OVERWEIGHT, OBESITY AND CANCER: EPIDEMIOLOGICAL EVIDENCE AND PROPOSED MECHANISMS

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The prevalence of obesity is rapidly increasing globally. Epidemiological studies have associated obesity with a range of cancer types, although the mechanisms by which obesity induces or promotes tumorigenesis vary by cancer site. These include insulin resistance and resultant chronic hyperinsulinaemia, increased bioavailability of steroid hormones and localized inflammation. Gaining a better understanding of the relationship between obesity and cancer can provide new insight into mechanisms of cancer pathogenesis.

The prevalence of overweight and obesity in most developed countries (and in urban areas of many less developed countries) has been increasing markedly over the past two decades[1]. By the year 2000, nearly two-thirds of adults in the United States were overweight or obese[2], and there were 300 million obese adults worldwide. The incidence of type-II diabetes during this same time period has mirrored, and is presumed to be a direct result of, the obesity epidemic[3]. Although obesity has long been recognized as an important cause of diabetes and cardiovascular diseases, the relationship between obesity and different types of cancer has received less attention than its cardiovascular effects.

Results from epidemiological studies that largely began in the 1970s indicate that adiposity contributes to the increased incidence and/or death from cancers of the colon, breast (in postmenopausal women), endometrium, kidney (renal cell), oesophagus (adenocarcinoma), gastric cardia, pancreas, gallbladder and liver, and possibly other cancers. It has been estimated that 15–20% of all cancer deaths in the United States can be attributed to overweight and obesity[4]. At present, the strongest empirical support for mechanisms to link obesity and cancer risk involves the metabolic and endocrine effects of obesity, and the alterations that they induce in the production of peptide and steroid hormones[5]. As the worldwide obesity epidemic has shown no signs of abating, insight into the mechanisms by which obesity contributes to tumour formation and progression is urgently needed, as are new approaches to intervene in this process.

TRIGLYCERIDE
A fat that is synthesized from carbohydrates and stored in animal adipose cells. On hydrolysis, it releases free fatty acids into the blood.

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Methods for assessing overweight and obesity

Adipose tissue in humans functions to store energy in the form of fat. TRIGLYCERIDES, are the main storage lipid[1,6]. There are two main types of adipose tissue — subcutaneous and visceral. Subcutaneous adipose is largely defined as fat tissue between the skin and muscle, whereas visceral adipose is found within the main cavities of the body, primarily in the abdominal cavity. Abdominal visceral adipocytes are more metabolically active than abdominal subcutaneous adipocyes, as they have high lypolytic activity and release large amounts of free fatty acids[1]; so ideal measurements of adiposity would consider both the amount and the site of deposition of the adipose.

Many methods of estimating total body fat mass in individuals have been developed[1], including underwater weighing (hydrodensitometry), dilution methods (hydrometry), duel-energy X-ray absorptiometry (DXA), measurement of skinfolds, bioimpedance analysis, and imaging methods including computed tomography (CT) and magnetic resonance imaging (MRI). Of these methods, only CT and MRI are able to distinguish between subcutaneous and visceral abdominal adipose tissue. Although these methods vary in their complexity, costs and results,

ANTHROPOMETRIC
A measurement of the size or proportions of the human body; for example, weight, height and waist circumference.

Summary

- The International Agency for Research on Cancer has determined that, based on results from epidemiological studies, people who are overweight or obese are at increased risk of developing several cancer types, including adenocarcinoma of the oesophagus, colon cancer, breast cancer (in postmenopausal women), endometrial cancer and kidney (renal-cell) cancer.
- Epidemiological evidence also indicates that cancers of the liver, gallbladder and pancreas are obesity related, and that obesity might also increase risk for haematopoietic cancers and for aggressive prostate cancer. No association is seen between obesity and lung cancer. Results for other cancers have been inconsistent.
- Insulin resistance develops as a metabolic adaptation to increased levels of circulating free fatty acids released from adipose tissue, especially intra-abdominal adipose. Insulin resistance is generally compensated by increased pancreatic insulin secretion. There is mounting epidemiological and experimental evidence to indicate that chronic hyperinsulinaemia increases risk of cancers of the colon and endometrium, and probably other tumours (for example, of the pancreas and kidney).
- Serum levels of insulin-like growth factor 1 (IGF1) are also associated with different forms of cancer. However, there is no simple, direct relationship between circulating levels of IGF1 and the degree of adiposity.
- Circulating levels of oestrogens are strongly related to adiposity. For cancers of the breast (in postmenopausal women) and endometrium, the effects of overweight and obesity on cancer risk are largely mediated by increased oestrogen levels.
- In 4–8% of premenopausal women, obesity and ensuing insulin resistance can either cause or aggravate syndromes of ovarian androgen excess (polycystic ovary syndrome) and chronic progesterone deficiency. There is strong evidence that such syndromes, along with reduced progesterone production, increase the risk of endometrial cancer.
- Successful intervention strategies for weight loss and maintenance at the individual and community level are needed to reduce cancer risk.

both are generally too costly and complex to be used to estimate adiposity in large general populations or large-scale epidemiological studies. Definitions for classifying and reporting healthy weight, overweight and obesity in populations have historically been based on ANTHROPOMETRIC measures rather than clinical measures of adiposity[6,7] (BOXES 1, 2).

Global trends in overweight and obesity

There are large between-country and within-country differences in levels of obesity, and overweight and obesity can co-exist with malnutrition, especially in developing countries and countries undergoing economic and cultural transition. The prevalence of adult obesity is high in eastern Europe, the eastern Mediterranean, North America (especially the United States), Central and South America (especially Argentina, Chili, Paraguay and Mexico), and some parts of western Europe (Finland, Germany, Spain and the United Kingdom)[5,8–10]. Obesity is still relatively uncommon in China, Japan and most parts of Africa. Since the 1980s, large increases in the prevalence of obesity have been observed in the United States (FIG. 1) and the United Kingdom, and smaller increases have been reported in many other European countries[2,5,9,10]. The incidence of obesity is also increasing in developing countries in other parts of the world including the Caribbean, South America and south-east Asia[10,11].

