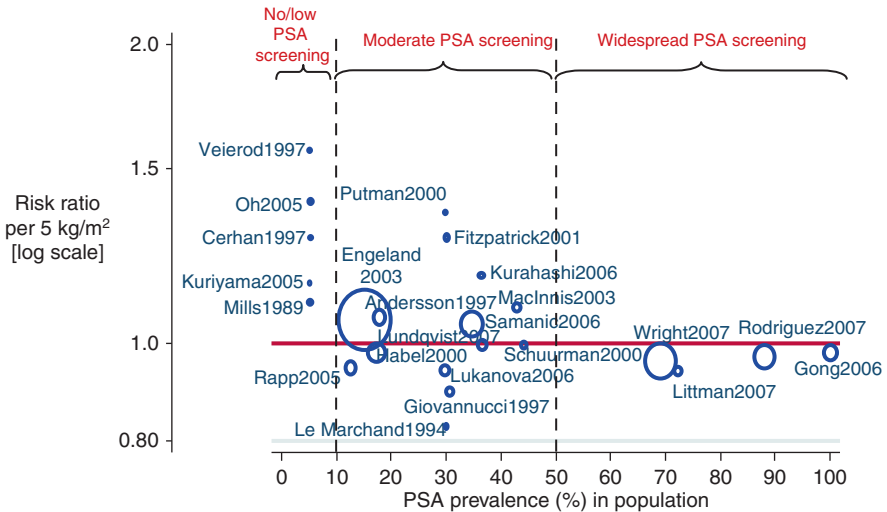
oesophageal squamous cell carcinoma and lung cancer (in the latter two, these inverse relationships were in both genders). Clearly, the public health message here is not one that if a population is overweight and obese, they are at less risk of these cancers. As pointed out in an earlier section, the associations between adiposity and pre-menopausal breast cancer and oesophageal squamous cell carcinoma may be better expressed using indices of central obesity. For lung cancer, given the well-recognized observation that smokers consistently have a lower mean BMI [59] and the strong association between smoking and lung cancer risk, it is reasonable to hypothesize that smoking may be an effect modifier in the relationship between BMI and lung cancer risk. This indeed seems to be the case (Fig. 2.3) – when sex-specific risk estimates per 5 kg/m<sup>2</sup> (derived from the analysis in ref. [9]) are plotted against the prevalence of smoking in the sex-specific populations of each study, the greater the percentage ever smokers, the greater the inverse association. In the absence of smoking, it appears that the association between BMI and lung cancer risk is null.

Interestingly, when the European Prospective Investigation into Cancer and Nutrition investigators [15] recently examined the question of the relationship between adiposity and oesophageal cancer risk recognizing that two main histological types exist – oesophageal adenocarcinoma and oesophageal squamous cell carcinoma – they found, as in our meta-analysis [9], a strong association between BMI and oesophageal adenocarcinoma. This was essentially unaffected when the data were analysed by smokers and non-smokers. In sharp contrast, the association between BMI and oesophageal squamous cell carcinoma, which was significantly

inverse among smokers (risk estimate for uppermost quintile versus lowermost quintile: 0.09, 0.03–0.29) was null among non-smokers (0.68, 0.11–4.10).

7.4 PSA Screening and Prostate Cancer Risk

Initial epidemiologic data appeared to suggest that increasing BMI was positively associated with prostate cancer risk. For all invasive prostate cancers, when we meta-analysed risk estimates across 27 cohort studies [9], the summary estimate was only very modestly positive (1.03, 1.00–1.07). However, there was considerable heterogeneity judged by the heterogeneity statistic  $I^2$  value of 73%. A variety of commentaries [60–62] suggest that BMI is associated with high-grade and/or aggressive histological types of prostate cancer (and possibly a reduced risk of low-grade/less aggressive prostate cancer). Supporting this posit, obesity is consistently associated with an increased rate of prostate cancer progression and mortality [62]. In turn, the proportion of high-grade/aggressive histology prostate cancers in a cohort reflects the level of prostate-specific antigen screening in that population and hence the high level of heterogeneity noted may be partly explained by the level of prostate-specific antigen screening. This would appear to be true – Fig. 2.4 shows risk ratios per 5 kg/m<sup>2</sup> increment increases in BMI per study plotted against the



**Fig. 2.4** BMI, PSA screening and prostate cancer risk. Plot of sex-specific risk ratios per 5 kg/m<sup>2</sup> increment increase in BMI (i.e. ‘slopes’) for cohort studies of prostate cancer risk versus prevalence of PSA screening per study. The references for the studies are available from the supplemental file of ref. [9] and author. The size of each circle is proportional to the sample size of each cohort. Where exact prevalence was not reported in each paper, the prevalence was allotted to the mid-point of respective categories: ‘no routine PSA screening or very low prevalence’; ‘moderate level of PSA screening’; or ‘widespread PSA screening’. The plot demonstrates that as the level or prevalence of PSA screening in a population increases, the ‘study-slope’ or BMI–cancer association approaches one or ‘null’

prevalence of prostate-specific antigen screening. In recent studies with large sample sizes and greater than 50% prevalence of prostate-specific antigen screening in the populations, the associations between overall prostate cancer risk and BMI are essentially null.

There are a number of site-specific mechanisms that need to be considered in the interpretation of associations between obesity and prostate cancer risk as follows:

- increasing BMI is correlated with a reduction in mean serum prostate-specific antigen concentrations;
- there is an inherent bias in a clinician's ability to detect prostate cancer in obese men as larger sized prostates make biopsy less accurate for finding an existing cancer;
- obesity (and type 2 diabetes) is associated with lower testosterone mean levels compared with normal weight men;
- recent genetic studies have highlighted a potential genetic link between insulin resistance and prostate cancer: One study identified an allele in the *HNFB* (also known as *TCF2*) gene that predisposes to type 2 diabetes, while also protecting men from prostate cancer; another study identified different variants in the *JAZF1* gene, one associated with insulin resistance, another associated with prostate cancer [63].

## 8 Future Directions

Important questions remain in relation to the cumulative effects of excess body weight over several decades, the effect of key weight change periods in the life-course of individuals and interactions with other risk factors [64]. Other unresolved questions relate to the most appropriate measure of adiposity in terms of cancer risk, the mechanisms underpinning the observed gender differences and whether there are differences across ethnicities. Finally, while public health policies aimed at curbing the underlying causes of the obesity epidemic are being implemented, there is a parallel need to better understand the biological processes linking obesity and cancer as a pre-requisite to the development of new approaches to the prevention and treatment of obesity-related cancers.

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