Global Patterns in Excess Body Weight and the Associated Cancer Burden

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Abstract: The prevalence of excess body weight and the associated cancer burden have been rising over the past several decades globally. Between 1975 and 2016, the prevalence of excess body weight—defined as a body mass index (BMI) ≥ 25 kg/m²—increased from nearly 21% in men and 24% in women to approximately 40% in both sexes. Notably, the prevalence of obesity (BMI ≥ 30 kg/m²) quadrupled in men, from 3% to 12%, and more than doubled in women, from 7% to 16%. This change, combined with population growth, resulted in a more than 6-fold increase in the number of obese adults, from 100 to 671 million. The largest absolute increase in obesity occurred among men and boys in high-income Western countries and among women and girls in Central Asia, the Middle East, and North Africa. The simultaneous rise in excess body weight in almost all countries is thought to be driven largely by changes in the global food system, which promotes energy-dense, nutrient-poor foods, alongside reduced opportunities for physical activity. In 2012, excess body weight accounted for approximately 3.9% of all cancers (544,300 cases) with proportion varying from less than 1% in low-income countries to 7% or 8% in some high-income Western countries and in Middle Eastern and Northern African countries. The attributable burden by sex was higher for women (368,500 cases) than for men (175,800 cases). Given the pandemic proportion of excess body weight in high-income countries and the increasing prevalence in low- and middle-income countries, the global cancer burden attributable to this condition is likely to increase in the future. There is emerging consensus on opportunities for obesity control through the multisectoral coordinated implementation of core policy actions to promote an environment conducive to a healthy diet and active living. The rapid increase in both the prevalence of excess body weight and the associated cancer burden highlights the need for a rejuvenated focus on identifying, implementing, and evaluating interventions to prevent and control excess body weight. CA Cancer J Clin 2019;69:88-112. © 2018 American Cancer Society.

Keywords: adiposity, body fatness, cancer, cancer burden, cancer incidence, excess body weight, global obesity epidemic, overweight, population-attributable fraction, prevalence

Introduction

Overweight and obesity, collectively referred to as “excess body weight,” are defined as abnormal or excessive fat accumulation that causes many chronic diseases and reduces life expectancy.1 The prevalence of excess body weight has been increasing worldwide since the 1970s, and in 2016, approximately 40% of adults and 18% of children (ages 5-19 years) had excess body weight, equating to almost 2 billion adults and 340 million children.4 This trend is taking a toll on health; in 2015, an estimated 4 million deaths were attributable to excess body weight.2 The economic impact of illness related to excess body weight is daunting, estimated at US $2.0 trillion globally in 2014.3 Except for a possible plateau in high-income countries in recent years, the prevalence of excess body weight has increased rapidly in most...
countries across all population groups. Some of the steepest increases are in low- and middle-income countries, likely as a result of the introduction of the “Western lifestyle,” consisting of energy-dense, nutrient-poor foods alongside reduced physical activity levels.

Excess body weight is associated with the risk of various cancers. Although the effects of excess body weight on cancer risk are modest for most cancer sites, excess body weight is highly prevalent in high-income countries and elsewhere, leading to a substantial burden of cancers. In 2012, it was estimated at 544,300 cases, or 3.9% of all cancers worldwide, and this number undoubtedly will rise in the coming decades given current trends.

In this review, we present global and regional patterns in excess body weight, drivers of the epidemic, a summary of epidemiological evidence supporting the causal link of excess body weight to cancer risk, and the attributable cancer burden. Core policy actions to prevent and control excess body weight also are discussed.

**Defining Excess Body Weight**

Body mass index (BMI), defined as body mass in kilograms divided by the square of height in meters (kg/m²), is the most commonly used anthropometric measure to approximate overall body fatness for the purposes of classifying and reporting overweight and obesity. The World Health Organization (WHO) classifies adults with a BMI below 18.5 kg/m² as “underweight” and 18.5 and 24.9 kg/m² as “normal.” Above the normal range, there are conventional gradings for “overweight” (25-29.9 kg/m²) and “obesity” (30 kg/m² or greater). Obesity can be further divided into class 1 (30.0-34.9 kg/m²), class 2 (35.0-39.9 kg/m²), and class 3 (40 kg/m² or greater). Among children, overweight and obesity are defined not by absolute BMI cutoff points but relative to a historical healthy-weight group. The WHO provides different sets of standards for school-aged children (ages 5-19 years) and children younger than 5 years, and its reference populations and definitions of overweight and obesity differ from those used by the International Obesity Task Force and the US Centers for Disease Control and Prevention. Studies comparing the different definitions have found that the WHO classification produces slightly higher estimates of overweight and obesity prevalence than those of the International Obesity Task Force and the US Centers for Disease Control and Prevention, indicating a need to harmonize these standards. In this article, data are presented from the Noncommunicable Disease Risk Factor Collaboration, which uses the WHO standard.

