University of Dundee

European Code against Cancer 4th Edition

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European Code against Cancer 4th Edition: Obesity, body fatness and cancer☆

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ABSTRACT

It is estimated that over half the population of the European Union (EU) is overweight or obese due to an imbalance between energy expenditure and energy intake; this is related to an obesogenic environment of sociocultural, economic and marketing challenges to the control of body weight. Excess body fat is associated with nine cancer sites – oesophagus, colorectum, gall bladder, pancreas, postmenopausal breast, endometrium, ovary, kidney and prostate (advanced) – and 4–38% of these cancers (depending on site and gender) can be attributed to overweight/obesity status. Metabolic alterations which accompany excess body weight are accompanied by increased levels of inflammation, insulin, oestrogens and other hormonal factors. There are some indications that intentional weight loss is associated with reduced cancer incidence (notably in postmenopausal breast and endometrial cancers). Excess body weight is also a risk factor for several other diseases, including diabetes and heart disease, and is related to higher risk of premature death.

In reviewing the current evidence related to excess body fat and cancer, the European Code against Cancer Nutrition Working Group has developed the following recommendation: 'Take action to be a healthy body weight'.

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1. Introduction

1.1. European prevalence of overweight and obesity

In 2012 over half the population of the European Union (EU) was estimated to be overweight [1], and one person in six was obese [2]. In adults, the proportion of men who are obese is between 8% (Romania) and 26% (Hungary), and the proportion of women who are obese is between 8% (Romania) and 30% (Hungary) (Fig. 1).

1.1.1. Overweight and obesity by age group and level of education

The proportion of people who are overweight or obese is higher in older than in younger people (Fig. 2). At ages 18–24, the proportion of men who are overweight or obese is below 30% in all countries except the Czech Republic, Cyprus, Poland, Slovenia and the UK, and the proportion of women who are overweight or obese is below 20% in all countries except the UK (Figs. 3 and 4). At ages 65–74, the proportion of men who are overweight or obese is above 60% in all countries, and the proportion of women who are overweight or obese is above 60% in all countries except Belgium, France, Italy and Romania (Figs. 2 and 3).

Among adolescents (15-year-olds) in EU member states, boys report excess weight more often than girls; one in six boys and one in 10 girls report being overweight or obese. More than 15% of adolescents in southern European countries (Greece, Italy, Portugal and Spain), as well as in Croatia, Iceland, Luxembourg and Slovenia, report being overweight or obese. Fewer than 10% of children in Latvia and Lithuania, as well as in Denmark, France and the Netherlands, report being overweight or obese (Fig. 4).

The proportion of overweight and obese people varies with educational level. In women the pattern is clear in that the proportion of obese or overweight women falls as the educational level rises (Fig. 5). In men, however, the educational level with the highest prevalence of overweight and obesity varies between countries, with some countries having the highest proportion in the least educated men, some having the highest proportion in the most educated, and some having the highest proportion in those with a medium level of education (Fig. 6).

1.2. Definition of overweight, obesity, body fatness and waist circumference

When energy intake is equal to energy expenditure, then energy balance is reached and the body neither gains nor loses weight. If excess energy intake or low energy expenditure occurs then weight gain will follow, mostly in the form of fat storage. Body fat

