

# Obesity and cancer

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**Large prospective studies show a significant association with obesity for several cancers, and the International Agency for Research on Cancer has classified the evidence of a causal link as ‘sufficient’ for cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell), and esophagus (adenocarcinoma). These data, and the rising worldwide trend in obesity, suggest that overeating may be the largest avoidable cause of cancer in nonsmokers. Few obese people are successful in long-term weight reduction, and thus there is little direct evidence regarding the impact of weight reduction on cancer risk. If the correlation between obesity and cancer mortality is entirely causal, we estimate that overweight and obesity now account for one in seven of cancer deaths in men and one in five in women in the US.**

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## Introduction

Nearly two-thirds of adults in the United States (Flegal *et al.*, 2002) and an increasing percentage of the population worldwide (Seidell, 2003) are overweight or obese as defined by the World Health Organization (WHO Expert Committee on Physical Status, 1995). While the increase in obesity over the last 25 years has been most extreme in the United States and other wealthy industrialized countries, similar trends are mirrored in urban areas of many developing countries. Fat storage increases when caloric intake routinely exceeds caloric expenditure. Environmental factors such as urbanization, increased supply of calorie-dense, palatable foods, and decreased energy expenditure due to physical inactivity disrupt energy balance and increase the prevalence of excess adiposity in the population.

Obesity has long been recognized to be an important cause of type II diabetes mellitus, hypertension, and dyslipidemia (National Institutes of Health and National Heart Lung and Blood Institute, 1998; National Task Force on the Prevention and Treatment of Obesity, 2000). The adverse metabolic effects of excess

body fat are known to accelerate atherogenesis and increase the risk of coronary heart disease, stroke, and early death. The relationship of obesity to cancer has received less attention than its cardiovascular effects. Overweight women are known to have increased risk of endometrial cancer and breast cancer after menopause (due to increased levels of circulating estrogen). Accumulating evidence suggests that increased adiposity may increase incidence and/or death rates from a wide variety of human cancers, including colon and rectum, esophagus, kidney, pancreas, gallbladder, ovary, cervix, liver, prostate, and certain hematopoietic cancers.

In this review, we discuss the measurement of overweight and obesity used in epidemiologic and clinical studies and the definitions of overweight and obesity agreed upon by the international research community. We describe the global trends in the prevalence of overweight and obesity in adults and children. We briefly discuss genetic and biological factors that affect energy balance and the metabolic consequences of overweight and obesity, particularly in relation to cancer. We summarize the epidemiologic data that relate obesity to various cancers and discuss animal models of obesity and/or caloric excess and cancer. Finally, we present the challenges associated with current intervention strategies and identify important research questions that remain unanswered.

## Measurement of overweight and obesity

Definitions for classifying and reporting healthy weight, overweight, and obesity in populations have historically been based on measures of weight and height rather than clinical measures of adiposity (Willett, 1998; Kuczmarski and Flegal, 2000). Although weight is the simplest anthropometric index of excess body fat, it does not distinguish between lean body mass (comprised primarily of muscle, bone, and extracellular water) and adipose tissue (Willett, 1998). Thus, measures of weight adjusted for height provide a better approximation of the proportion or total amount of adipose tissue in the body than does weight alone.

Since the 1980s, indices of weight adjusted for height have gained favor because they provide a single estimate of adiposity regardless of height and can be easily 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),

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**Table 1** Cutpoints of BMI for the classification of weight

BMI (kg/m <sup>2</sup> )	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

Source: WHO Expert Committee on Physical Status, 1995.

which is defined as weight (in kilograms) divided by height (in meters squared) (Willett, 1998). 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 (Willett, 1998).

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. Historically, weight-for-height standards prepared by the Metropolitan Life Insurance Company provided 'ideal' and 'desirable' gender-specific weight ranges for each inch of height based on actuarial data (Metropolitan Life Insurance Company, 1959). Standards based on BMI have been reported for the US adult population since 1980 in the *Dietary Guidelines for Americans* (US Department of Agriculture and US Department of Health and Human Services, 2000). Widely accepted current standards based on BMI criteria for overweight and obesity are recommended by the World Health Organization (WHO Expert Committee on Physical Status, 1995) and supported by other advisory committees and expert panels to federal agencies (National Institutes of Health and National Heart Lung and Blood Institute, 1998; US Department of Agriculture and US Department of Health and Human Services, 2000). The WHO cutpoints for BMI and their corresponding interpretations are shown in Table 1. While the exact cutpoints are somewhat arbitrary, this BMI classification scheme was derived largely from observational and epidemiologic studies of BMI and disease outcomes, and thus reflects the relationship of BMI to morbidity and mortality (WHO Expert Committee on Physical Status, 1995; National Institutes of Health and National Heart Lung and Blood Institute, 1998). The cutpoint for the underweight category is based on adverse health consequences of malnutrition in developing countries (WHO Expert Committee on Physical Status, 1995).

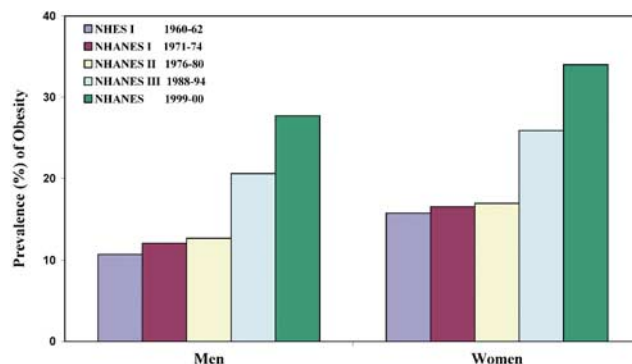
Weight and height can be self-reported, and thus are more easily determined in epidemiologic studies of morbidity and mortality than measured weight and height or clinical measures of adiposity. While some systematic error exists in self-reported weight and height (weight tends to be underestimated and height overestimated), self-reported data are highly correlated with measured weight and height (0.8 to >0.9) (Willett, 1998) and are sufficiently accurate to establish associations

with diseases known to be related to obesity in epidemiologic studies (Stevens *et al.*, 1990; Willett, 1998; Willett *et al.*, 1999). However, prevalence estimates of overweight and obesity based on self-reported data tend to be lower than those based on measured values (Mokdad *et al.*, 1999).