**Measuring Excess Body Weight Beyond Body Mass Index**

BMI is strongly correlated (r² = 0.82-0.91) with absolute adiposity measured by densitometry, which is the gold standard for measuring overall adiposity, and allows for convenient comparisons of weight status within and across populations. However, care is needed when interpreting results based on BMI in epidemiologic studies and making public health recommendations for several reasons. First, BMI is an indirect measure and does not differentiate between fat and lean body mass, nor does it specify the location of adiposity, ie, whether central, peripheral, or in the organ at risk. Second, the meaning of BMI with respect to body composition may vary by age, sex, and ethnicity. For example, BMI may not be an accurate predictor of adiposity in the elderly, because of the loss of lean body mass that accompanies aging, or in highly muscled individuals, who usually have relatively high BMI. In addition, at the same BMI, women usually have a higher percentage of fat, whereas men have higher lean body mass. In conjunction with BMI, waist circumference and the waist-to-hip ratio are commonly used as approximations of central adiposity and intra-abdominal visceral fat in large-scale epidemiological studies. However, like BMI, these anthropometric measures do not distinguish visceral from subcutaneous adiposity. Adiposity location is important because, relative to subcutaneous fat, visceral adipose tissue is metabolically more active and more strongly associated with insulin resistance and metabolic syndrome. In addition, for a given BMI, African Americans generally have higher lean body mass with lower visceral fat compared with whites, whereas Asians tend to have lower lean body mass and higher visceral fat. The BMI categories for overweight and obesity used by the WHO are based on data primarily from populations of European origin living in high-income countries. A WHO expert consultation concluded that substantial proportions of Asians with a high risk of type 2 diabetes and cardiovascular disease are classified as having a “normal” weight, suggesting that using the same categories for all racial/ethnic groups may result in overlooking a large proportion of at-risk individuals in some populations.

Measurement of specific body fat compartments requires costly medical equipment. Computed tomography or magnetic resonance imaging currently provides the most accurate measures for whole-body fat mass as well as tissue and organ adiposity. Intragastric fat accumulation is now increasingly appreciated as a tumor-promoting microenvironment and appears to be relevant to the development of
Excess Body Weight and Cancer Burden

Breast carcinogenesis\textsuperscript{24,25} and possibly other types of cancers, including liver\textsuperscript{26} and pancreatic cancers.\textsuperscript{26–29} However, due to excessive cost and lack of portability, these imaging techniques have rarely been used in large-scale epidemiological studies. Comprehensive imaging projects are underway such as in the Framingham study\textsuperscript{30} and UK Biobank.\textsuperscript{31} These efforts have the potential to increase our understanding of the complex biology of adiposity in relation to the risk of cancer and other chronic diseases.

Prevalence and Trends in Excess Body Weight

Between 1975 to 2016, the global age-standardized mean BMI of adults aged 20 years and older increased from 21.7 to 24.5 kg/m\textsuperscript{2} for men and from 22.1 to 24.8 kg/m\textsuperscript{2} for women.\textsuperscript{4} During the same period, the global age-standardized prevalence of excess body weight (BMI ≥ 25 kg/m\textsuperscript{2}) nearly doubled among adults, from 21% for men and 24% for women in 1975 to approximately 40% in 2016 for both sexes (Fig. 1).\textsuperscript{4} Notably, the prevalence of obesity (BMI ≥ 30 kg/m\textsuperscript{2}) quadrupled for men, from approximately 3% to 12%, and more than doubled for women, from 7% to 16%. These changes, along with population growth, resulted in a more than 6-fold increase in the number of obese adults worldwide, from 100 million in 1975 to 671 million in 2016. During the same period, the age-standardized mean BMI among children aged 5 to 19 years increased from 16.8 to 18.5 kg/m\textsuperscript{2} for boys and from 17.2 to 18.6 kg/m\textsuperscript{2} for girls.

The prevalence of excess body weight increased from 5% to 27% for boys and from 6% to 24% for girls, with a greater relative increase in obesity prevalence, from 0.9% to 8% for boys and from 0.7% to 6% for girls (Fig. 1).