	Men	Women
Romania	7.6	8
Norway	11	9
Netherlands	11.2	12.8
Switzerland	11.2	9.4
Italy	11.3	9.5
Bulgaria	11.6	11.3
Sweden	11.7	11.8
Austria	12	12.7
Latvia	12	20.9
Belgium	13.1	14.4
Denmark	13.7	13.1
Turkey	13.7	20.9
France	14.5	14.6
Portugal	14.6	16.1
Germany	15.7	13.8
Finland	16.1	15.7
Poland	16.6	15.2
Cyprus	16.7	14.5
Slovak Rep.	17.1	16.7
Spain	17.5	15.6
Greece	17.7	18.5
Estonia	18.6	19.3
Czech Rep.	21	21
Slovenia	21.1	15.4
Ireland	22	24
Iceland	22.7	19.3
United Kingdom	24.4	25.1
Luxembourg	24.7	20.9
Malta	24.7	21.1
Hungary	26.3	30.4
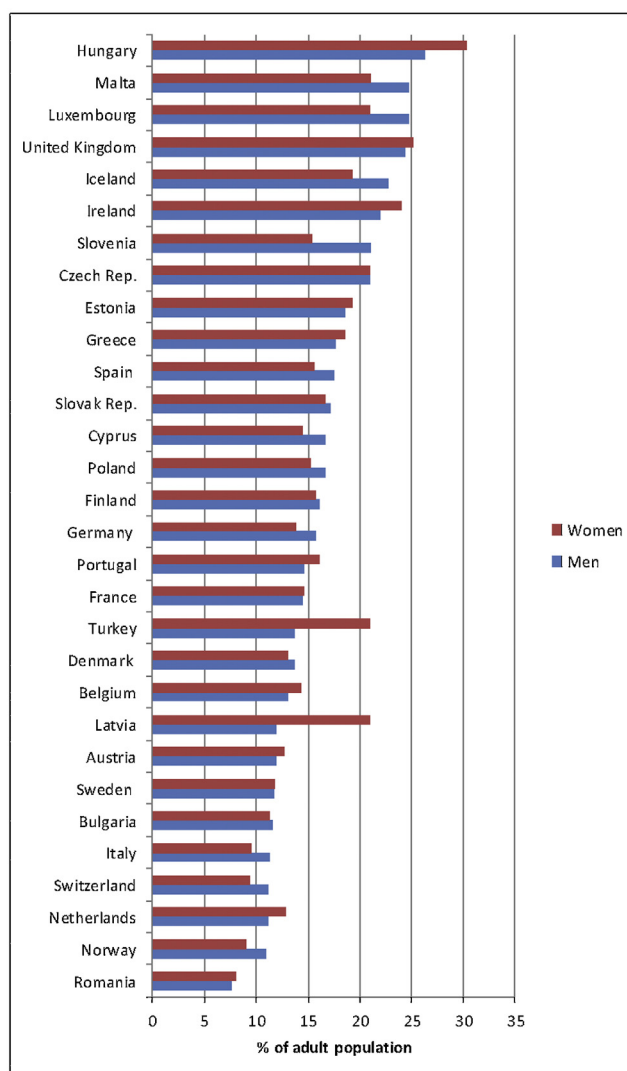
Fig. 1. Prevalence of obesity among adults in Europe, 2012 (or nearest year). Calculations provided by the OECD based on 'OECD. Health at a glance: Europe 2012. OECD Publishing' [2].
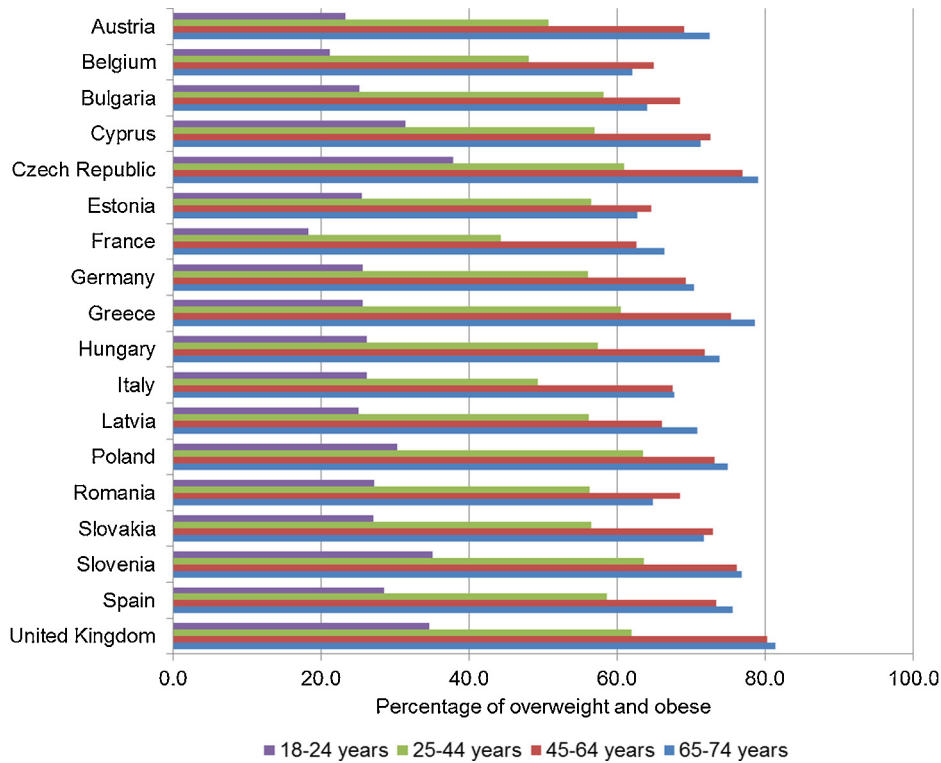
Fig. 2. Prevalence of overweight and obesity in men in Europe by age. Calculations provided by the Eurostat database [3].

stores cannot be easily measured, so body mass index (BMI) is commonly used as a proxy. BMI is assessed as weight (in kg) divided by the square of height (in m^2). This measure is generally a good index of obesity, but can be misleading for people who have a very high muscle mass because they will have a high BMI but not a high mass of stored fat. Increasingly, it is also recognised that intra-abdominal fat (visceral fat) assessed by waist circumference is a

good indicator of disease risk, and both BMI and waist circumference are informative in body fat assessment.

The principal BMI cut-offs defined by the World Health Organization (WHO) are overweight (25.00–29.99 kg/m^2) and obesity (30.00 kg/m^2 or more) (Table 1). These categories have been widely applied, although the associations between BMI, percentage of body fat, body fat distribution and disease

Fig. 3. Prevalence of overweight and obesity in women in Europe by age. Calculations provided by the Eurostat database [3] (http://epp.eurostat.ec.europa.eu/portal/page/portal/health/health_status_determinants/data/database).

Fig. 4. Prevalence of overweight and obesity among adolescents in Europe, 2009–2010. Calculations provided by the OECD based on 'OECD. Health at a glance: Europe 2014. OECD Publishing' [2].

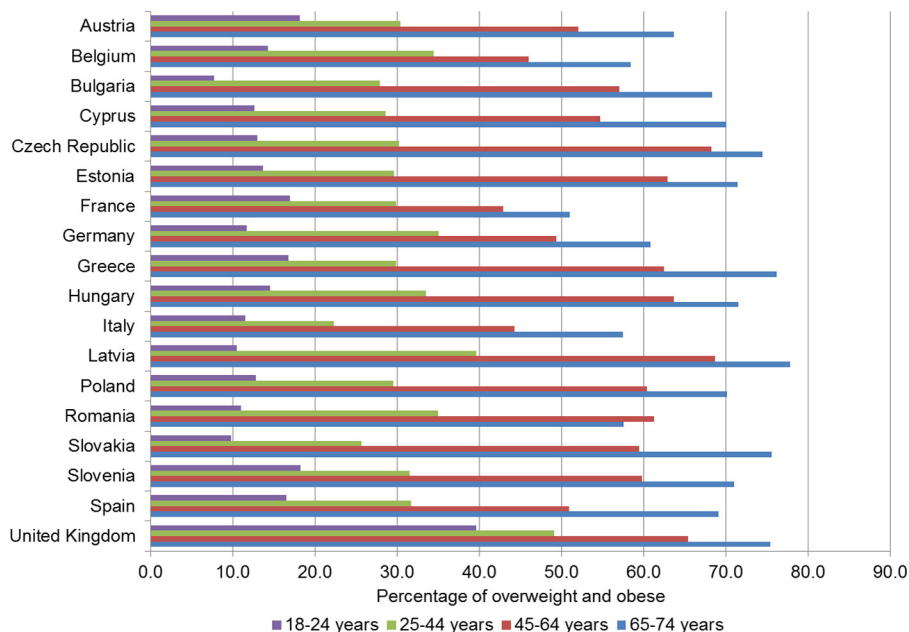risk are continuous and curvilinear, and differ between populations.