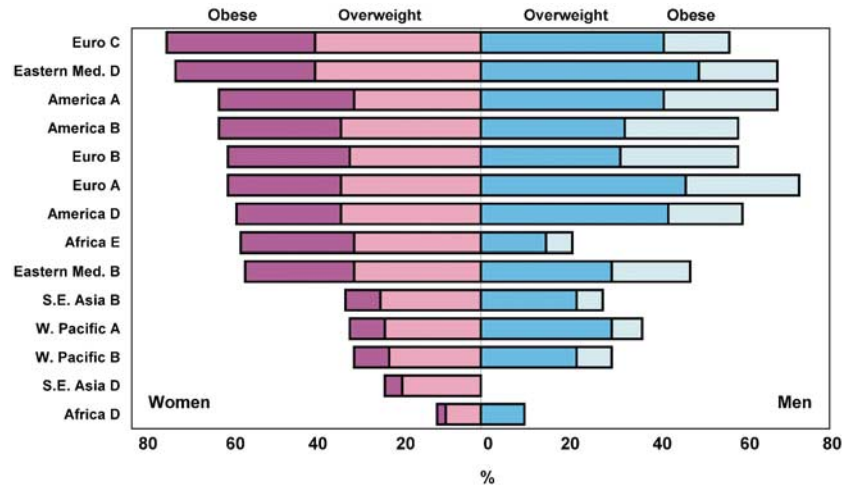
Many studies have found moderate to strong correlations (0.6 to 0.9) between BMI and densitometry estimates of body fat composition in adult populations (Willett, 1998). The validity of BMI as a measure of adiposity is further supported by its association with obesity-related risk factors, such as blood triglycerides, total cholesterol, blood pressure, and fasting glucose (Willett, 1998). BMI may 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 (WHR) at the same level of BMI (Borkan *et al.*, 1983). For such populations, and with increasing evidence of health risks associated with abdominal (visceral) fat, two measures of central adiposity, the WHR and, more recently, waist circumference, have been commonly used in epidemiologic studies.

### Trends in the prevalence of overweight and obesity

Measured weight and height have been collected on nationally representative samples of United States adults beginning in 1960. These data, collected in the National Health and Nutrition Examination Survey (NHANES) by the National Center for Health Statistics (<http://www.cdc.gov/nchs/nhanes.htm>), allow valid comparisons of trends over time. The prevalence of overweight (BMI of 25 or higher) and obesity (BMI of 30 or higher) in US adults aged 20–74 years was relatively stable from 1960 to 1980, with only small increases noted (Figure 1) (Flegal *et al.*, 2002). This situation changed dramatically in the 1980s and 1990s when large increases in the prevalence of both overweight and obesity occurred nationally in men and women (Figure 1). By the year 2000, 64.5% of US adults were overweight or obese and 30.5% were obese. Within



**Figure 1** Trends in the age-adjusted prevalence of obesity for adults aged 20–74 years, United States, 1960–2000. Data source: Flegal, KM *et al.* *JAMA* 2002; **288**: 1723–1727



**Figure 2** Prevalence of overweight and obesity in 45–59 year olds in different parts of the world. The three countries with the biggest populations in each subregion is defined as follows – Afr D: Nigeria, Algeria, Ghana; Afr E: Ethiopia, Congo, South Africa; Amr A: United States, Canada, Cuba; Amr B: Brazil, Mexico, Colombia; Amr D: Peru, Ecuador, Guatemala; Emr B: Iran, United Arab Emirates, Saudi Arabia; Emr D: Pakistan, Egypt, Sudan; Eur A: Germany, France, United Kingdom; Eur B: Turkey, Poland, Uzbekistan; Eur C: Russian Federation, Ukraine, Kazakhstan; Sear B: Indonesia, Thailand, Sri Lanka; Sear D: India, Bangladesh, Myanmar; Wpr A: Japan, Australia, Singapore; Wpr B: China, Vietnam, Philippines. Source: James PT *et al.* *Obes Res* 2001; 9: 228S–233S

the population of adults, 4.7% were morbidly obese with a BMI of 40 or greater (Flegal *et al.*, 2002).

The increase in obesity is not limited to the United States, but is increasing globally, in both developed and developing countries. There are large between-country and within-country differences in the levels of obesity (Figure 2), and overweight and obesity can coexist with undernutrition, especially in developing countries and countries undergoing economic and cultural transition. The prevalence of adult obesity in Eastern Europe, the Eastern Mediterranean, Spain, and Italy is as high or higher than in the US. Obesity is still relatively uncommon in China, Japan, and most parts of Africa.

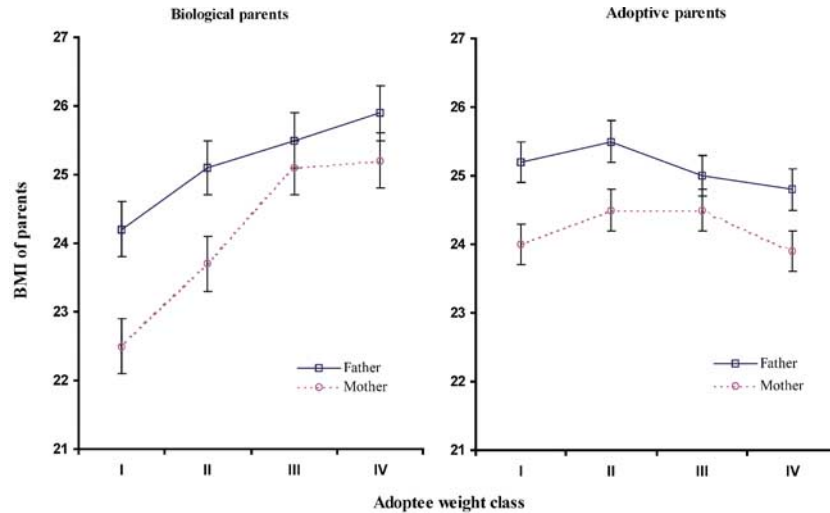
Since the 1980s, large increases have been observed in the United Kingdom, and smaller increases have been reported in many other European countries (IARC, 2002; Seidell, 2003). In countries other than the US and the UK, the temporal increases in overweight and obesity generally have been larger in men than in women (James *et al.*, 2001; IARC, 2002; Seidell, 2003). In eastern Europe, the prevalence of obesity in women may have stabilized or decreased in the last decade (James *et al.*, 2001; IARC, 2002; Seidell, 2003), but remains high (Figure 2). Increases in obesity are also occurring in developing countries in other parts of the world, including the Caribbean, South America, and South-East Asia (Bjorntorp, 1997).

In almost all Western countries, the prevalence of obesity is inversely associated with education and other measures of socioeconomic status, especially in women. The prevalence of obesity in adulthood increases with increasing age until approximately age 65 years when it begins to decline slightly. The highest rates of obesity typically occur in persons aged 45–64 years. In general, women have higher levels of obesity and extreme obesity than men (IARC, 2002).