Epidemiology of adiposity and cancer risk

The International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Cancer-Preventive Strategies recently published a comprehensive evaluation of the available literature on weight and cancer that considered epidemiological, clinical and experimental data[5]. Their report concluded that the avoidance of weight gain reduces the risk of developing cancers of the colon, breast (in postmenopausal women), endometrium, kidney (renal cell) and oesophagus (adenocarcinoma)[5]. These conclusions are based on epidemiological studies of overweight and/or obese individuals compared with leaner individuals — not on studies of individuals who have lost weight. Unfortunately, few individuals manage to maintain a significant weight loss after intentional weight reduction, making it extremely

Box 1 | The body-mass index

One of the simplest anthropometric indices of adiposity is weight adjusted for stature (height). Since the 1980s, indices of weight adjusted for height have gained favour because they provide a single estimate of adiposity (regardless of height) that can easily be compared across studies and across populations. By far the most widely used weight-for-height measure is the body-mass index (BMI, also called Quetelet's Index), which is defined as weight (in kilograms) divided by height (in metres squared)[6]. The assumption underlying the BMI (and all other such indices) is that true adiposity is unrelated to height. Indeed, among the many indices of weight-for-height that have been proposed, the correlation with height has generally been lowest for BMI[6]. Many studies have found moderate to strong correlations (0.6–0.9) between BMI and densitometry estimates of body fat composition in adult populations[6]. The validity of BMI as a measure of adiposity is further supported by its association with obesity-related risk factors such as blood triglycerides, total cholesterol, blood pressure and fasting glucose levels[6]. BMI could be a less valid indicator of adiposity among the elderly, who tend to have a shift of fat from peripheral to central sites with a concomitant increase in waist-to-hip ratio at the same level of BMI[180]. For such populations, and with evidence of health risks associated with abdominal (visceral) fat, two measures of central adiposity, the waist-to-hip ratio and, more recently, waist circumference, have been commonly used in epidemiological studies.

Box 2 | **Definitions of healthy weight, overweight and obesity**

Standards defining healthy weight, overweight and obesity have evolved over time and reflect existing knowledge of and assumptions about the relation of weight to disease outcomes. The only globally accepted criteria for overweight and obesity are based on body-mass index (BMI). Standards based on BMI have been reported for the adult population in the United States since 1980 in the *Dietary Guidelines for Americans*[181]. Widely accepted current standards based on BMI criteria for overweight and obesity are recommended by the World Health Organization (WHO)[182] and supported by other advisory committees and expert panels to federal agencies[181,183]. The WHO classifications of BMI ranges are shown in the accompanying table. Although the cut-off points are somewhat arbitrary, this BMI classification scheme was derived largely from observational and epidemiological studies of BMI and overall mortality[182,183]. (The cut-off point for the underweight category is based on adverse health consequences of malnutrition in developing countries[182].) It is important to note that within each category of BMI there can be substantial individual variation in total and visceral adiposity, and in several related metabolic variables. This is also true within what is at present considered the 'normal' or 'healthy' range of BMI (18.5–24.9). Individuals at opposite ends of the normal range of BMI can experience considerable differences in adiposity-related risks and health outcomes.

BMI (kg/m^2)	WHO classification	Popular description
< 18.5	Underweight	Thin
18.5–24.9	Normal range	'Healthy', 'normal' or 'acceptable' weight
25.0–29.9	Grade 1 overweight	Overweight
30.0–39.9	Grade 2 overweight	Obesity
≥ 40.0	Grade 3 overweight	Morbid obesity

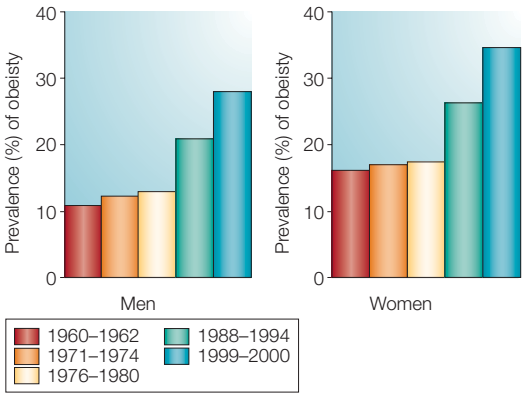

Figure 1 | **Obesity trends.** The graph shows trends in the age-adjusted prevalence of obesity for adults aged 20–74 years in the United States from 1960–2000 (REF. 2) as percentage of the total population. Measured weight and height data have been collected for nationally representative samples of adults since 1960. These data, which were collected in the National Health and Nutrition Examination Survey by the National Center for Health Statistics (for further information, see the online links box), allow valid comparisons of trends over time. The prevalence of overweight (body-mass index (BMI) ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) in adults aged 20–74 was relatively stable from 1960–1980. This situation changed markedly in the 1980s and 1990s when large increases in the prevalence of both overweight and obesity occurred nationally in men and women. By the year 2000, 64.5% of adults in the United States were overweight or obese, and 30.5% were obese. Within the population of adults, 4.7% were morbidly obese (BMI ≥ 40kg/m^2; not shown).

RELATIVE RISK
The risk of cancer (or other disease) in a group of exposed persons divided by the risk in a group of unexposed persons. The relative risk is a commonly used measure of association in epidemiological studies.

CENTRAL ADIPOSITY
The storage of adipose tissue preferentially in adipocytes on or within the trunk rather than the extremities.

difficult to examine cancer outcomes in large populations of weight losers. Consequently, the IARC report concluded that there is inadequate evidence that weight loss reduces the risk of cancer. However, there have been many studies since the IARC review that have added to our knowledge of the association between adiposity and cancer risk.

Obesity-related cancers. Obesity has been consistently associated with higher risk of colorectal cancer in men (RELATIVE RISKS ~1.5–2.0) and women (relative risks ~1.2–1.5) in both case–control and cohort studies (TABLE 1)[5]. In studies that were able to separately examine the colon and rectum, relative risks were consistently higher for developing cancers of the colon[5]. Similar relationships are seen for colon adenomas, with stronger associations between obesity and the incidence of larger (versus smaller) colon adenomas[12]. A gender difference, in which obese men are more likely to develop colorectal cancer than obese women, has been observed consistently across studies and populations. The reasons for this gender difference are speculative. One hypothesis is that CENTRAL ADIPOSITY, which occurs more frequently in men, is a stronger risk factor for colon cancer than peripheral adiposity or general overweight. Support for the role of central obesity in the development of colorectal cancer comes from studies reporting that waist circumference and the waist-to-hip ratio are strongly related to risk of colorectal cancer and large adenomas in men[13]. However, several studies have reported that in women, the association between the waist-to-hip ratio and colorectal cancer was not greater than the association between body-mass index (BMI) and colorectal cancer, leaving doubts as to whether body fat distribution completely explains the observed gender differences.