Abdominal obesity can be assessed using a standard protocol for measuring waist circumference (Fig. 7). The waist–hip ratio (i.e. the waist circumference divided by the hip circumference) is a measure of body fat distribution; a high waist–hip ratio indicates that proportionally more fat is stored around the middle of the body, both subcutaneously and within the abdominal cavity, than around the hips. The waist–hip ratio has been shown to be positively associated with risk for several types of cancer. Gender-specific cuts-offs for increased disease risk as indicated by fat storage distribution have been proposed by WHO (Table 2).

1.3. Modifiable lifestyle factors and environmental factors associated with overweight and obesity

An unhealthy weight is often seen as a result of individual choices with regard to diet, physical activity and lifestyle, all of which can be controlled and modified to some extent. However, it is recognised that people live in an obesogenic environment of sociocultural, economic and marketing challenges to the achievement of healthy ways of life [4]. Low cost, widely available energy-dense food and drink, combined with few opportunities to easily engage in work, home and leisure physical activity, stack the odds against successful weight management for the majority of the population [5].

Excessive intake of energy-dense foods and drinks is a major factor in the development of obesity from infancy onwards. Dietary habits including consumption of sugary drinks [6], fast foods and energy-dense foods (such as processed foods which are high in saturated fat, sugar and salt) [7] will increase the likelihood of positive energy balance and excessive fat storage. Regular consumption of large portions of foods with energy density >225 kcals/100 g (941 kJ/100 g) are associated with increased risk of weight gain [7].

Regular, sustained physical activity of all types protects against weight gain, overweight and obesity [7]. In addition, large amounts of sedentary behaviour (notably television viewing) are likely to increase the risk for weight gain [7]. A review by Boulos et al. [8] on weight gain suggests that television viewing is a substitute for
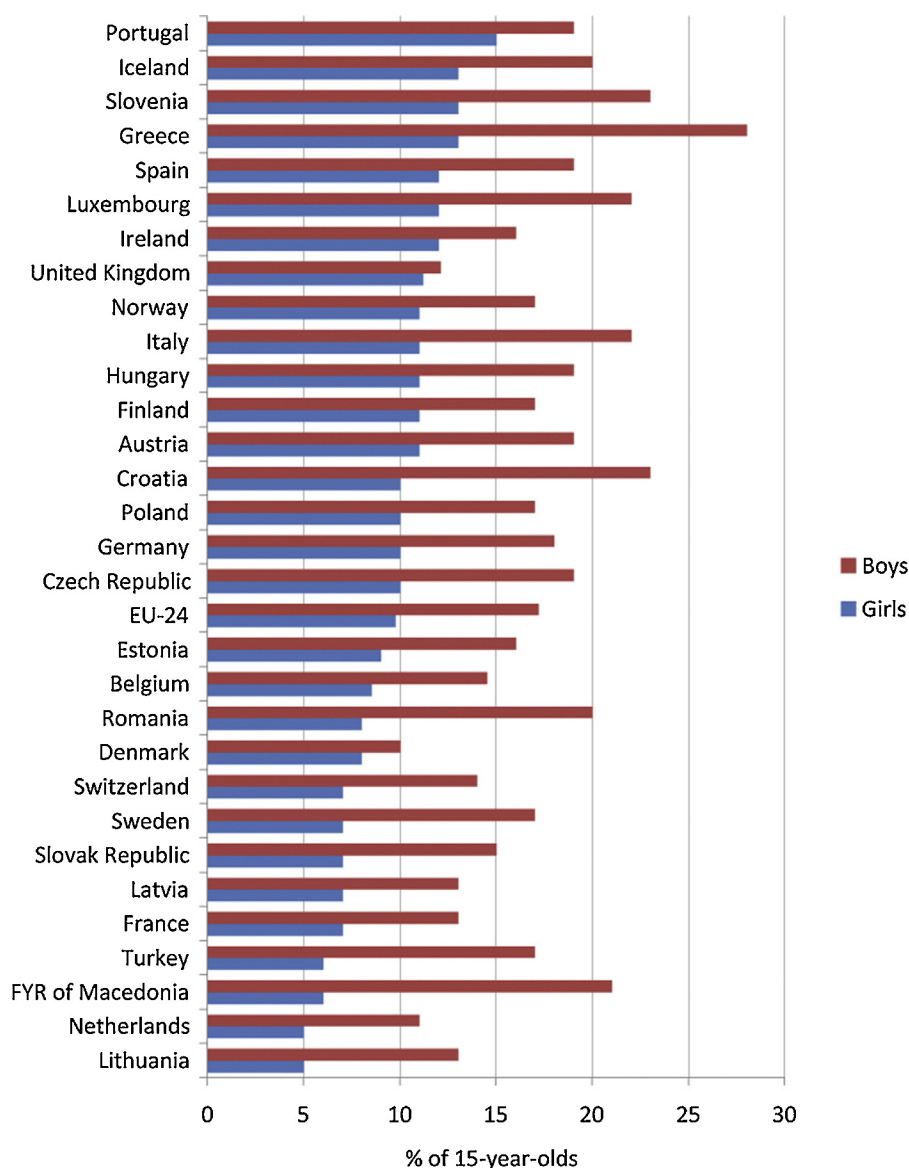
Fig. 5. Prevalence of overweight and obesity in women in Europe by level of education. Calculations provided by the Eurostat database [3] (http://epp.eurostat.ec.europa.eu/portal/page/portal/health/health_status_determinants/data/database).

being physically active as well as stimulating food intake and 'mindless eating' through advertising and product placements.