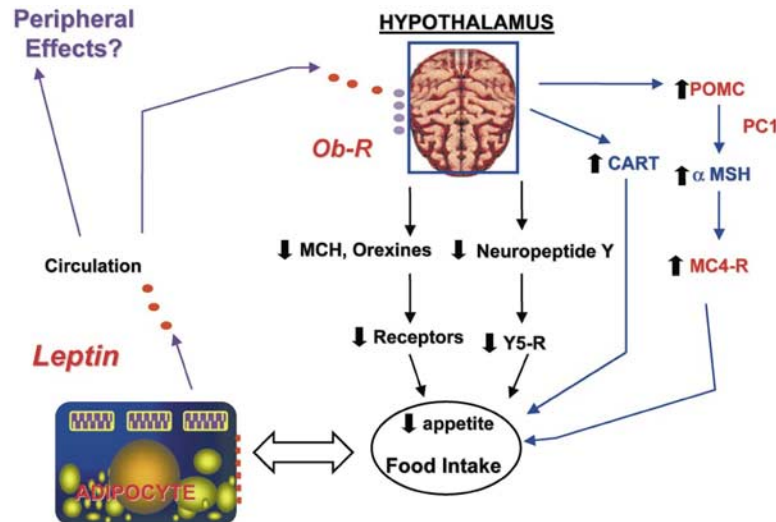
Equally troubling is the increasing global trend towards overweight in children. In the US, the prevalence of overweight in children and adolescents aged 6–19 years has tripled since the mid-1960s. This percentage, defined as at or above the 95th percentile of BMI-for-age growth charts, increased from 4.2% in 1965 to over 15% in 2000 (Ogden *et al.*, 2002). Another 15% of children aged 6–19 years are considered to be ‘at risk for overweight’ (at or above the 85th percentile, but less than the 95th percentile) (Ogden *et al.*, 2002). The worldwide prevalence of childhood overweight and obesity is difficult to assess, however, because there are no international standards for overweight and obesity in childhood. Childhood obesity seems to be increasing in most countries where adult obesity is increasing and has been documented wherever temporal comparisons have been made (IARC, 2002). As overweight children usually become overweight adults (Serdula *et al.*, 1993), these trends portend continuing increases in adult obesity and attendant health risks.

### Genetics of obesity

It is clear from family, twin, and adoption studies that genetic factors contribute to the obesity phenotype (Figure 3) (Stunkard *et al.*, 1986a, b; Fabsitz *et al.*, 1994; Allison *et al.*, 1996; Austin *et al.*, 1997; Rice *et al.*, 1999; Coady *et al.*, 2002). Such studies, conducted in countries where food is plentiful, suggest that 40–70% of individual variability in body mass in these settings may be explained by heritable factors. It should be noted that genetic and biologic determinants of obesity only become manifest in social environments that provide abundant calorie-dense foods and facilitate



**Figure 3** Mean BMI of biological and adoptive parents by weight class of the adoptee (I, thin; II, medium; III, overweight; IV, obese). Source: Stunkard AJ *et al.* *N Engl J Med* 1986; **314**: 193–198



**Figure 4** Leptin pathway for bodyweight control. All the monogenic obesity gene-encoded proteins (in red) are strongly connected as part of the same loop of regulation of food intake. CART = cocaine- and amphetamine-related transcript; MC4R = melanocortin-4 receptor; MCH = melanin concentrating hormone; Ob-R = leptin receptor gene; PC1 = prohormone convertase-1; POMC = proopiomelanocortin;  $\alpha$ MSH =  $\alpha$ -melanocyte-stimulating hormone; Y5-R = neuropeptide Y5 receptor. Source: Boutin P and Froguel P. *Clin. Endocrinol. Metab.* 2001; **15**: 391–404

physical inactivity. Genetic factors predispose individuals to gain weight. Only environmental factors cause sudden large shifts in the prevalence of obesity in populations.

Genes that influence energy balance in humans may operate through multiple central and peripheral homeostatic pathways that influence caloric intake, expenditure, and/or storage (Rosenbaum *et al.*, 1997; Woods *et al.*, 1998; Clement *et al.*, 2002). Energy balance is mediated through endocrine and neural signals coming from a variety of peripheral tissues to the central nervous system. Afferent signals received in the hypothalamus modulate the release of peptides and generate efferent signals that regulate energy expenditure (through the sympathetic and parasympathetic

nervous systems and thyroid hormones) and energy intake. Genes and proteins that play a role in common obesity may regulate appetite and satiety (e.g. cholecystokinin, neuropeptide Y, melanocortins, leptin), insulin sensitivity and glucose metabolism in muscle and other peripheral tissues (e.g. insulin and insulin receptor), and energy storage and expenditure in adipose tissue (e.g. lipoprotein lipase) (Woods *et al.*, 1998; Clement *et al.*, 2002).

Several spontaneously occurring single gene mutations in rodents have led to the identification of rare human mutations that invariably result in obesity. Positional cloning of the mouse *ob* 'obese' gene led to the identification of leptin, a hormone secreted by adipocytes that acts in the hypothalamus to inhibit food

**Table 2** Examples of candidate genes for obesity, grouped according to pathways in which they are involved

<i>Food intake regulation by the CNS</i>
Leptin and the leptin receptor ( <i>LEP</i> and <i>LEPR</i> )
Cholecystokinin and receptors ( <i>CCK</i> and <i>CCKR</i> )
Glucagon-like peptide 1 ( <i>GLP1</i> )
Serotonin transporter ( <i>5HTT</i> )
Dopamine receptors
Melanocortin-3 receptor ( <i>MC3R</i> )
Ghrelin
<i>Modulation of insulin action and glucose metabolism in target tissues</i>
Insulin
Insulin receptor ( <i>INSR</i> )
Insulin receptor substrate 1 ( <i>INSI</i> )
Sulfonylurea receptors ( <i>SUR</i> )
Fatty acid-binding proteins ( <i>FABP</i> )
Tumor necrosis factor $\alpha$ ( <i>TNF<math>\alpha</math></i> )
<i>Energy expenditure, lipid metabolism,<sup>a</sup> adipose tissue metabolism</i>
Lipoprotein lipase ( <i>LPL</i> )
Hormone-sensitive lipase ( <i>HSL</i> )
Apoprotein C2 ( <i>apoC2</i> )
Peroxisome proliferator-activated receptor $\gamma$ ( <i>PPAR<math>\gamma</math></i> )

<sup>a</sup>Including lipid oxidation, lipolysis and lipogenesis. Source: Clement K *et al.* *Am J Pharmacogenom* 2002;2:177–187.

intake (Zhang *et al.*, 1994). Homologous human mutations have since been documented for the leptin gene (*LEP*) the leptin receptor gene (*LEPR*) (Montague *et al.*, 1997; Clement *et al.*, 1998), the melanocortin-4 receptor gene (*MC4R*) (Yeo *et al.*, 1998), the pro-opiomelanocortin gene (*POMC*) (Krude *et al.*, 1998), and the prohormone convertase 1 gene (*PC1*) (Jackson *et al.*, 1997). The protein products of these genes are all involved in the leptin pathway and one of its targets, the melanocortin pathway, and act together to regulate food intake (Figure 4) (Boutin and Froguel, 2001; Clement *et al.*, 2002). However, while providing evidence for the importance of the leptin pathway in human energy homeostasis, single gene mutations are an extremely rare cause of human obesity (Chagnon *et al.*, 2003). The *MC4R* gene is the most prevalent obesity gene in humans and is estimated to be involved in 1–4% of cases of morbid obesity (Vaisse *et al.*, 2000).