Another explanation is that there might be an offsetting beneficial effect of obesity on colorectal cancer risk in women; this suggestion is based on evidence that exogenous oestrogens (in the form of postmenopausal hormone therapy) reduce the risk of colorectal cancer in women[14,15]. However, this hypothesis is also quite speculative, as circulating levels of endogenous oestrogens are higher in obese men as well as obese women, compared with lean individuals[16], and oral intake of exogenous oestrogens could have different effects than endogenous oestrogens on the risk of colon cancer.

Many epidemiological studies since the 1970s have assessed the association between anthropometric measures and breast cancer occurrence and/or prognosis[5,17]. Early studies established that the association between body size and risk of breast cancer varied based on menopausal status — that heavier women were at increased risk of developing postmenopausal, but not premenopausal, breast cancer[5]. In fact, among premenopausal women, there is consistent evidence of a modest reduction in risk among those with a high (≥ 28 kg/m^2) BMI. This reduction in risk could be because of the increased tendency for young obese women to have ANOVULATORY menstrual cycles and lower levels of circulating steroid hormones, notably of progesterone and oestradiol[18].

Table 1 | **Obesity-related cancers**

Type of cancer	Relative risk* with BMI of 25–30 kg/m²	Relative risk* with BMI of ≥ 30 kg/m²	PAF (%) for US population‡	PAF (%) for EU population§
Colorectal (men)	1.5	2.0	35.4	27.5
Colorectal (women)	1.2	1.5	20.8	14.2
Female breast (postmenonopausal)	1.3	1.5	22.6	16.7
Endometrial	2.0	3.5	56.8	45.2
Kidney (renal-cell)	1.5	2.5	42.5	31.1
Oesophageal (adenocarcinoma)	2.0	3.0	52.4	42.7
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5–4.0	ND‖	ND‖
Gallbladder	1.5	2.0	35.5	27.1
Gastric cardia (adenocarcinoma)	1.5	2.0	35.5	27.1

Relative risks associated with overweight and obesity, and the percentage of cases attributable to overweight and obesity in the United States (US) and the European Union (EU). *Relative risk estimates are summarized from the literature cited in the main text. ‡Data on prevalence of overweight and obesity are from the National Health and Nutrition Examination Survey (1999–2000)[205] for men and women from the United States aged from 50–69 years. §Data on prevalence of overweight and obesity are from a range of sources[206] for adult men and women residing in 15 European countries in the 1980s and 1990s. ‖PAFs were not estimated because the magnitude of the relative risks across studies are not sufficiently consistent. BMI, body mass index; ND, not determined; PAF, population attributable fraction (BOX 3).

Obesity has been consistently shown to increase rates of breast cancer in postmenopausal women by 30–50% (TABLE 1)[19–22]. Some studies have found central adiposity to be an independent predictor of postmenopausal breast cancer risk beyond the risk attributed to overweight alone, but a recent systematic review has indicated that this is not the case[23]. In addition, adult weight gain has generally been associated with a larger increase in risk of postmenopausal breast cancer than has BMI in studies that examined both factors[24–27]. Both BMI and weight gain are more strongly related to risk of breast cancer among postmenopausal women who have never used hormone-replacement therapy, compared with women who have used hormones[25,27–29]. This finding lends support to the hypothesis that adiposity increases breast cancer risk through its oestrogenic effects.

Studies of mortality and survival among patients with breast cancer illustrate that adiposity is associated both with reduced likelihood of survival and increased likelihood of recurrence, regardless of menopausal status and after adjustment for stage and treatment[17,30,31]. Very obese women (BMI ≥ 40.0 kg/m²) have breast cancer death rates that are three times higher than very lean (BMI < 20.5 kg/m²) women[32]. The greater risk of death among heavier women probably reflects both a true biological effect of adiposity on survival and delayed diagnosis in heavier women. In addition to the direct effects of adiposity (see below), there is evidence that heavier women are less likely to receive mammography screening[33], and among women who self-detect their tumours, a high BMI increases the likelihood of non-localized disease[34].

Endometrial cancer (cancer of the uterine lining) was the first cancer to be recognized as being related to obesity. There is convincing and consistent evidence from both case–control and cohort studies that overweight and obesity are associated strongly with endometrial cancer[5,35]. A linear increase in the risk of endometrial cancer with increasing weight or BMI has been observed in most studies[4,5]. The increase in risk generally ranges from 2–3.5-fold in overweight and/or obese women (TABLE 1), and might be higher in studies of mortality than in studies of incidence[4,5,36].

Studies of populations worldwide have revealed that the risk of kidney cancer (specifically, renal-cell cancer) is 1.5–3 times higher in overweight and obese individuals than in men and women of normal weight (TABLE 1); most studies reported a dose-response relationship with increasing weight or BMI[5,37–40]. In several studies, the increase in risk with increasing BMI was greater in women than in men[4,41–47], although at present this finding remains unexplained and was not confirmed in a review of published studies[37]. Importantly, the obesity-associated risk of renal-cell cancer seems to be independent of blood pressure, indicating that hypertension and obesity might influence renal-cell cancer through different mechanisms[48].

The incidence of adenocarcinoma of the oesophagus has been rapidly increasing in westernized countries in recent decades[49,50], whereas rates for the other main histological subtype of cancer, squamous-cell carcinoma, have remained stable or decreased. As a result, an increasing proportion of all oesophageal cancers in western countries are adenocarcinomas. Obesity increases risk for adenocarcinoma of the oesophagus by 2–3-fold[5,51] (TABLE 1), but is not associated with an increased risk of squamous-cell carcinoma of the oesophagus.

Independent of obesity, gastro-oesophageal reflux disease (GERD) has been associated with oesophageal adenocarcinoma and with its metaplastic precursor, Barrett's oesophagus[50,52,53]. Obesity has therefore been proposed to increase the risk of adenocarcinoma of the oespophagus indirectly, by increasing the risk of GERD and Barrett's oesophagus[54,55]. Some studies,

ANOVULATORY
A menstrual cycle that is not accompanied by the discharge of an egg from the ovary.