1.3.1. Breastfeeding

Infants who are breastfed appear to have a reduced risk of obesity in childhood and adolescence compared to those who are formula fed. A recent review [9] of prospective studies with children up to the age of 16 reported a 15% decrease in the odds of childhood obesity for breastfed infants. Such effects are likely to persist into adulthood [10]. However, it is recognised that potential confounders (e.g. education of the mother) may not have been fully accounted for in this analysis. In addition, Ip et al. [11] noted that
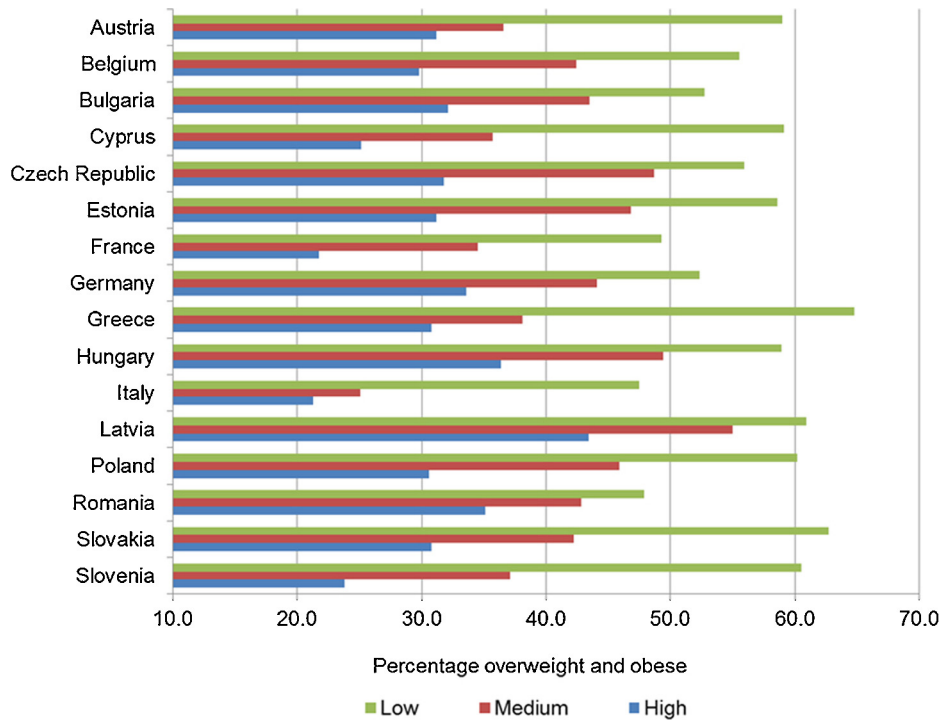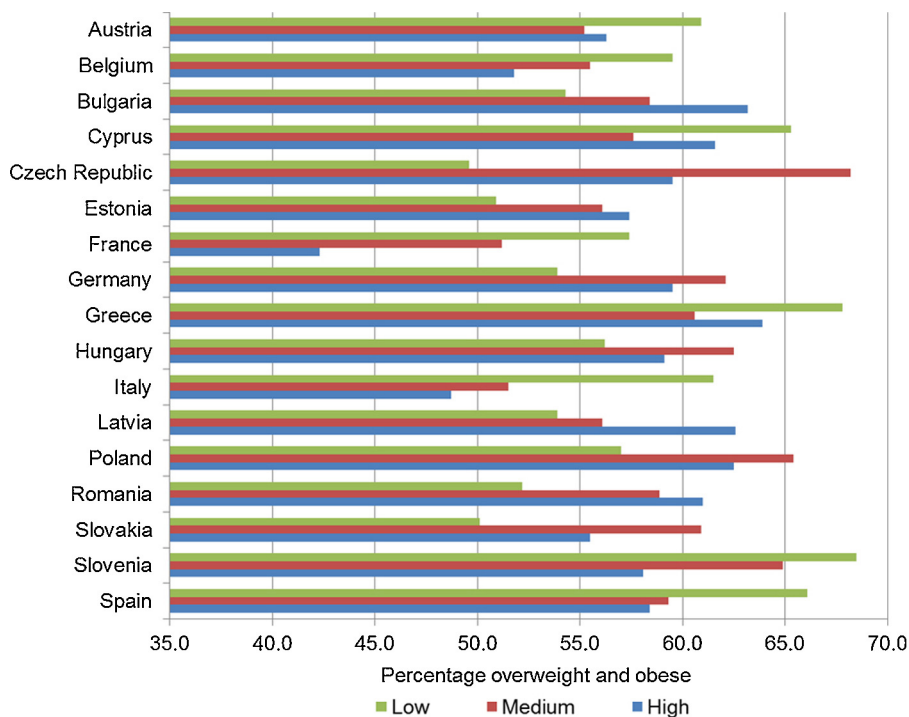

Fig. 6. Prevalence of overweight and obesity in men in Europe by level of education. Calculations provided by the Eurostat database [3] (http://epp.eurostat.ec.europa.eu/portal/page/portal/health/health_status_determinants/data/database).

Table 1
The international classification of adult underweight, overweight and obesity according to body mass index (BMI) [90].

Classification	BMI (kg/m^2)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Normal range	18.50–24.99	18.50–22.99
		23.00–24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00–29.99	25.00–27.49
		27.50–29.99
Obese	≥30.00	≥30.00
Obese class I	30.00–34.99	30.00–32.49
		32.50–34.99
Obese class II	35.00–39.99	35.00–37.49
		37.50–39.99
Obese class III	≥40.00	≥40.00

Adapted from WHO (1995, 2000, 2004).

observed associations between breastfeeding and a reduced risk of obesity may reflect selective reporting and/or publication bias. In most studies the exclusivity of breastfeeding is not described. The mechanisms by which breastfeeding may impact on weight development have not been identified, although it is notable that breastfed infants consume less total energy and less protein than formula-fed infants [12].