While single gene mutations rarely account for obesity in humans, it is likely that obesity is influenced by the interaction of multiple genes, each with modest effects, and further interactions with environmental factors such as energy availability, physical activity, and smoking. Recent advances in our understanding of the genome and in the technology to conduct high-throughput genotyping have greatly improved our ability to examine the relation of common polymorphisms to obesity. While knowledge of the genetics of obesity has greatly advanced in recent years, at present, we remain limited in our understanding of the genetic variation in populations that accounts for diverse susceptibility to obesity.

Researchers have attempted to identify important obesity susceptibility genes using two approaches. First, by investigating candidate genes likely to play a biologic

role in three pathways related to obesity: food intake regulation by the central nervous system; modulation of insulin action and glucose metabolism in target tissues that may contribute to excess fat deposition and insulin resistance; and regulation of energy expenditure, lipid metabolism and oxidation, lipolysis, lipogenesis, and adipose tissue metabolism (Table 2) (Clement *et al.*, 2002). Over 200 association studies have been conducted relating genetic variation in candidate genes to obesity phenotypes (Chagnon *et al.*, 2003). These studies generally have observed small, uncertain, or inconsistent effects. Significant positive associations have been observed in five or more studies for about 15 genes, including common polymorphisms in the beta-adrenergic receptors ( $\beta$ -AR2,  $\beta$ -AR3), the peroxisome proliferator-activated receptor gamma (*PPAR $\gamma$* ), *LEP*, *LEPR*, uncoupling protein genes (*UCP-1*, *UCP-2*, and *UCP-3*), and tumor necrosis factor alpha (*TNF $\alpha$* ) (Chagnon *et al.*, 2003).

The second approach to identifying obesity susceptibility genes has been through genome-wide scans in large numbers (several hundred to several thousand) of obese individuals and their family members in diverse ethnic populations. Genome-wide scans identify chromosomal regions that show linkage with obesity in collections of families. Such scans have been conducted in widely diverse populations (Clement *et al.*, 2002). Genome-wide scans require no *a priori* assumptions about gene function; this method attempts to identify susceptibility genes simply by position. After regions of linkage are identified, specific genes can be identified by positional cloning within these regions. Such studies have suggested at least 68 human obesity loci on several chromosomes; 18 loci have been replicated in at least two studies of different populations (Chagnon *et al.*, 2003). Positional cloning of genes in these regions is underway.

### Metabolic consequences of overweight and obesity

Body weight has strong effects on metabolic factors that may subsequently affect cancer risk; in particular, on circulating levels of peptide and steroid hormones and their binding factors. Specific effects vary somewhat by gender and by menopausal status in women and are summarized in Table 3.

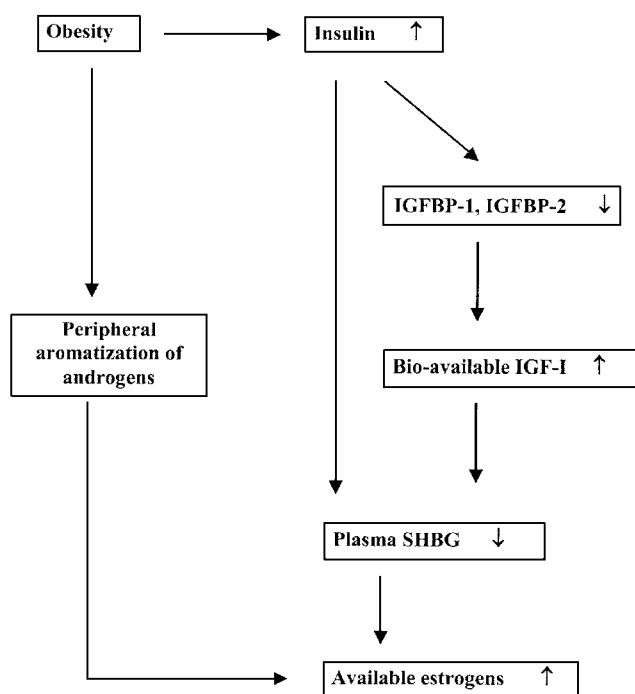
A linear increase in circulating levels of insulin occurs with increasing BMI in both men and women. Insulin acts to control the uptake and use of glucose in peripheral tissues. With excessive calorie consumption and weight gain, tissues become insensitive (resistant) to insulin and the body compensates by producing more insulin, resulting in a chronic state of hyperinsulinemia. Obesity, particularly abdominal obesity, is a major determinant of insulin resistance and hyperinsulinemia.

Insulin-like growth factors (*IGFs*) are mitogens that regulate energy-dependent growth processes (Le Roith, 1997). *IGF-I* stimulates cell proliferation and inhibits apoptosis and has been shown to have strong mitogenic

**Table 3** Associations of obesity and weight reduction with selected hormones and binding globulins

Hormone or binding globulin	Obesity (cross-sectional)	Weight reduction
Insulin	↑	↓
Insulin-like growth factor-I (IGF-I)	↓ or NE; ↑ (free IGF-I)	↑ or NE
IGF binding protein-1	↓	↑ ?
IGF binding protein-3	↓ or NE	↑ ?
Human growth hormone	↑	↑
Sex-hormone binding globulin	↓	↑
Total testosterone	? (F); ↓ (M)	↓ or NE (F); ? (M)
Free testosterone	↑ (F); ↓ (M)	↓ or ↑ or NE
Estradiol	↑ (M, postmenopausal F) NE ? (premenopausal F)	↓ ↓
Dehydroepiandrosterone (sulfate)	↓ or NE	↓ or NE
Prolactin	NE	↑ or NE

↑, increased levels; ↓, decreased levels; NE, no observed effect; ?, very uncertain; M, Males; F, females. Source: IARC Handbooks of Cancer Prevention, Volume 6: Weight Control and Physical Activity, 2002, p. 54.



**Figure 5** Mechanisms underlying relationships between overall and central adiposity and differences in total and bioavailable plasma sex steroid levels. ↑ Increased levels, ↓ decreased levels. Adapted from IARC, (2002, p. 59)

effects in a wide variety of cancer cell lines. The synthesis of IGF-I and its main binding protein, IGFBP-3, are regulated primarily by pituitary growth hormone (GH). In the circulation, more than 90% of IGF-I is bound to IGFBP-3. Obesity and other conditions related to chronic hyperinsulinemia result in elevated blood glucose levels, decreased levels of IGF-binding proteins (IGFBP-1 and IGFBP-2), and higher levels of free plasma IGF-I, the small fraction of IGF-I unbound to any binding protein (Figure 5). Obesity does not increase absolute plasma IGF-I levels, and the mild decrease in IGF-I levels observed in obese and hyperinsulinemic individuals can be explained by the negative feedback of free IGF-I on GH secretion, which is also lower in obese individuals.

Insulin and free IGF-I interact with and regulate the synthesis and bioavailability of sex steroids that affect the development and progression of certain cancers (Figure 5) (Kaaks, 1996). Chronic hyperinsulinemia inhibits hepatic synthesis of sex hormone-binding globulin (SHBG), thus increasing bioavailable androgens and estrogens unbound to SHBG. The unbound fraction determines the actual biological activity of androgens and estrogens, hormones essential for the growth, differentiation and function of many tissues in both men and women. There is a strong inverse association between amount and distribution of body fat and circulating levels of SHBG (Potischman *et al.*, 1996; Madigan *et al.*, 1998).