PROXY RESPONDERS
Also called surrogate responders, individuals who provide information regarding exposure in place of the individual involved in the study.

however, have shown that the association between obesity and oesophageal adenocarcinoma is independent of GERD[56,57].

Cancers likely to be obesity related. Results from many recent studies indicate that obesity is associated with an almost twofold increased risk for pancreatic cancer in men and women (TABLE 1)[4,39,58–62]. Earlier studies, however, reported either no association or a smaller association between the two, so further research is needed[40,63,64]. It is important to note that case–control studies of this topic conducted in the early 1990s obtained information on weight and height from PROXY RESPONDERS, rather than from the patients themselves[65–68]. This could underlie the lack of association reported between obesity and pancreatic cancer in these studies.

Four studies have found an increased risk (1.5–4-fold) of liver cancer, or hepatocellular carcinoma (HCC), among obese individuals[4,40,58,69], whereas a fifth study did not[39]. Taken together, these studies indicate that obesity increases the risk of liver cancer, but the magnitude of the observed relative risk from existing studies is not consistent. There have also been a limited number of studies of gallbladder cancer and obesity, and most have been relatively small, as gallbladder cancer is quite rare, especially in men. However, these few studies have consistently found that obesity increased risk by about two-fold[4,36,40,58,69–71] (TABLE 1). Obesity increases the risk of gallstones, which, in turn, causes chronic inflammation and increased risk of biliary-tract cancer[41].

Risk for adenocarcinoma of the gastric cardia has been found to be related to obesity[56,72,73], but the magnitude of the association is not as great as for adenocarcinoma of the oesophagus. Relative risks are in the range of 1.5–2.0. It is unclear why risks associated with obesity are greater for oesophageal adenocarcinoma than for gastric-cardia adenocarcinoma. It is possible that reflux mechanisms are more closely related to adenocarinoma of the oesophagus than of the gastric cardia. Data are limited for non-cardia cancers of the stomach, but there is no indication of increased risk with obesity[56,72].

Other cancers. BMI has been reported to be inversely associated with lung cancer in several study populations that did not exclude smokers from the analysis[5]. This inverse correlation is explained by the confounding effects of smoking — smoking is the primary cause of lung cancer and is inversely associated with BMI[74]. No association has been reported between BMI and lung cancer in non-smoking populations[4,39].

Studies of the association between BMI and cervical cancer are limited and inconclusive. Two prospective studies of mortality from cervical cancer found it was associated with high BMI (2–3-fold increased risk)[4,36], whereas much lower relative risks were observed in two cohorts of obese women, compared with general populations[58,69]. No association was observed in a cohort study of Swedish women[75]. A recent case–control study that was controlled for human papilloma virus infection found about a twofold increased risk of cervical adenocarcinoma among overweight and obese women; smaller increased risks were seen for cervical squamous-cell carcinoma[76]. However, differential screening behaviour (obese women might be less likely to go for screening on a regular basis than women of normal weight) could also explain some of these observations.

Although endogenous hormones are believed to be involved in the aetiology of ovarian cancer[77], and obesity is a well-established risk factor for other hormone-related cancers in women (breast and endometrial cancers), ovarian cancer has not been consistently linked to obesity[5,39,69,78–83]. Some studies have reported an association between the two, and relative risks have been in the range of 1.5–2.0 for the highest categories of BMI studied. Many studies have not found an association between ovarian cancer and obesity, so no solid conclusions should be drawn at this time. It is not clear what factors might explain the divergent results among studies. Weight loss several years before the time of cancer diagnosis would bias the relative risk downward in case–control studies, but such a bias would not be operative in several prospective cohort studies that found no association. It is possible that obesity increases the risk of specific histological subtypes of ovarian cancer (for example, endometroid), but not others. Most studies have not examined risk by histological subtype of ovarian cancer, and this might contribute to the inconsistent findings.

A large number of available studies do not support an association between body mass and incidence of prostate cancer[5,84], although three very large recent studies — two cohort studies in the United States and Norway and a Canadian case–control study — found modest (9–27%), but statistically significant, increased risks of prostate cancer among obese (BMI $\geq 30.0\ kg/m^2$) men[39,40,85]. In addition, there is evidence that obesity is associated with an increase in risks of advanced prostate cancer or death from prostate cancer[86–88]. Recent studies indicate that obese men with prostate cancer are more likely to have aggressive disease that recurs after radical prostatectomy than non-obese men[89,90].

Box 3 | Population attributable fraction

The population attributable fraction (PAF) is defined as the proportion or percentage of disease in a population that is attributable to a given risk factor[184], and is useful in measuring the public-health impact of that risk factor. The PAF is sometimes referred to as the population attributable risk, population attributable risk percent and excess fraction. The magnitude of the PAF depends both on the prevalence of the risk factor in the population and on the strength of the relative association (relative risk) between the risk factor and the disease under investigation. It is calculated as $PAF = (\Sigma_i P_i(RR_i - 1)) / (1 + \Sigma_i P_i(RR_i - 1))$ **where** P_i **is the proportion of the study population in the** i**th body-mass index (BMI) category (overweight or obese) and** RR_i **is the corresponding relative risk. Because the PAF is very sensitive to the population prevalence of the risk factor, it is not generalizable to populations with different distributions of the risk factor. The PAFs presented in TABLE 1 are estimates of the percentage of cancer cases at each indicated site that could be attributed to excess adiposity, defined as BMI above the normal range (BMI >** $25.0\ kg/m^2$**). These estimates were based on summary relative risks estimated from the existing published literature for each cancer site and on the distribution of BMI in adults in the United States and the European Union.**

Box 4 | **The insulin-resistance syndrome or metabolic syndrome**

Nutritionally induced insulin resistance develops as a metabolic adaptation to increased circulating levels of free fatty acids (FFAs), which are constantly released from adipose tissue, especially from intra-abdominal fat stores. Increased FFA levels force liver, muscle and other tissues to shift towards increased storage and oxidation of fats for their energy production[185–187]. The latter is compensated by a reduced capacity of these tissues to absorb, store and metabolize glucose. In addition to FFAs, adipose tissue releases several endocrine signalling factors, such as tumour-necrosis factor-α (TNFα), adiponectin, leptin and resistin, which all also have some role in the regulation of insulin sensitivity in liver, skeletal muscle and other tissues[188–193]. The cellular and molecular mechanisms leading to insulin resistance include reductions in cellular insulin-receptor levels and reduced responsiveness of some intracellular transduction pathways mediating the effects of insulin binding to its receptor[194–196].