Mothers who breastfeed are likely to gain both short- and long-term benefits in body weight change. Observational studies show favourable effects on return to pre-pregnancy weight and metabolic profiles [11,13–15]. Data from the North American CARDIA study [16] have demonstrated that longer duration of lactation is associated with lower incidence of metabolic syndrome many years after weaning. Bobrow et al. [17] reported favourable associations with previous breastfeeding among postmenopausal women in the UK Million Women Study; at every parity level, the mean standardised BMI was significantly lower among women (mean age 57.4 years) who had previously breastfed, decreasing

0.22 kg/m^2 for every 6 months of breastfeeding. There is, however, some inconsistency in results from intervention studies – including a large cluster-randomised trial of 17,046 women from Belarus, which reported that women randomly assigned to a successful breastfeeding intervention did not have lower adiposity after 11.5 years follow-up [18].

2. Association with cancer

2.1. Cancer cases attributable to weight gain, overweight and obesity

Renehan et al. [19] estimated the incident cancer burden attributable to excess body mass in 30 European countries from data available in 2008. The estimated population-attributable risk (PAR) due to overweight and obesity was 3.2% (2.1–4.3%) in men and 8.6% (5.6–11.5%) in women. Country-specific data have been estimated for the UK by Parkin et al. [20] who suggest that an estimated 17,294 excess in cancer cases occurring in 2010 were due to overweight and obesity (5.5% of all cancers, 4.1% in men and 6.9% in women).

More recent UK preventability estimates from the World Cancer Research Fund (WCRF) [21] for all nine sites – oesophagus, colorectum, gall bladder, pancreas, breast (postmenopausal), endometrium, ovaries, kidney and prostate (advanced) – to which obesity is related [6] indicate that 4–38% of these cancers (depending on site and gender) can be attributed to excess weight.

2.2. Cancer types associated with overweight and obesity

Numerous observational studies have associated different measures of adiposity and excess body weight (notably self-reported BMI and waist circumference) with increased risks of several cancers. The evidence has increased over the last 10 years. In 2002, a working group of experts convened by the International Agency for Research on Cancer (IARC) concluded that in humans there was sufficient evidence that avoiding overweight and obesity reduces the risk of cancers of the colorectum, endometrium, kidney (renal cell), oesophagus (adenocarcinoma) and postmenopausal breast cancer [22]. In 2007, a major review of food, nutrition, physical activity and cancer prevention, the World Cancer

- Measure the *waist circumference* at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line

- Measure the *hip circumference* at a level parallel to the floor, at the largest circumference of the buttocks

- Make both measurements with a stretch-resistant tape that is wrapped snugly around the subject, but not to the point that the tape is constricting. Keep the tape level and parallel to the floor at the point of measurement

- Ensure that the subject is standing upright during the measurement, with arms relaxed at the sides, feet evenly spread apart and body weight evenly distributed

Fig. 7. Measurement protocol for waist and hip circumference.

Table 2
Proposed cut-off points and risk of metabolic complications.

Indicator	Cut-off points	Risk of metabolic complications
Waist circumference	>94 cm (M); >80 cm (W)	Increased
Waist circumference	>102 cm (M); >88 cm (W)	Substantially increased
Waist–hip ratio	≥0.90 (M); ≥0.85 (W)	Substantially increased

Research Fund/American Institute for Cancer Research Second Expert Report, judged that the evidence of a causal association with excess body fatness was convincing for those cancers [23]. These associations were confirmed by a meta-analysis of prospective cohort studies [24], in which the positive association with BMI became evident for some other cancers including thyroid, liver, leukaemia, malignant melanoma, multiple myeloma and non-Hodgkin lymphoma. Other recent quantitative summaries of observational prospective studies have provided further evidence of positive associations between BMI and gastric cardia cancer [25] and advanced prostate cancer [26,27]. In the observational studies, most of the risk increases are in the range of 10–30% for an increase of 5 kg/m² of BMI, and obese subjects have approximately a 1.5–3.5-fold increased risk of developing the cancers for which an association has been observed with body fatness, compared with normal-weight subjects (Table 3).

The existing data indicate that the influence of excess body fatness on the risk of cancer may differ between men and women,

and according to subtypes within a specific cancer. Stronger associations have been observed in men for colon cancer, and in women for gallbladder cancer. As for cancer subtypes, stronger associations for breast cancer have been observed for the oestrogen- and progesterone-receptor-positive tumours [28], for type I endometrioid tumours rather than for type II [29], and – although the evidence is still limited – for cardia gastric adenocarcinomas rather than non-cardia gastric malignancies [25] and for the papillary subtype of thyroid carcinoma [30]. Menopausal hormone therapy use may modify the association of body fatness with hormone-related cancers in women, with larger relative risks (but not absolute risks) observed in never users of hormone therapy for breast [24], endometrial [29] and ovarian cancers [31]. These patterns are complex. Taking breast cancer as an example, the lowest risk group includes lean women who do not take menopausal hormone therapy; obese women who do not take menopausal hormone therapy have a higher risk, as do women who take menopausal hormone therapy regardless of whether or not they are obese [32].

Waist-to-hip ratio or waist circumference have been interpreted as measures of central adiposity but may also be markers of overall adiposity. In most studies these measures have shown associations with cancer that are similar to those for BMI. However, some studies have reported associations of waist and waist-to-hip ratio independent of BMI for some cancers [33], and in a longitudinal study [34] visceral adiposity measured by using multidetector computed tomography was associated with overall risk of cancer after adjustment for generalised adiposity. These results suggest that the influence of visceral adiposity on cancer risk may be at least partially independent of total body adiposity;

Table 3
Summary of estimated associations between body mass index (BMI) and risk of some cancers in prospective studies by strength of the evidence (as judged by the Panels of Experts of the 2007 WCRF-AICR Second Expert Report and the CUP).