In addition to the effects of insulin on the bioavailability of sex hormones, adipose tissue itself increases the concentration of circulating estrogens in men and postmenopausal women through the aromatization of androstenedione to estrone (Figure 5) (Madigan *et al.*, 1998). In postmenopausal women, ovarian production of estrogen falls to very low levels and the adipose is the primary source of circulating estrogen.

Weight loss has been shown to reduce insulin resistance and circulating levels of insulin, glucose, and estradiol, and to increase levels of SHBG (Table 3) (IARC, 2002). In most studies, a 5–10% weight reduction is sufficient to improve these metabolic parameters. The influence of weight loss on the levels of IGFs and associated binding proteins is less clear. Unfortunately, few studies of the metabolic changes associated with weight loss have measured long-term effects, and there is little empirical evidence with regard to the clinical manifestations of weight loss sustained over long periods of time (Mann, 2000; National Task Force on the Prevention and Treatment of Obesity, 2000; IARC, 2002).

## Epidemiologic studies of obesity and cancer

### Historical perspective of epidemiologic studies of weight

The relationships between excess body weight and mortality from all causes and from cardiovascular

disease have been well-established in epidemiologic studies (Manson *et al.*, 1995; Willett *et al.*, 1995; Lindsted and Singh, 1998; Stevens *et al.*, 1998; Calle *et al.*, 1999). Excess weight is also known to be associated with an increased risk of morbidity, including cardiovascular diseases, type II diabetes mellitus, hypertension, dyslipidemia, glucose intolerance, and osteoarthritis (National Institutes of Health and National Heart Lung and Blood Institute, 1998; National Task Force on the Prevention and Treatment of Obesity, 2000).

The association of overweight and obesity with most of these noncancer outcomes is generally stronger than the association with all cancer or specific cancer sites. In populations experiencing temporal increases in the prevalence of obesity, increases in hypertension, hyperlipidemia, and diabetes emerge earlier than increases in cancer outcomes. As the incidence and mortality of specific types of cancer are less common than these noncancer outcomes, the relation of obesity to particular cancer sites has been more difficult to study. Moreover, a biologic mechanism that clearly links obesity to forms of cancer without an endocrine component has not been established.

For these reasons, understanding the associations between overweight, obesity, and a wide variety of cancers, as well as the biological mechanisms contributing to these associations, remains an evolving and currently very active area of research. Accumulating research on obesity and cancer suggests that this relationship is not confined to just a few forms of cancers.

#### *Evaluation by the International Agency for Research on Cancer (IARC)*

An 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 epidemiologic, clinical, and experimental data (IARC, 2002). Their report concluded that there is *sufficient evidence* in humans for a cancer-preventive effect of avoidance of weight gain for cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell), and esophagus (adenocarcinoma) (IARC, 2002). With regard to premenopausal breast cancer, the report concluded that available evidence on the avoidance of weight gain *suggests lack of a cancer-preventive effect*. For all other sites, IARC characterized the evidence for a cancer-preventive effect of avoidance of weight as *inadequate* in humans.

The conclusions with regard to the evidence in humans are based on epidemiologic studies of overweight and/or obese individuals compared to leaner individuals, not on studies of individuals who have lost weight. Unfortunately, few individuals lose and maintain significant amounts of weight, making it extremely difficult to examine cancer outcomes in large populations of weight losers. Consequently, the IARC report concluded that there is *inadequate evidence* in humans

for a cancer-preventive effect of intentional weight loss for any cancer site.

The IARC also concluded that in experimental animals, there is *sufficient or limited evidence* for a cancer-preventive effect of avoidance of weight gain by calorie restriction, based on studies of spontaneous and chemically induced cancers of the mammary gland, liver, pituitary gland (adenoma), and pancreas, for chemically induced cancers of the colon, skin (non-melanoma), and prostate, and for spontaneous and genetically induced lymphoma. An association between overweight and obesity and cancer at many sites is consistent with animal studies showing that caloric restriction dramatically decreases spontaneous and carcinogen-induced tumor incidence, multiplicity, and size (Dunn *et al.*, 1997; Hursting *et al.*, 1997; Kritchevsky, 1999). Possible mechanisms for these observations include altered carcinogen metabolism, decreased oxidative DNA damage, greater DNA repair capacity (IARC, 2002), and a reduction of IGF-I levels in calorie-restricted animals (Dunn *et al.*, 1997).

#### *Colorectal cancer*

Obesity has been consistently associated with higher risk of colorectal cancer in men (relative risks of approximately 1.5–2.0) and women (relative risks of approximately 1.2–1.5) in both case-control and cohort studies (IARC, 2002). Similar relationships are seen for colon adenomas, with stronger associations for larger adenomas (Giovannucci *et al.*, 1996). The gender difference, in which stronger associations are seen in men than women, has been observed consistently across studies and populations. The reasons for the gender difference are speculative. One hypothesis is that central adiposity is a stronger predictor of colon cancer risk than peripheral adiposity or general overweight. As men are more likely to deposit fat centrally, BMI may be a more accurate indicator of the relevant exposure in men than in women. Support for the role of central obesity on colorectal cancer comes from studies suggesting that waist circumference and WHR are related strongly to risk of colorectal cancer and large adenomas in men (Giovannucci *et al.*, 1995). However, the association between WHR and colorectal cancer in women was not stronger than the association between BMI and colorectal cancer in several studies that examined both measures, making it unlikely that body fat distribution completely explains the gender differences. Another possible explanation is that there may be an offsetting beneficial effect of obesity on colorectal cancer risk in women. Substantial evidence supports the protective role of exogenous estrogens (in the form of postmenopausal hormone therapy) on the risk of colorectal cancer in women (Calle *et al.*, 1995; Writing Group for the Women's Health Initiative Investigators, 2002). The high levels of circulating estrogens associated with postmenopausal obesity in women may diminish the obesity-associated risk of colorectal cancer.

Giovannucci was the first to propose the mechanistic hypothesis that high body mass, and central obesity in

particular, increased colon cancer risk through their effect on insulin production (Giovannucci *et al.*, 1995; Sandhu *et al.*, 2002; Komninou *et al.*, 2003). Insulin and IGFs have been shown to promote the growth of colonic mucosal cells and colonic carcinoma cells *in vitro* studies (Macaulay, 1992; LeRoith *et al.*, 1995). This hypothesis has received recent support from many epidemiologic studies. Higher risk of colorectal cancer has been associated with elevated fasting plasma glucose and insulin levels following a standard dose of oral glucose challenge (Giovannucci *et al.*, 1995; Schoen *et al.*, 1999) and with elevated serum C-peptide (a marker of insulin secretion) levels (Kaaks *et al.*, 2000). Several prospective cohort (Ma *et al.*, 1999; Giovannucci *et al.*, 2000; Kaaks *et al.*, 2000) and case-control studies (Manousos *et al.*, 1999; Renehan *et al.*, 2000) have found increased risk of colorectal cancer and large adenomas with increasing absolute levels of IGF-I and decreasing levels of IGFBP-3.