International Variation and Regional Trends

The increasing prevalence of obesity (BMI ≥ 30 kg/m\textsuperscript{2}) is apparent across all regions to various degrees, beginning in the 1970s and 1980s in most high-income Western countries and somewhat later in low-income and middle-income countries (Fig. 2; for regions, subregions, and countries, see Supporting Table 1).\textsuperscript{4} Between 1995 and 2016, the largest absolute increase occurred among men in high-income Western countries (from 9% to 30%) and among women in Central Asia, the Middle East, and North Africa (from 12% to 35%). The smallest absolute increase occurred among men in South Asia (from 0.2% to 3%) and among women in high-income Asian Pacific countries (from 1% to 4%). The largest relative increases occurred in historically low-risk regions. For example, there was more than a 20-fold increase in East and South-Eastern Asia, from 0.3% to 6% among men; an approximately 10-fold increase among men in sub-Saharan Africa, from 0.5% to 5%; and a 5-fold increase among women in sub-Saharan Africa, from 3% to 15%.

Similar regional patterns occurred among children aged 5 to 19 years, with the largest absolute increase in

FIGURE 1. Global Trends in the Prevalence of Excess Body Weight among Adults and Children by Sex Between 1975 and 2016. Among adults (aged 20 years and older), overweight was defined as a body mass index ≥ 25 and <30 kg/m\textsuperscript{2} and obesity was defined as a body mass index ≥ 30 kg/m\textsuperscript{2}. Among children (ages 5–19 years), overweight was defined as more than one standard deviation (SD) but less than 2 SDs above the median, and obesity was defined as more than 2 SDs above the median of the World Health Organization growth reference. Data available from: ncdrisk.org/obesity-prevalence-map.html.
obesity among boys in high-income Western countries, from 4% in 1975 to 17% in 2016, and among girls in Central Asia, the Middle East, and North Africa, from 0.9% to 11% (Fig. 2). Additional regions with absolute increases greater than 10% were East and South-Eastern Asia (boys); Latin America and the Caribbean (boys); and Central Asia, the Middle East, and North Africa (boys and girls). The largest relative increases, however, occurred in South Asia (from 0.05% to 3% among boys and from 0.01% to 2% among girls), in East and South-Eastern Asia (from 0.2% to 12% among boys and from 0.07% to 6% among girls), and in sub-Saharan Africa.
(from 0.04% to 2% and from 0.07% to 3% among boys and girls, respectively).

Between 1975 and 2016, there was more than a 9-fold increase in the number of obese men (from 30.7 million to 281 million), and more than a 5-fold increase in obese women (from 69.3 million to 390 million; Fig. 3). The global obesity burden also shifted from predominantly high-income Western countries and Central and Eastern

![Figure 3](ncdrsc.org/obesity-prevalence-map.html)
Europe in 1975 to more diverse regions in 2016. Most notably, East and South-Eastern Asia accounted for 3% of the world’s obese men and women in 1975 but for 15% to 17% in 2016, reflecting population growth and extended longevity as well as increased obesity prevalence. Increases were also substantial in South Asia (from 1% to 6% in men and from 2% to 8% in women); sub-Saharan Africa (from 1% to 4% in men and from 3% to 8% in women); and Central Asia, the Middle East, and North Africa in men (from 7% to 14%). Nevertheless, high-income Western

FIGURE 4. International Variation in the Prevalence of Obesity among Adults and Children by Sex in 2016. Among adults (aged 20 year and older), obesity was defined as a body mass index ≥ 30 kg/m^2. Among children (ages 5-19 years), obesity was defined as more than 2 standard deviations above the median of the World Health Organization growth reference. Data available from: ncdrisc.org/obesity-prevalence-map.html.
countries remained the largest contributor to the global obesity burden in 2016 among both men (33%) and women (26%).

Among men, obesity prevalence in 2016 was highest in Polynesian countries (range, 41%-60%) and in the United States, Canada, Kuwait, Qatar, Saudi Arabia, Australia, and New Zealand (range, 31%-37%), and lowest in most of sub-Saharan Africa (eg, Uganda, 2%) and South-Eastern Asia (eg, Vietnam, 2%) (Fig. 4). Among women, obesity prevalence was highest in Polynesian countries (range, 52%-65%), South Africa, Puerto Rico, Bermuda, and several Middle Eastern countries (range, 40%-50%), and lowest in parts of sub-Saharan Africa (eg, Ethiopia, 7%), most countries in South-Eastern Asia (eg, Vietnam, 3%), and Japan (4%). The lowest obesity prevalence among high-income Western countries was in Switzerland for women (18%), boys (7%), and girls (5%), and in Italy for men (21%). In sub-Saharan Africa, the highest prevalence was in South Africa for women (41%), men (16%), and girls (13%), and in Seychelles for boys (11%). The international variation in the prevalence of excess body weight by age and sex is presented in Supporting Figure 1.