		Men			Women		
	Studies	Risk ratio[*] (95%CIs)	I^2 (%)[§]	Studies	Risk ratio (95% CIs)	I^2 (%)[§]	Reference
Convincing							
Oesophageal adenocarcinoma	5	1.52 (1.33–1.74)	24	3	1.51 (1.31–1.74)	0	Renehan et al. [24]
Pancreas	14	1.13 (1.04–1.22)	45.6	15	1.10 (1.04–1.16)	41.8	WCRF–CUP SLR, 2012 [95]
Colon	22	1.21 (1.16–1.27)	49.9	24	1.10 (1.05–1.15)	52.7	WCRF–CUP SLR, 2010 [95]
Rectum	18	1.10 (1.05–1.15)	0	18	1.05 (1.00–1.10)	32	WCRF–CUP SLR, 2010 [95]
Endometrium	–			25	1.18 (1.08–1.29)	0	WCRF–CUP, SLR 2013 [95]
Post-menopausal breast cancer	–			19	1.12 (1.07–1.18)	59.8	WCRF–CUP, SLR 2008 [95]
Kidney	13	1.27 (1.21–1.33)	NA	15	1.33 (1.27–1.40)	NA	Ildaphonse et al. [91] Renehan et al. [24] Mathew et al. [92]
Probable							
Gallbladder cancer	4	1.09 (0.99–1.21)	0	2	1.59 (1.02–2.47)	67	Renehan et al. [24]
Ovarian cancer	–	–	–	25	1.06 (1.02–1.11)	55%	WCRF–CUP, SLR 2014 [95]
Limited suggestive							
Liver	11	1.26 (1.11–1.44)	79.1	5	1.07 (0.55–2.08)	NA	Wang et al. [96]
		–					WCRF–CUP SLR, 2013 [95]
Limited, no conclusion							
Leukaemia	7	1.08 (1.02–1.14)	0	7	1.17 (1.04–1.32)	80	Renehan et al. [24]
Malignant melanoma	6	1.17 (1.05–1.30)	44	5	0.96 (0.92–1.01)	39	Renehan et al. [24]
Multiple myeloma	8	1.15 (1.05–1.25)		10	1.10 (1.05–1.15)		Wallin and Larsson [93]
Non-Hodgkin lymphoma	8	1.09 (1.04–1.14)	0	10	1.07 (1.00–1.13)	44.1	Larsson and Walk [94]
Thyroid cancer	4	1.33 (1.04–1.70)	77	3	1.14 (1.06–1.23)	5	Renehan et al. [24]
Advanced prostate cancer	13	1.09 (1.02–1.16)	38.1		–		Discacciati et al. [26]
Pre-menopausal breast cancer				16	0.92(0.87–0.97)	50.1	WCRF–CUP, SLR 2008 [95]
Gastric	8	0.97 (0.88–1.06)	35	5	1.04 (0.90–1.20)	4	Renehan et al. [24]
Cardia gastric	7	1.32 (1.07–1.64)	81.9	(men and women combined)			Chen et al. [25]
Lung	11	0.76 (0.70–0.83)	63	6	0.80 (0.66–0.97)	84	Renehan et al. [24]

From WRCF Continuous Update Project (CUP) systematic literature reviews [94].

[*] Risk ratios estimates for an increase of 5 kg/m² of BMI.

[§] The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity. Low heterogeneity might account for less than 30% of the variability in point estimates, and high heterogeneity for substantially more than 50%.

however, the public health relevance may be limited because the main determinant of total visceral adiposity is overall adiposity itself.

2.3. Mechanisms linking excess body weight to cancer

Chronic positive energy balance – due to excess energy intake and/or low energy expenditure – can lead to obesity and its associated metabolic alterations, such as increased levels of insulin and changes in the bioavailabilty of insulin-like-growth factor (IGF)-I and steroid hormones. Adipose tissue is now recognised as metabolically active and a source of adipose-tissue-derived hormones and cytokines (adipokines) such as leptin, adiponectin and inflammatory cytokines. These metabolic alterations have been implicated as key contributors to the effects of obesity on cancer incidence through mechanisms that may be general (operating for several cancer sites) or cancer-specific [35,36].

The increased risk of postmenopausal breast cancer in obese women is generally explained by the higher rates of conversion of androgenic precursors to oestradiol through the activity of adipose-tissue aromatase. After menopause, when ovarian oestrogen production stops, the adipose tissue becomes the major source of endogenous oestrogens. Further, obesity-related hyperinsulinaemia inhibits hepatic secretion of sex-hormone-binding globulin. Both effects result in an increase in bioavailable oestradiol and testosterone [37]. Alterations in endogenous hormone metabolism may also provide the main links between obesity and endometrial cancer risk. The 'unopposed oestrogen' hypothesis proposes that endometrial cancer may develop as a result of the mitogenic effects of oestrogens when these are insufficiently counterbalanced by progesterone [38]. There is abundant experimental evidence from in vitro and animal models that oestrogens increase endometrial cell proliferation, inhibit apoptosis, and stimulate the local synthesis of IGF-I in endometrial tissue [35].