### Breast cancer

Many epidemiologic studies since the 1970s have assessed the association between anthropometric measures and breast cancer occurrence and/or prognosis (IARC, 2002; Stephenson and Rose, 2003). Early studies established that the association between body size and risk of breast cancer differed according to menopausal status, and that heavier women were at increased risk of postmenopausal, but not premenopausal breast cancer (IARC, 2002). In fact, among premenopausal women, there is consistent evidence of a modest reduction in risk among women with high ( $\geq 28$ ) BMI. This reduction in risk is likely due to the increased tendency for young obese women to have anovulatory menstrual cycles and lower levels of circulating steroid hormones (Potischman *et al.*, 1996).

Obesity has been shown consistently to increase rates of breast cancer in postmenopausal women by 30–50% (Hunter and Willett, 1993; Ballard-Barbash and Swanson, 1996; Trentham-Dietz *et al.*, 1997; Galanis *et al.*, 1998). Some studies have found central adiposity to be an independent predictor of postmenopausal breast cancer risk beyond the risk attributed to overweight alone (Folsom *et al.*, 1993; Kaaks *et al.*, 1998). 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 (Folsom *et al.*, 1990; Barnes-Josiah *et al.*, 1995; Huang *et al.*, 1997).

Studies of breast cancer mortality and survival among breast cancer cases illustrate that adiposity is associated both with poorer survival and increased likelihood of recurrence among those with the disease, regardless of menopausal status and after adjustment for stage and treatment (Boyd *et al.*, 1981; Greenberg *et al.*, 1985; Coates *et al.*, 1990; Tretli *et al.*, 1990; Maehle and Tretli, 1996). Very obese women (BMI  $\geq 40.0$ ) have breast cancer death rates that are three times higher than very lean (BMI  $< 20.5$ ) women (Petrelli *et al.*, 2002). The greater risk of death among heavier women likely

reflects both a true biological effect of adiposity on survival and delayed diagnosis in heavier women. Estrogen receptor (ER)-positive tumors are exposed to more continuous stimulation in obese than in leaner women. Studies suggest that the association between BMI and poorer prognosis is limited to or more pronounced among women with ER-positive tumors and stage I and II disease (Coates *et al.*, 1990; Tretli *et al.*, 1990; Maehle and Tretli, 1996). In addition to the estrogenic effects of adiposity, there is evidence that heavier women are less likely to receive mammography screening (Wee *et al.*, 2000), and among women who self-detect their tumors, high BMI increases the likelihood of nonlocalized disease (Reeves *et al.*, 1996).

The association between BMI and postmenopausal breast cancer is stronger among women who have never used hormone replacement therapy (Collaborative Group on Hormonal Factors in Breast Cancer, 1997; Huang *et al.*, 1997; Schairer *et al.*, 2000). It is likely that the uniformly high levels of circulating estrogens among women who use exogenous hormones, regardless of weight, obscure much or all of the association between BMI and breast cancer.

The consistent observation that BMI is more strongly associated with breast cancer in women who do not use hormone replacement therapy supports the mechanistic hypothesis that BMI increases risk by increasing endogenous estrogen production. In addition, high levels of circulating estrogens and low levels of SHBG have been shown to be associated with increased risk of breast cancer in postmenopausal women (The Endogenous Hormones and Breast Cancer Collaborative Group, 2002).

Another mechanism by which obesity may affect the risk of breast cancer involves insulin and/or IGFs. IGF-I is a potent mitogen for normal and transformed breast epithelial cells (Lee and Lee, 1999), and is associated with mammary gland hyperplasia (Ng *et al.*, 1997) and mammary cancer (Bates *et al.*, 1995) in animals. In addition, IGF-I receptors are present in most human breast tumors and in normal breast tissue (Papa *et al.*, 1993; Peyrat *et al.*, 1993). Two case-control studies (Peyrat *et al.*, 1993; Bruning *et al.*, 1995) and two prospective cohort studies (Hankinson *et al.*, 1998; Toniolo *et al.*, 2000) have found positive associations between serum or plasma IGF-I concentrations and breast cancer in premenopausal, but not postmenopausal, women. In two studies, the magnitude of the association increased when both IGF-I- and IGF-binding protein 3 (IGFBP-3) were considered (Bruning *et al.*, 1995; Hankinson *et al.*, 1998). That the association with IGF-I is stronger in studies of premenopausal than postmenopausal breast cancer has been interpreted as suggesting that IGF-I may increase risk only in the presence of high levels of endogenous estrogens (IARC, 2002).

Two case-control studies found that women with either premenopausal (Del Giudice *et al.*, 1998) or postmenopausal (Bruning *et al.*, 1992) breast cancer had increased circulating insulin or C-peptide levels. However, these findings were not confirmed in either

pre- or postmenopausal women with breast cancer in a recent prospective cohort study (Toniolo *et al.*, 2000).

### Endometrial cancer

There is convincing and consistent evidence from both case-control and cohort studies that overweight and obesity is strongly related to endometrial cancer (IARC, 2002). A linear increase in the risk of endometrial cancer with increasing weight or BMI has been observed in most but not all studies (IARC, 2002; Calle *et al.*, 2003). The increase in risk generally ranges from two- to fourfold in overweight and/or obese women, and may be somewhat higher in studies of mortality than incidence (Lew and Garfinkel, 1979; IARC, 2002; Calle *et al.*, 2003).

As with breast cancer, the probable mechanism for the increase in risk of endometrial cancer associated with obesity is the increase in circulating estrogens. Many studies have shown large increases in endometrial cancer risk among postmenopausal women who take unopposed estrogen (i.e. estrogen in the absence of progesterone) (Key and Pike, 1988), as well as increases in risk among women with higher circulating levels of total and bioavailable estrogens (IARC, 2002).

### Kidney cancer

The risk of renal cell cancer is 1.5- to 2.5-fold higher in overweight and obese persons than in normal weight men and women in study populations worldwide; most studies have found a dose-response relationship with increasing weight or BMI (IARC, 2002). In several studies, the increase in risk with increasing BMI is greater in women than in men (McLaughlin *et al.*, 1984, 1992; Mellemegaard *et al.*, 1994; Chow *et al.*, 1996; Hill and Austin, 1996; Wolk *et al.*, 1996; World Cancer Research Fund & American Institute for Cancer Research, 1997; Calle *et al.*, 2003), although at present this finding remains unexplained. Importantly, the obesity-associated risk of renal cell cancer appears to be independent of blood pressure, suggesting that hypertension and obesity may influence renal cell cancer through different mechanisms (Chow *et al.*, 2000). The hypothesis that chronic hyperinsulinemia contributes to the association of BMI and renal cell cancer is supported indirectly by the increased risk of kidney cancer seen in diabetics (Lindblad *et al.*, 1999).