Other than excess weight, determinants of insulin resistance are lack of physical activity[197,198], genetic susceptibility factors[199] and dietary composition (for example, types and amounts of fats and carbohydrates in the diet[200–202]).

To prevent an excessive rise of blood glucose levels, insulin resistance is generally compensated by increased pancreatic insulin secretion, in both fasting and non-fasting states. So, body-mass index generally shows a direct linear relationship with insulin levels. In addition, insulin-resistant individuals tend to have increased glucose concentrations, both in fasting state and after the consumption of a given amount of carbohydrate, and often also have increased fasting and non-fasting levels of triglycerides and very-low-density lipoproteins (VLDLs), and low levels of high-density lipoprotein (HDL) cholesterol. Individuals with this group of metabolic markers are often referred to as having the 'insulin resistance syndrome' or 'metabolic syndrome'[94,203,204].

Few studies have examined the relationship between haematopoietic cancers and BMI, and results from most of these studies are based on relatively small numbers of events[4,36,39,40,58,69,91,92]. Still, most of the available studies have observed modest obesity-associated increases in the risk of non-Hodgkin's lymphoma[4,36,39,58,69,91], multiple myeloma[4,39], and leukaemia[4,36,39,40,58,69]. Relative risks from these studies have generally been in the range of 1.2–2.0.

Summary of epidemiological evidence. The individual cancers presented in TABLE 1 represent those cancers for which the available epidemiological evidence supports a positive association with adiposity, and for which the magnitude of the relative risks across studies are sufficiently consistent to allow for a summary estimate. Two sets of population attributable fractions (PAFs; BOX 3) have been calculated using these relative risks — one assuming a population with the same extent of overweight and obesity that existed in the adult population of the United States in 2000 and the second assuming a population with the same extent of overweight and obesity that existed in the adult population in countries of the European Union during the 1980s and 1990s. Depending on the specific cancer site and the level of overweight and obesity in the underlying population, the PAFs range from 14.2% (for colorectal cancer in women) to 56.8% (for endometrial cancer). These calculations illustrate that a substantial proportion of these cancers could be avoided with maintenance of normal weight throughout adult life.

Mechanisms relating adiposity to cancer risk

Adipose tissue constitutes an active endocrine and metabolic organ that can have far-reaching effects on the physiology of other tissues[93]. In response to endocrine and metabolic signals from other organs, adipose tissue responds by either increasing or decreasing the release of free fatty acids — an energy-providing fuel for skeletal muscle and other tissues. Adipose tissue is also important in the regulation of energy balance and lipid metabolism through the release of peptide hormones such as leptin, adiponectin, resistin and tumour necrosis factor-α (TNFα). Increased release of free fatty acids, resistin

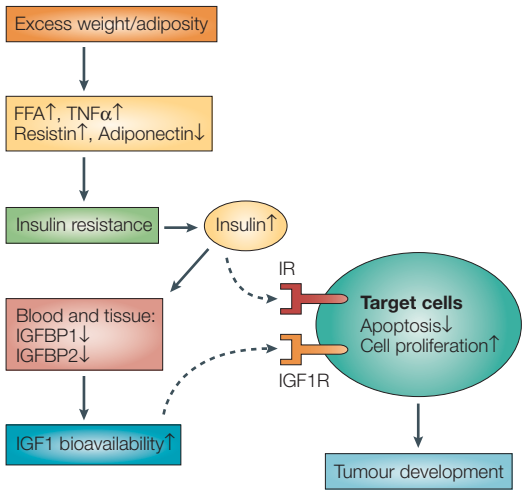

Figure 2 | **Effects of obesity on growth-factor production.** In obesity, increased release from adipose tissue of free fatty acids (FFA), tumour-necrosis factor-α (TNFα) and resistin, and reduced release of adiponectin lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia (BOX 4). Increased insulin levels, in turn, lead to reduced liver synthesis and blood levels of insulin-like growth factor binding protein 1 (IGFBP1), and probably also reduce IGFBP1 synthesis locally in other tissues. Increased fasting levels of insulin in the plasma are generally also associated with reduced levels of IGFBP2 in the blood. This results in increased levels of bioavailable IGF1. Insulin and IGF1 signal through the insulin receptors (IRs) and IGF1 receptor (IGF1R), respectively, to promote cellular proliferation and inhibit apoptosis in many tissue types. These effects might contribute to tumorigenesis.

Table 2 | **Associations of obesity with selected hormones and proteins**

Hormone or binding globulin	Obesity versus normal weight
Insulin	Increased levels with obesity
IGF1	Non-linear relation, with peak levels in people with BMIs of 24–27 kg/m^2
Free IGF1	Increased levels with obesity
IGFBP1	Decreased levels with obesity
IGFBP3	Increased levels with obesity or no observed effect
SHBG	Decreased levels with obesity
Total testosterone	Decreased levels with obesity (men); no observed effect (women); increased levels with obesity (premenopausal women with polycystic ovary syndrome)
Free testosterone	No observed effect or decreased levels with obesity (men); increased levels with obesity (women)
Total oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Free oestradiol	Increased levels with obesity (men and postmenopausal women); no observed effect (premenopausal women)
Progesterone	No observed effect or decreased levels with obesity in women with a susceptibility to develop ovarian hyperandrogenism (premenopausal women only)

BMI, body mass index; IGF1, insulin-like growth factor 1; IGFBP, IGF-binding protein; SHBP, sex-hormone-binding globulin.

and TNFα by adipose tissue and reduced release of adiponectin give rise to insulin resistance — a metabolic state characterized by reduced metabolic response of tissues (muscle, liver, adipose) to insulin — and to compensatory hyperinsulinaemia[94,95] (BOX 4; FIG. 2).

As well as its role in regulating energy balance, lipid metabolism and insulin sensitivity, adipose-tissue cells express various steroid-hormone-metabolizing enzymes and are an important source of circulating oestrogens in postmenopausal women (TABLE 2; FIG. 3).