Insulin or hyperinsulinaemia stimulate the proliferation of tumour cells in vitro and in animal studies and lead to increased growth of colon, breast, prostate, and bladder cancers [39]. In prospective epidemiological studies, increased risks of colon [40], pancreatic [41], endometrial [42], and postmenopausal breast [43] cancers have been observed in relation to higher levels of circulating C-peptide levels, a biomarker of insulin secretion. Indirect evidence for a role of insulin on cancer development is provided by studies showing that type 2 diabetic patients who get insulin therapy or drugs to stimulate insulin secretion have a significantly higher incidence of cancer than those who get metformin, an antidiabetic drug that reduces glucose production in the liver [44,45]. Hyperinsulinaemia could also promote carcinogenesis indirectly by increasing the levels of circulating free IGF-I that has mitogenic and anti-apoptotic activity [39]. In epidemiological studies higher circulating concentrations of IGF-I are associated with increased risk of prostate [46] and colorectal, pre- and postmenopausal breast cancers [47,48]. Adiponectin and leptin are the most abundant adipokines. Although studies have not been entirely consistent, leptin has been shown to be mutagenic, pro-inflammatory, anti-apoptotic, and pro-angiogenic; adiponectin is inversely related to BMI and visceral adiposity, may stimulate apoptosis and inhibit angiogenesis and cell migration. In prospective studies, adipokines have been found to be associated with risk of cancers of the breast [49], endometrium [50] and colon [51]. Leptin enhances the production of inflammatory factors, and different pathways link inflammation and cancer by a number of oncogenes [51].

The increase in risk of adenocarcinoma of the oesophagus through the effects of obesity is thought to be due largely to reflux of stomach contents into the lower oesophagus [52,53].

3. Justification for recommendation

3.1. The importance of obesity in prevention

Diet (including alcohol) [54,55] and physical inactivity [56] are both directly implicated in the aetiology of cancer, as well as being indirect contributors via their impact on energy balance and contribution to weight gain. It is useful, however, to consider the relative contribution of each factor.

Parkin et al. [20] estimated the fraction of all cancers occurring in the UK in 2010 that could be attributed to suboptimal past exposures of 14 lifestyle and environmental risk factors. The relative importance of exposures differed by sex. In men, overweight and obesity accounted for 4.1% of cancers, compared to 4.6% for excess alcohol consumption and 0.4% for insufficient physical activity. In women, overweight and obesity accounted for 6.9% of cancers, compared to 3.3% for excess alcohol and 1.7% for insufficient physical activity. Insufficient intake of fruit and vegetables was also estimated to cause 6.1% of cancers in men and 3.4% of cancers in women.

In a recent international review of preventability estimates, WCRF (2014) [23] report that of the nine cancer sites in which excess body fat has been identified as a risk factor, five have no other identifiable direct diet and physical activity factors – kidney, pancreas, gall bladder, ovaries, prostate (advanced) – and in the UK excess body fat is responsible for 19%, 15%, 16%, 4% and 10% of cancers respectively in these sites. In oesophageal cancer, physical activity has not been shown to be directly related to the aetiology, but the impact of alcohol intake (51%) exceeds both the contribution of excess body fat (31%) and dietary vegetables and fruit (26%). In cancer of the endometrium, body fatness accounts for 38% with a further 10% contributed by low levels of physical activity with no dietary factors. In breast cancer, alcoholic drinks make the dominant contribution to preventability (22%), followed by excess body fat (16%) and low physical activity (12%). Revised estimates for colorectal cancer [21] suggest that body fat accounts for 14% of the disease, followed by dietary factors – low intake of foods containing fibre, and high intakes of red and processed meat (27%) – and low physical activity (16%).

3.2. Body weight in cancer survivors

After (pre- and post-menopausal) breast cancer diagnosis, obese women have on average a 33% higher risk of total (95%CI: 21–47%) and breast-cancer-specific mortality (95%CI: 19–50%) compared to non-obese women [57]. However, a recent review on breast cancer survivors [58] from WCRF International suggests that more work is needed to examine the relationship between survivorship and obesity because of inadequate ascertainment, reporting and correction of potential confounders (notably stage of disease or type of treatment).

Mortality after ovarian cancer is 17% (95%CI: 3–34%) higher among obese compared to non-obese women [59]. Although the number of studies is still small, there is emerging evidence that higher BMI is associated with poorer cancer-specific mortality from endometrial cancer [60]. Obesity has been consistently associated with prostate cancer mortality in cohort studies [61,62], and a meta-analysis by Cao and Ma [63] reported that a 5 kg/m^2 increase in BMI was significantly associated with a 21% increased risk of biochemical recurrence of the disease. See also the recent review on prostate cancer from WCRF/AICR [27].

For colorectal cancer, poorer outcomes have been reported in obese patients with BMI >35 kg/m^2 with up to a 38% increased risk of recurrence and a 36% increased risk of disease-specific mortality [64]. Little association has been demonstrated between post-diagnosis changes in weight or BMI on cancer recurrence and

survival, suggesting that pre-diagnosis obesity status may be a more important influence on cancer outcomes [65,66].

Many cancer patients increase in weight after diagnosis and during treatment, and they commonly experience adverse changes in body composition – including loss of lean body mass and gain of adipose tissue. Weight gain is associated with chemotherapy, increased BMI at diagnosis, and younger age, and may in part relate to decreased physical activity during treatment [67]. Weight gain can also contribute to psycho-social distress.

No long-term trials of weight loss and cancer recurrence have yet been reported. However, two US randomised trials of dietary modifications on cancer outcomes in breast cancer survivors have provided indirect evidence that weight loss after diagnosis could lead to lower rates of recurrence. The WINS (Women's Interventional Nutrition Study) trial [68] reported a 24% reduction in the risk of recurrence at 5 years in breast cancer survivors randomly assigned to a low-fat intervention group. The intervention group lost an average of 6 lb (4% of body weight) compared with controls, and demonstrated significantly lower rates of recurrence (HR, 0.76; 95%CI, 0.60–0.98) notably among women with oestrogen-receptor-negative disease (HR, 0.58; 95%CI, 0.37–0.91).

A number of lifestyle intervention trials in cancer survivors have demonstrated that cancer survivors are motivated and able to make dietary and lifestyle modifications and to lose clinically relevant amounts of body weight. Favourable outcomes include reduction in co-morbidities and improvements in quality of life, fitness, and fatigue. There may be additional reasons for focusing on weight loss in cancer survivors, including co-morbidities such as cardiovascular disease and diabetes, treatment side-effects, and reduction in the risk of second malignancies. For cancer survivors, weight loss programmes for the overweight/obese patient should embrace both dietary and physical activity components which meet cancer prevention guidelines.