### Esophageal cancer

Obesity is associated with a two- to threefold increase in risk for adenocarcinoma of the esophagus (Vaughan *et al.*, 1995; Chow *et al.*, 1998; Tretli *et al.*, 1999; IARC, 2002), with stronger associations seen in nonsmokers (Chow *et al.*, 1998; Calle *et al.*, 2003). High BMI is associated with gastroesophageal reflux and frequent reflux is very strongly associated with esophageal adenocarcinoma (Chow *et al.*, 1995; Lagergren *et al.*, 1999). Thus, the increased occurrence of reflux is

hypothesized to explain the association of obesity and esophageal adenocarcinoma.

### Other cancers

There have been few previous studies of gall bladder cancer and obesity, and most have been relatively small. Available studies have consistently found elevated risks for women (of about twofold), but generally have had too few cases to evaluate the association in men (Lew and Garfinkel, 1979; Moller *et al.*, 1994; Strom *et al.*, 1995; Zatonski *et al.*, 1997; Wolk *et al.*, 2001; Calle *et al.*, 2003). Obesity is thought to operate indirectly to increase the risk of gallbladder cancer by increasing the risk of gallstones, which, in turn, causes chronic inflammation and increased risk of biliary tract cancer (World Cancer Research Fund and American Institute for Cancer Research, 1997).

Several recent studies have suggested that high body mass may be associated with approximately a doubling of risk for pancreatic cancer in men and women (Moller *et al.*, 1994; Silverman *et al.*, 1998; Gapstur *et al.*, 2000; Michaud *et al.*, 2001; Calle *et al.*, 2003). However, smaller, earlier studies did not support an association and further research is needed. Chronic hyperinsulinemia and glucose intolerance may contribute to an increased risk of pancreatic cancer, as suggested by the well-established positive association between diabetes and pancreatic cancer in prospective studies (Everhart and Wright, 1995; Calle *et al.*, 1998).

In contrast, a large number of available studies do not support an association between body mass and prostate cancer (Calle, 2000; IARC, 2002). However, there are some data to suggest a modest increase in the risk of advanced prostate cancer or death with high body mass (Andersson *et al.*, 1997; Giovannucci *et al.*, 1997; Rodriguez *et al.*, 2001).

Positive associations with ovarian cancer and body mass have been in the range of 1.5–2.0 for the highest categories studied (Cramer *et al.*, 1884; Lew and Garfinkel, 1979; Farrow *et al.*, 1989; Purdie *et al.*, 2001; Calle *et al.*, 2003), although several studies have not shown an association (Slattery *et al.*, 1989; Moller *et al.*, 1994; Mink *et al.*, 1995; Wolk *et al.*, 2001).

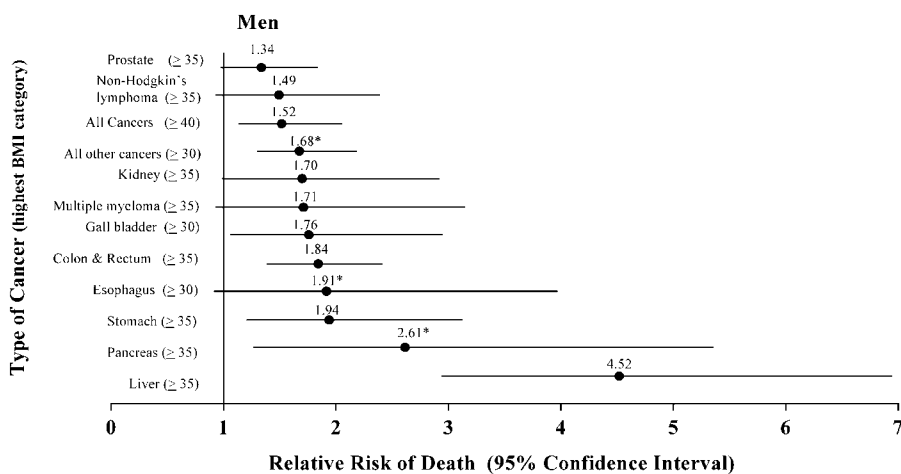
BMI has been reported to be inversely associated with lung cancer in several study populations that did not exclude smokers from the analysis (IARC, 2002). This finding is explained by the confounding effects of smoking; smoking is the primary cause of lung cancer, and is inversely associated with BMI (Henley *et al.*, 2002). Studies that do not exclude smokers cannot separate the effects of BMI on the risk of death from the effects of smoking, namely, decreased BMI and increased risk of death. No association is seen between BMI and lung cancer in nonsmoking populations (Calle *et al.*, 2003).

Few studies have investigated the association of body mass with cancers of the liver, stomach, uterine cervix, and hematopoietic system. Three studies that have examined obesity and liver cancer found excess relative risk in both men and women in the range of 2.0–4.0

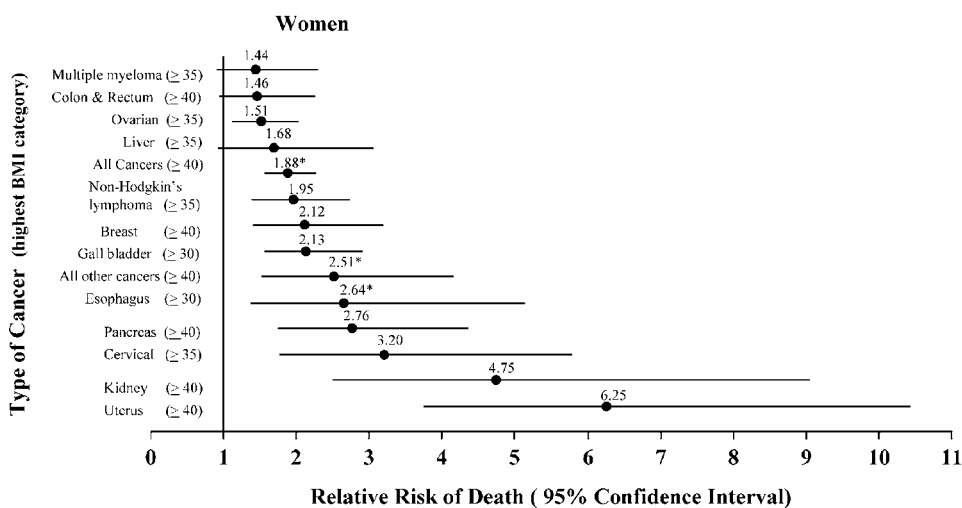
(Moller *et al.*, 1994; Wolk *et al.*, 2001; Calle *et al.*, 2003). Risk for adenocarcinoma of the gastric cardia has been found to be obesity related (Vaughan *et al.*, 1995; Ji *et al.*, 1997; Chow *et al.*, 1998), but data are limited and inconsistent for noncardia cancers of the stomach (Ji *et al.*, 1997; Chow *et al.*, 1998). Studies on BMI and cervical cancer are limited and inconclusive. Two prospective mortality studies found positive associations with high BMI (two- to threefold increased risk) (Lew and Garfinkel, 1979; Calle *et al.*, 2003), while much smaller increased risks were observed in two cohorts of hospitalized patients diagnosed with obesity compared to rates in the general population (Moller *et al.*, 1994; Wolk *et al.*, 2001). Data are scarce and inconsistent on the relationship between hematopoietic cancers and BMI (Lew and Garfinkel, 1979; Moller *et al.*, 1994; Holly *et al.*, 1999; Wolk *et al.*, 2001; Calle *et al.*, 2003).