Chronic hyperinsulinaemia. Excess weight, increased plasma triglyceride levels, low levels of physical activity and certain dietary factors can all raise circulating insulin levels. Chronically increased insulin levels have been associated with colon cancer pathogenesis[96,97] and with cancers of the breast[98,99], pancreas[100] and endometrium[35] (FIG. 2). These tumorigenic effects of insulin could be directly mediated by insulin receptors in the (pre)neoplastic target cells, or might be due to related changes in endogenous hormone metabolism, secondary to hyperinsulinaemia. For example, insulin promotes the synthesis and biological activity of insulin-like growth factor 1 (IGF1) — a peptide hormone that has a molecular structure very similar to that of insulin and that regulates cellular proliferation in response to available energy and nutrients from diet and body reserves (FIG. 2). In addition, insulin has effects on the synthesis and biological availability of the male and female sex hormones, including androgens, progesterone and oestrogens — see section on endogenous SEX STEROIDS below (FIG. 3).

SEX STEROIDS
A family of hormones that all share a basic chemical (steroidal) structure. These hormones include androgens, oestrogens and progesterone, and have important effects on sexual development and reproductive functions.

FASTING AND NON-FASTING GLUCOSE LEVELS
Glucose is the end product of carbohydrate metabolism and the chief source of energy for living organisms; its utilization is controlled by insulin. It is found in the blood of all animals. Fasting plasma glucose levels are a measurement of the concentration of glucose in the plasma after the patient has not eaten for at least 8 hours.

In vitro studies have clearly established that both insulin and IGF1 act as growth factors that promote cell proliferation and inhibit apoptosis[101–105]. Experiments with insulin-deficient (diabetic) animals have shown that insulin promotes tumour growth and development in xenograft models and in chemical models of carcinogenesis[106–111]. Similarly, animal experiments have also shown reduced tumour growth after inactivation of the IGF1 receptor, or after manipulations to reduce circulating or tissue IGF1 levels[105,112].

There is also substantial epidemiological evidence in support of the hypothesis that chronic hyperinsulinaemia increases cancer risk. Type-II diabetes, which is usually associated with insulin resistance and increased pancreatic insulin secretion for long periods both before and after disease onset, is associated with increased risks of cancers of the colon[96,97], endometrium[35], kidney[113,114] and pancreas[100,115]. In addition, prospective cohort studies have shown increased risks of cancers of the colon or of the colorectum among individuals with increased prediagnostic blood levels of C-peptide (a marker for pancreatic insulin secretion)[116,117], FASTING GLUCOSE[118] or insulin measured 2 hours after absorption of a standard oral dose of glucose[118]. Similarly, for endometrial cancer, one prospective study combining data and blood samples from three different cohorts in New York, Umeå (northern Sweden) and Milan also showed a direct relationship between cancer risk and prediagnostic C-peptide levels. The study also reported inverse relationships of cancer risk and blood levels of IGF-binding protein 1 (IGFBP1) and IGFBP2 (REF. 119), which reduce the amount of bioavailable IGF1. Several case–control studies[120–123], but not all[124], showed an increase in risk among pre- and postmenopausal women with increased blood insulin concentrations, but these findings were not confirmed by several prospective studies[125–128].

Growth hormone and IGF1. Over 80% of IGF1 in the circulation is bound to IGFBP3, whereas most of the remainder is bound to at least five additional binding proteins (IGFBP1, IGFBP2, IGFBP3, IGFBP4, IGFBP5 and IGFBP6). The IGFBPs have many functions, including the stabilization of a large pool of IGF1 in the circulation, the regulation of the efflux of IGF1 from this pool towards target tissues and, at the tissue level, the regulation of the availability of IGF1 for binding to its receptor. In addition, some of the binding proteins have been shown to exert effects (for example, a pro-apoptotic effect of IGFBP3) independently of IGF1, through specific binding sites on cellular membranes[129].

The principal stimulus for the synthesis of IGF1 in liver, which is the source of over 80 percent of circulating IGF1, is provided by growth hormone (GH). Nutritional energy balance can have profound effects on the synthesis and biological activity of IGF1 (for reviews, see REFS 130,131). In people who have been chronically fasting, or in those with type-I diabetes, low production levels of insulin cause a reduction in hepatic GH-receptor levels, resulting in GH resistance

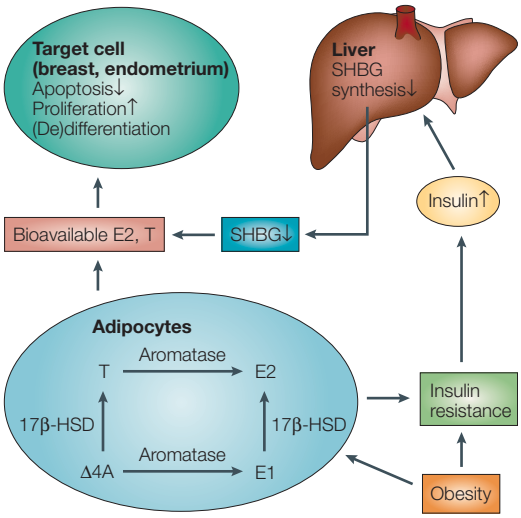

Figure 3 | **Effects of obesity on hormone production.** Adipose tissue produces the enzymes aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD). So in obese individuals, there is typically an increased conversion of the androgens Δ4-androstenedione (Δ4A) and testosterone (T) into the oestrogens oestrone (E1) and oestradiol (E2), respectively, by aromatase. 17β-HSD converts the less biologically active hormones Δ4A and E1 into the more active hormones T and E2, respectively. In parallel, obesity leads to hyperinsulinaemia, which in turn causes a reduction in the hepatic synthesis and circulating levels of sex-hormone-binding globulin (SHBG). The combined effect of increased formation of oestrone and testosterone, along with reduced levels of SHBG, leads to an increase in the bioavailable fractions of E2 and T that can diffuse to target cells, where they bind to oestrogen and androgen receptors. The effects of sex steroids binding their receptors can vary, depending on the tissue types, but in some tissues (for example, breast epithelium and endometrium) they promote cellular proliferation and inhibit apoptosis.

and reduced synthesis and blood levels of IGF1. In addition, levels of IGFBP1 and IGFBP2 are increased, further reducing IGF1 bioavailability to tissue receptors. In overnourished states, but also in patients with type-II diabetes, endogenous insulin levels and hepatic GH-receptor levels are high, and large amounts of IGF1 are produced. Paradoxically, however, obese people also have lower blood levels of IGF1 than normal-weight, well-nourished individuals[130]. In line with the observation of reduced blood concentrations of IGF1 in undernourished as well as obese people, several large cross-sectional studies have recently shown a non-linear relationship of IGF1 with anthropometric indices of adiposity, with highest levels of IGF1 at a BMI of around 24–27 kg/m^2, and lower levels for men and women in either the lower or higher BMI categories[132–134]. A probable explanation for the reduced blood levels of IGF1 in obese individuals, despite increased GH sensitivity of liver and other tissues, is that reductions in IGFBP1 and IGFBP2 levels lead to increased negative feedback by free IGF1 (unbound to IGFBPs) on pituitary GH secretion. This results in reduced synthesis of IGF1 and reduced plasma IGF1 concentrations[130,135,136].