3.3. Avoiding weight-related co-morbidities (diabetes and heart disease)

Co-morbid chronic diseases are common in persons with cancer, and the disease and its treatment are associated with an increased risk for co-morbid conditions including heart disease, diabetes, and stroke [69]. It is likely that many pre-diabetic metabolic changes (notably insulin resistance) may also increase cancer risk. Type 2 diabetes is positively associated with cancers of the colon, breast (postmenopausal) and pancreas. Patients with type 2 diabetes are at increased risk of cancers of the liver, pancreas, endometrium, colorectum, breast, and bladder [70–72]. Current estimates show an overall hazard ratio (HR) of 1.23 for breast cancer incidence, and 1.26 for colorectal cancer incidence in patients with diabetes compared to those without diabetes [73]. Body weight reduction has been demonstrated to show proven benefit with regard to risk reduction of type 2 diabetes and cardiovascular disease, and a comprehensive programme of lifestyle modification – which includes diet, exercise, and behavioural techniques – has been demonstrated to achieve successful weight loss and avoidance of weight gain.

3.4. Body weight in older people

Excess body weight is associated with increased total mortality [74]. In a large prospective study in 10 European countries, the lowest risks of death related to BMI were observed at a BMI of 25.3 kg/m^2 for men and 24.3 kg/m^2 for women [75]. In older people, stable body weight is a predictor of lower subsequent mortality. Weight loss is associated with increased mortality (in the short term) and weight gain (>1 kg), especially amongst the overweight or obese, is also associated with increased mortality (in the long term) [76]. Ageing is associated with an increase in adiposity (fat mass) and a loss of muscle (fat free) mass (sarcopenia). Sarcopenia is associated with poor muscle strength, functional impairment and disability, and greater morbidity from cancer, stroke and coronary heart disease [77]. Prevalence estimates of sarcopenia range from 5 to 15% in people aged 60–70 years and from 11 to 50% in those aged over 80 years, with women at greatest risk. Simultaneous occurrence of obesity and sarcopenia (sarcopenic obesity) is thought to elevate morbidity risk and may be masked by high BMI.

3.5. Body weight in childhood

Growth in infancy is influenced by birth weight and early feeding experiences which in turn influence growth patterns, the so-called 'adiposity rebound' (period of increasing BMI after the early childhood nadir, which usually occurs at about 6 years of age) and body fatness in childhood. The development of overweight in childhood appears to track into adult life [78], and although it is recognised that there is a dearth of longitudinal studies that examine the development of excess body weight in childhood and adolescence, a recent review has reported a positive association between genetic factors and physical activity, but an inconsistent association with dietary intake [79].

Childhood BMI has been shown to be associated with adult adiposity [80]; thus interventions which prevent or reduce excess weight gain in childhood provide a window of opportunity for overall cancer risk reduction. The evidence for the relationship between childhood obesity and cancer in adult life is inconsistent. One UK cohort study reported that the overall risk of adult cancer was increased with increased childhood BMI, particularly in smoking-related cancers [81]. There is limited evidence in relation to higher childhood weight and later development of colorectal and kidney cancer [82]. In breast cancer, greater body fatness during childhood and adolescence appears to be associated with a reduced risk of breast cancer in later life (particularly premenopausal breast cancer) [83]. The reasons for this are unclear but are thought to relate to endogenous sex hormone levels and greater anovulation in overweight adolescents [84].

3.6. Intentional weight loss and cancer risk

There is as yet no clear demonstration that avoiding excess body weight can reduce cancer risk. The number of studies on intentional weight loss is sparse, but at least six studies (including three surgical studies) have reported that cancer incidence is reduced after intentional weight loss in individuals with excess weight, and they suggest that the time needed to obtain a reduction in cancer incidence could be relatively short (longest follow-up was 10.9 years) [85]. Estimates for reduction in overall cancer incidence in males and females from bariatric surgery are in the order of 30%. Risk reduction is greatest for obesity-related cancers and in women. Apart from the reduction in incidence for overall cancer, significant findings have mostly been reported for postmenopausal breast cancer and endometrial cancer [86]. In breast cancer, there is increasing interest in exploring the beneficial effects of weight loss in overweight and obese, post-menopausal women with respect to decreased levels of oestrogens, insulin, and leptin, and increased levels of sex-hormone-binding globulin (SHBG) as mediators of cancer risk reduction [87].

There are limited observational data on the impact of intentional weight loss on colorectal cancer [88], although one Austrian study [89] has reported that weight loss (>0.10 kg/m^2/year) was strongly associated with reduced risk of colorectal cancer in men (HR = 0.50, 95%CI, 0.29–0.87).

Box 1. European Code Against Cancer.

EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk
1. Do not smoke. Do not use any form of tobacco
2. Make your home smoke free. Support smoke-free policies in your workplace
3. Take action to be a healthy body weight
4. Be physically active in everyday life. Limit the time you spend sitting
5. Have a healthy diet:
   • Eat plenty of whole grains, pulses, vegetables and fruits
   • Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks
   • Avoid processed meat; limit red meat and foods high in salt
6. If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention
7. Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds
8. In the workplace, protect yourself against cancer-causing substances by following health and safety instructions
9. Find out if you are exposed to radiation from naturally high radon levels in your home; take action to reduce high radon levels
10. For women:
    • Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby
    • Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT
11. Ensure your children take part in vaccination programmes for:
    • Hepatitis B (for newborns)
    • Human papillomavirus (HPV) (for girls)
12. Take part in organised cancer screening programmes for:
    • Bowel cancer (men and women)
    • Breast cancer (women)
    • Cervical cancer (women)

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.

In conclusion, taking the available evidence relating to excess body fat and cancer, the Nutrition Working Group of the 4th edition of the European Code against Cancer (Box 1) has developed the following recommendation: 'Take action to be a healthy body weight'.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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