### Overweight, obesity, and cancer mortality

Recent results from a large American Cancer Society prospective mortality study illustrate that increased body weight is associated with increased death rates from all cancers combined and for cancers at multiple specific sites in both men and women (Figures 6 and 7). These results were based on a population of more than 900 000 US adults who were followed from 1982 to 1998 and on more than 57 000 deaths from cancer that occurred during the 16-year follow-up period (Calle *et al.*, 2003). The results are based on cancer mortality, and thus may reflect the influence of BMI on either cancer incidence or survival. Survival may be influenced by adiposity-related differences in diagnosis or treatment of cancer, as well as by true biologic effects of adiposity on cancer progression.



**Figure 6** Summary of mortality from cancer according to BMI for US men in the Cancer Prevention Study II, 1982–1998. For each relative risk, the comparison was between men in the highest BMI category (indicated within parentheses) and men in the reference category (BMI, 18.5–24.9). Asterisks indicate relative risks for men who never smoked. Results of the linear test for trend were significant ( $P \leq 0.05$ ) for all cancer sites. Source: Calle EE *et al.* *N Engl J Med* 2003; **348**: 1625–1638



**Figure 7** Summary of mortality from cancer according to BMI for US women in the Cancer Prevention Study II, 1982–1998. For each relative risk, the comparison was between women in the highest BMI category (indicated within parentheses) and women in the reference category (BMI, 18.5–24.9). Asterisks indicate relative risks for women who never smoked. Results of the linear test for trend were significant ( $P \leq 0.05$ ) for all cancer sites. Source: Calle EE *et al.* *N Engl J Med* 2003; **348**: 1625–1638

### *Population-attributable fraction (PAF)*

The proportion of disease in a population that can be attributed to a risk factor is termed the 'PAF' or 'population-attributable risk' and is used as a measure of the public health impact of the risk factor. Such estimates depend on both the magnitude of the association between the risk factor and the disease (i.e. the size of the relative risk) and the prevalence of the risk factor in the population of interest. The PAF will increase as either one of its components increases. We estimated that the fraction of all cancer deaths in the year 2000 attributable to overweight and obesity in US adult men and women was 14 and 20%, respectively (Calle *et al.*, 2003). This corresponds to over 90 000 deaths from cancer per year. Estimates of the number of annual deaths from all causes attributable to obesity in US adults range from 280 000 to 325 000 (Allison *et al.*, 1999).

### **Intervention strategies**

#### *Individual interventions*

While many individuals are able to lose significant amounts of weight, long-term maintenance of weight loss is difficult to achieve and quite rare. Most studies of weight loss show very poor weight maintenance, regardless of the method used to lose weight (Glenny *et al.*, 1997). Substantial research suggests that changes to both dietary intake and physical activity are critical to long-term success (IARC, 2002). There is some suggestion that the amount of physical activity needed to prevent relapse after prior weight reduction may be higher than the amount needed for primary prevention of weight gain (Fogelholm and Kukkonen-Harjula, 2000). While 29% of US men and 44% of US women report trying to lose weight, few report both reducing caloric intake and increasing physical activity simultaneously (Serdula *et al.*, 1999).

Understanding the combination of behaviors and other factors that enable long-term maintenance of weight loss is critical to the development of effective interventions. The National Weight Control Registry (NWCR) has enrolled close to 3000 adult men and women in the US since 1994 who have maintained a weight loss of at least 13.6 kg (30 lbs) for at least 1 year (average 5.5 years). Weight loss was achieved through a variety of methods, with about half of the subjects engaging in formal programs and half losing weight on their own. However, almost all registry members share common behavioral strategies to maintain their weight loss, including eating a diet that is low in energy and low in fat, engaging in frequent self-monitoring of weight and food intake, and engaging in high levels of regular physical activity (Wing, 2001). Physical activity appears to be the component of behavior that is most likely to promote long-term maintenance of weight loss (McGuire *et al.*, 1999). What distinguishes individuals who have been able to maintain weight loss is not the

novelty of their behavioral strategies, but the consistent use of these combined strategies over many years. There is some evidence from the NWCR that weight loss maintenance may get easier over time; if weight loss is maintained for 2–5 years, the likelihood of longer-term success greatly increases (Wing, 2001). While very informative, the results from this cohort of successful weight losers may not be entirely generalizable to the larger population of overweight individuals.

#### *Community interventions*

Individual choices with regard to diet and physical activity occur within a community context that either facilitates or interferes with healthy behaviors. It is clear from the temporal pattern of the obesity epidemic in the US (Figure 1) that the rapid increases in the weight of the population since 1980 are due to equally rapid and widespread environmental changes that influence food consumption and sedentary behavior. For the first time, the American Cancer Society has identified the need to develop effective community interventions in its Nutrition and Physical Activity Guidelines (Byers *et al.*, 2002). Public, private, and community organizations are encouraged to create social and physical environments that support the adoption and maintenance of healthful nutrition and physical activity behaviors. Specifically, organizations should increase access to healthful foods in schools, worksites, and communities, and provide safe, enjoyable, accessible environments for physical activity in schools, and for transportation and recreation in communities.

There are several examples of successful community-wide public health campaigns that have been of long duration and have led to positive, sustainable change. These include campaigns to promote immunization and seatbelt use, and to discourage tobacco use. However, the development and implementation of community-wide interventions to prevent obesity will undoubtedly be even more challenging than measures for tobacco control. Economic and social factors affect individual choices with regard to food and physical activity. Multiple industries at many levels are involved in the production, sale, and marketing of inexpensive, calorie-dense, refined foods to both adults and children. Most communities in the US are designed for transportation by automobile and are unfriendly and dangerous to pedestrians and cyclists. Occupational physical activity has become increasingly limited for most people, while hours spent on the job and in transportation to and from the job have increased. TV watching has now been supplemented with leisure hours spent at the computer. The goal of increasing the opportunities for physical activity in daily life is closely related to issues of urban design, safety, the availability of leisure time, and economic issues. While some individuals are currently successful at engaging in regular physical activity and maintaining a healthy body weight, this pattern is more achievable for individuals of higher socioeconomic status, who have greater knowledge of the behavioral strategies needed to maintain a healthy weight, and

greater resources to fully employ such strategies, in spite of the many environmental obstacles.

### Research questions

Further research defining the causal role of obesity and cancers of specific sites is needed, including mechanistic research, and studies that are able to separate the effects

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