BIOAVAILABLE
The portion of a substance that can be used physiologically by target tissues.

Epidemiological studies have indicated that increased serum levels of IGF1 could be directly related to risk of different forms of cancer. Increased levels of serum IGF1 have been found to be related to increased risks of breast cancers, especially among premenopausal women[125–128,137]. Similar increases in risk were also observed for cancers of the prostate[138,139] and colorectum[116,140–142]. With the exception of the colon, however, risks of these various cancer types generally have not shown any clear relationship with BMI or other indices of adiposity, and there is also no clear, linear relationship between circulating levels of IGF1 and the degree of adiposity[132–134].

Endogenous sex steroids. Adiposity influences the synthesis and bioavailability of endogenous sex steroids — the oestrogens, the androgens and progesterone (TABLE 2) — through at least three mechanisms (FIG. 3). First, adipose tissue expresses various sex-steroid-metabolizing enzymes that promote the formation of oestrogens from androgenic precursors, which are secreted by the gonads or adrenal glands. In men and postmenopausal women, adipose tissue is the main site of oestrogen synthesis, and BMI is directly related to circulating levels of oestrone and oestradiol (TABLE 2)[16,143,144]. Second, adipose cells increase the circulating levels of insulin and increase insulin-like growth factor 1 (IGF1) bioactivity. This results in reduced hepatic synthesis and blood concentrations of sex-hormone-binding globulin (SHBG), a plasmatic binding protein with high specific affinity for testosterone and oestradiol[145]. In both men and women, adiposity-related decreases in SHBG levels generally increase the fraction of BIOAVAILABLE oestradiol. In women, decreases in SHBG generally also lead to increased levels of bioavailable testosterone[16,35,145,146]. In men, by contrast, decreases in SHBG generally lead to reductions in total testicular testosterone production, and no increase in bioavailable testosterone[16,146,147]. In severely obese men, bioavailable testosterone might actually decrease, because of a strong reduction in gonadotropic stimulation of testicular testosterone synthesis (hypogonadotropic hypogonadism)[148,149]. Finally, high insulin levels can increase ovarian, and possibly also adrenal, androgen synthesis, and in some premenopausal women who are genetically susceptible, can cause the development of the polycystic ovary syndrome (PCOS)[150–152]. PCOS is characterized by ovarian hyperandrogenism, chronic anovulation and progesterone deficiency[151–153]. It is a relatively common disorder, with an estimated prevalence of around 4–6% in premenopausal women.

Epidemiological studies have provided a substantial amount of evidence that these adiposity-induced alterations in circulating levels of sex steroids could in large part explain the associations observed between anthropometric indices of excess weight and risks of cancers of the breast (postmenopausal women only) and endometrium (both pre- and postmenopausal women). For these two tissue types, a vast body of experimental and clinical evidence also indicates a

central role — especially of oestrogens and progesterone — in regulating cellular differentiation, proliferation and apoptosis induction[154–156].

With regard to breast cancer, prospective cohort studies have shown approximately twofold increases in breast cancer risk among postmenopausal women in the upper versus lower quintiles in production of various sex steroids, including dehydroepiandrosterone (DHEA) or its sulphate (DHEAS), Δ4-androstenedione, testosterone, oestrone and total oestradiol. Furthermore, risk was inversely related to blood levels of SHBG and directly related to indices of bioavailable oestradiol unbound to SHBG[157,158]. Further analyses of these nine pooled cohort studies indicated that the association of BMI with breast cancer risk[144] could be attributed almost entirely to increasing blood levels of total or bioavailable oestradiol with increasing BMI. Taken together, these studies indicate that much, if not all, of the relationship between BMI and breast cancer can be explained by the adiposity-related increase in endogenous oestrogen levels.

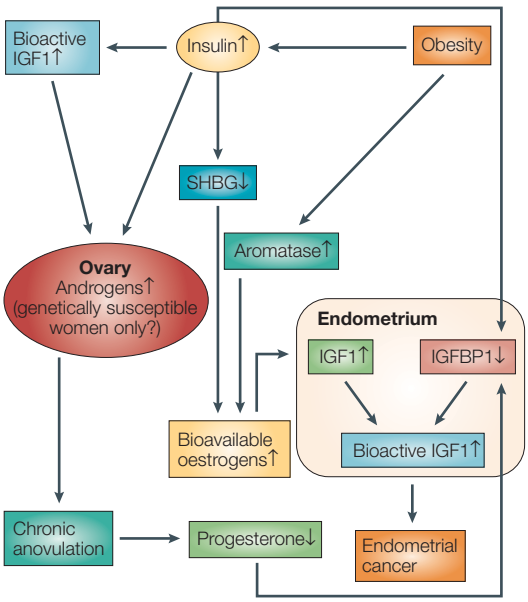

Figure 4 | **Obesity, hormones and endometrial cancer.** Obesity can increase risk of endometrial cancer through several parallel endocrine pathways. Obesity is associated with increased insulin levels, which lead to increases in insulin-like growth factor 1 (IGF1) activity and, in some individuals, an increased androgen production by the ovaries. An excessive increase in ovarian androgen production inhibits ovulation (chronic anovulation), which leads to progesterone deficiency. Increased adiposity also increases aromatase activity, leading to increased levels of bioavailable oestrogen levels in postmenopausal women. Oestrogens increase endometrial cell proliferation and inhibit apoptosis, partially by stimulating the local synthesis of IGF1 in endometrial tissue. Progesterone normally counteracts these effects through various mechanisms, in part by promoting synthesis of IGF-binding protein 1 (IGFBP1) — the most abundant IGFBP in endometrial tissue. Among premenopausal women, the lack of progesterone, because of ovarian androgen production and continuous anovulation, leads to reduced production of IGFBP1 by the endometrium. Loss of progesterone production therefore seems to be the most important physiological risk factor for cancer in premenopausal women. After menopause (and in the absence of exogenous oestrogen production), when ovarian progesterone synthesis has ceased altogether, the more central risk factor seems to be obesity-related increases in bioavailable oestrogen levels. In addition to oestrogens and progesterone, insulin itself could also promote endometrial cancer development by reducing concentrations of sex-hormone-binding globulin (SHBG) in the blood, which would increase the levels of bioavailable oestrogens that can diffuse into endometrial tissue. Figure modified from REF. 35.