Key Drivers and Moderators of the Global Increase in Excess Body Weight

The pace of the rise in excess body weight differs across and within populations because of complex interrelated factors that influence body weight. Several frameworks have been proposed to understand population-level obesity determinants. These frameworks commonly recognize multiple layers of determinants that involve systemic drivers (eg, policy and economic systems promoting high growth and consumption), environmental drivers (eg, food supply and marketing environments enabling and promoting high intake of energy-dense and nutrient-poor foods), environmental moderators (eg, sociocultural, socioeconomic, transportation, and built environments that amplify or attenuate the drivers), behavioral patterns (ie, high total energy intake coupled with insufficient physical activity, leading to a positive energy balance), and genetic predisposition to weight gain.

National wealth is the most apparent systematic driver of population obesity. The economic transition brings shifts that precipitate an obesogenic environment, including demographic (younger to older; rural to urban), technological (low to high mechanization and motorization), and nutritional (traditional diets to more processed energy-dense foods) changes. Increasing national wealth has been consistently associated with a rise in body weight: each US $10,000 increase in average national income is associated with a 0.4-unit increase in age-standardized mean BMI among adults (aged 18 years and older). However, prosperity is not always correlated with excess body weight; obesity prevalence is quite low in high-income Asian Pacific countries (range, 4%-7%), which is likely a result of adherence to traditional dietary habits, which are conducive to lower calorie consumption, and an active transportation system that usually entails walking as part of daily activity. In comparison, the prevalence of obesity is very high in some lower-income countries, such as some Pacific Island nations (range, 40%-65%) and Egypt (43% among women and 24% among men).

It should be noted that changes in the availability and quality of foods during the past 3 or 4 decades are generally accepted as key environmental drivers of the global rise in body weight. Between 1980 and 2013, global energy availability (ie, food calories based on national food supply data adjusted for wastage and assumed to be proportional to energy consumption) increased from 2390 to 2710 kcal per person per day, with greater contributions from fats and proteins and lower contributions from carbohydrates. A strong temporal correlation between the sharp increase in available calories and the onset of the obesity epidemic during the 1970s and 1980s has been well illustrated in high-income Western countries. The increased food energy supply in the United States was shown to be more than sufficient to explain the rise in obesity since the 1970s and most of the weight increase in the United Kingdom since the 1980s. Changes in the food environment that have promoted overconsumption of calories include rapid increases in both food portion size and the supply of affordable, palatable, energy-dense, ready-to-eat food; widespread use of sweetening agents, such as high-fructose corn syrup; improved distribution systems to make unhealthy food much more accessible and convenient; and more pervasive food marketing strategies consisting of abundant cues to overconsume palatable foods.

The increasingly sedentary nature of many forms of work and leisure-time activities (eg, screen time), the change from active modes of transportation (eg, walking, cycling) to motorized vehicles, and urbanization generally have contributed to a pervasive global phenomenon of physical inactivity. Reduced physical activity at a population level contributes to reduced energy expenditure and caloric imbalance. Therefore, the timing and pace of decline in physical activity may in part explain temporal variations in the obesity epidemic across populations. For example, the marked decline in physical activity, primarily in the domains of occupational, household, and...
transportation-related activity, took place earlier in the United States and the United Kingdom than in China and Brazil, and correspond with the timing of accelerations in obesity within these countries.

Environmental moderators that amplify or attenuate these primary drivers to weight gain include socioeconomic status, sociocultural environment, and transportation systems. Excess body weight is most prevalent among individuals from wealthy, urban environments in low-income countries and among disadvantaged groups (ie, those with lower income and less education) in high-income countries. Socioeconomic disparities in excess body weight are more striking among women than men in many countries. Increased body weight among women during pregnancy contributes to health risks in their children and amplifies health inequities across generations.

Cultural body-size preferences are thought to be related to obesity in some countries. Increased food access and reduced physical activity may have a stronger influence in countries where large body size is associated with positive attributes compared with countries where small body size is valued. Moreover, the obesity epidemic may be shifting societal norms. In the United States, the percentage of overweight (but not obese) individuals who described their weight as "about right" increased significantly between the early 1990s and the early 2010s, suggesting changes in perceptions about healthy body size. Considerably lower obesity rates in high-income Asian Pacific countries may be related in part to strong weight bias and a thin ideal for beauty. Among women living in some Middle Eastern countries, limited access to sports and exercise activities due to cultural and traditional restrictions may contribute to their high prevalence of excess body weight.