Further evidence that increased oestrogen levels might underlie the association between BMI and breast cancer comes from studies of hormone-replacement therapy. BMI is more strongly related to risk of breast cancer among postmenopausal women who have never received hormone-replacement therapy, compared with women who have[25,27–29]. One interpretation of this result is that only among women whose levels of oestrogens are low (after menopause and in those who have not received hormone-replacement therapy) does increased adiposity lead to a rise in breast cancer risk. Finally, mortality is higher among heavier women with breast cancer than among leaner women, and studies indicate that the association of increased BMI with poorer prognosis is limited to or more pronounced among women with tumours that are positive for oestrogen receptor[159–161].

With regard to endometrial cancer, several case–control studies[35] and prospective studies[162,163] have reported increased cancer risks among both pre- and postmenopausal women who have comparatively low plasma levels of SHBG and, therefore, have high levels of the androgens Δ4-androstenedione and testosterone. Among postmenopausal women only, risk was also found to be directly related to levels of oestrone and total and bioavailable oestradiol[35,162], with estimated relative risks up to about 5.0 for women in the upper quartiles or quintiles of oestradiol levels[162]. In premenopausal women, endometrial cancer risk is also increased among women with PCOS[35], which often develops together with, and in large extent as a consequence of, chronic hyperinsulinaemia, and which is generally related to progesterone deficiency. These various relationships all fit a coherent physiological model in line with the 'unopposed-oestrogen' theory and endometrial cancer[35,156]. This widely accepted theory is based on a diverse body of evidence, including the association between endometrial cancer and the use of postmenopausal oestrogen-replacement therapy. It stipulates that endometrial cancer development is increased by the mitogenic effects of oestrogens when these are insufficiently counterbalanced by progesterone (FIG. 4).

Among men, prostate cancer development is also thought to be related to endogenous hormone metabolism, such as by androgen production[147,164,165]. However, excess weight does not seem to be a key risk factor for prostate cancer, with the possible exception of advanced disease, and does not seem to be associated with any increase in circulating total or bioavailable testosterone, or other androgens (TABLE 2)[147,164].

NON-ALCOHOLIC STEATOHEPATITIS.
A liver lesion characterized by liver cell injury and death, and hepatic inflammation that can be accompanied by progressive hepatic fibrosis.

Non-alcoholic fatty liver disease. Obesity, and especially visceral adiposity, can result in non-alcoholic fatty liver disease (NAFLD), a chronic liver disease that occurs in non-drinkers, but which is histologically similar to alcohol-induced liver disease[166]. NAFLD is a new, emerging clinical problem among obese patients and is now recognized as the most common cause of abnormal liver tests[167]. Disorders of glucose regulation commonly occur in patients with NAFLD, indicating insulin resistance[167]. NAFLD is characterized by a spectrum of liver tissue changes ranging from accumulation of fat in the liver to NON-ALCOHOLIC STEATOHEPATITIS (NASH), cirrhosis and HCC at the most extreme end of the spectrum. Progression to NASH seems to represent the turning point from a seemingly non-progressive condition to fibrosis, necrosis and inflammation, and several cellular adaptations to the resulting oxidative stress[166]. Visceral adiposity contributes to the risk of HCC by promoting NAFLD and NASH.

Future directions

Further research to define the causal role of obesity in various types of cancers is needed. At present, the biological mechanisms that link overweight and obesity to many forms of cancer, other than those with an endocrine component, are poorly understood. In addition to causing changes in hormone metabolism (insulin, IGF1, sex steroids), proteins secreted by adipose tissue (adipokines) also contribute to the regulation of immune response (leptin), inflammatory response (TNFα, interleukin-6, serum amyloid A), vasculature and stromal interactions and angiogenesis (vascular endothelial growth factor 1), as well as extracellular matrix components (type-VI collagen)[93]. Obesity-associated dysregulation of adipokines is likely to contribute not only to tumorigenesis and tumour progression, but also to metastatic potential. Additional studies of these factors will add to our understanding of adipose tissue as an endocrine and regulatory organ.

It will also be important to develop successful intervention strategies, both at the individual and community levels, for weight loss and maintenance[168]. Obesity has become a crucial public-health problem in many parts of the world and shows no sign of abating. In the United States, overweight and obesity underlie 90,000 deaths from cancer per year[4], and 280,000–325,000 deaths from all causes per year[169]. In the European Union, annual deaths from all causes attributed to overweight and obesity have been estimated at 279,000–304,000 (REF. 170). Annual obesity-attributable medical expenditures in the Unites States were estimated to be $75 billion in 2003 dollars[171]. Recent studies estimate that the impact of overweight and obesity in terms of both mortality and health-care costs equals or exceeds that associated with tobacco use[172,173].

In response, many government and private agencies are establishing task forces and recommendations that will engage individuals, public services, local government, schools, volunteer organizations, industry and business in developing strategies and guidelines to reverse the epidemic of obesity[174–178]. The World Health Organization (WHO) has proposed an aggressive strategy to combat the obesity epidemic worldwide through the Global Strategy on Diet, Physical Activity and Health[179]. The tobacco control experience has taught us that policy and environmental changes are crucial to achieving changes in individual behaviour. Purposeful changes in public policy are needed to provide access to healthful foods and safe environments for physical activity in schools, worksites and communities. Such change will require multiple strategies and bold action, ranging from the implementation of community and work-site health-promotion programmes to policies that affect community planning, transportation, school-based physical education, and food services. The WHO global strategy proposes such action and, in doing so, strengthens the potential for individual behaviour change and positive health outcomes.

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Competing interests statement
The authors declare no competing financial interests.

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