Neighborhood built environments and transportation systems influence opportunities for physical activity, and consequently body weight. A study conducted in 8 provinces in China demonstrated that the likelihood of being obese was 80% higher for men and women in households that owned a motorized vehicle compared with those that did not own a vehicle in a multivariable model adjusting for several covariables, including energy intake and income. Road connectivity, proximity to local destinations, and the presence of paths for walking and bicycling are important for active transportation alongside policies and social norms conducive to an active lifestyle. An international study showed that adults in the most activity-supportive environments were twice as likely to meet physical activity guidelines as those in the least supportive neighborhoods. In countries where the default option (ie, "path of least resistance") and the social norm is active transport, the levels of transportation-related physical activity are high.

The high prevalence of active transport (cycling) in the Netherlands likely contributes to the country’s relatively low obesity. Denmark and Germany also have specific policies put in place to make cycling safe and convenient. Genetic susceptibility also influences body weight. Twin studies and more recent quantitative genetic studies have reported BMI heritability estimates ranging from 40% to 70%. However, very little is known regarding the genetic basis of body weight. The proportion of BMI variation attributable to identified common genetic variants remains as low as approximately 3% because of the small effect size of the known associations. Some populations may have increased genetic susceptibility to excess body weight. For example, among Samoans (65% of women and 59% of men are obese), a functionally relevant genetic variant in the CREBRF (CREB3 regulatory factor) gene (promoting fat storage and reducing energy use) was strongly associated with BMI, with an effect size much larger than that of the main BMI-associated variant in the FTO (alpha-ketoglutarate dependent dioxygenase, also known as fat mass and obesity-associated protein) gene. Interestingly, this “thrift” variant was identified in approximately 26% of Samoans, whereas it is reportedly absent among individuals of European, African, and Asian descent. Nevertheless, population gene pools are relatively constant for many generations and unlikely to play a large role in the dramatic change in body weight that has occurred over the last 30 to 40 years.

Global Burden of Cancers Attributable to Excess Body Weight

A report from the International Agency for Research on Cancer (IARC) Working Group on Body Fatness in 2016 concluded that there is sufficient evidence for a causal association between body fatness and the risk of 13 cancers: breast (postmenopausal), colon and rectum, corpus uteri (endometrium), esophagus (adenocarcinoma), gallbladder, kidney, liver, meningioma, multiple myeloma, ovary, pancreas, stomach (cardia), and thyroid. More recently, a World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) Expert Report included advanced prostate cancer and cancers of the mouth, pharynx, and larynx as cancers with probable evidence. The causal link of excess body weight to cancer risk is supported by evidence from numerous epidemiological studies demonstrating a robust dose-response relationship in the association as well as experimental studies proposing multiple, plausible biologic mechanisms.

Table 1 summarizes the current epidemiological evidence for the association between body fatness based on anthropometric measures and the risk of 15 different cancer
| CANCER SITE                              | RR PER 5 KILOGRAMS/M² IN BMI (95% CI) | RR PER 10 CENTIMETERS IN WAIST CIRCUMFERENCE (95% CI) | RR PER 0.1 UNIT IN WAIST-TO-HP CIRCUMFERENCE (95% CI) | RR PER 5 KILOGRAMS ADULT WEIGHT GAIN FROM YOUNG ADULTHOOD, AGE 18 TO 25 YEARS (95% CI) | RR PER 5 KILOGRAMS/M² IN BMI IN YOUNG ADULTHOOD, AGE 18 TO 30 YEARS (95% CI) |
|-----------------------------------------|--------------------------------------|------------------------------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Breast (postmenopausal)                 | 1.12 (1.09-1.15)                     | 1.11 (1.05-1.16)                                      | 1.10 (1.05-1.16)                                      | 1.06 (1.05-1.08)                                                                 | 0.82 (0.76-0.88)                                                              |
|                                         | MHT users: NS                        | 1.06 (1.01-1.12)                                     | Asia: 1.26 (1.14-1.39)                                | Asia: 1.26 (1.14-1.39)                                                              |                                             |
|                                         | MHT nonusers/former users: 1.20      | (1.15-1.25)                                           | Europe: 1.06 (1.03-1.10)                              | Europe: 1.06 (1.03-1.10)                                                            |                                             |
|                                         | Asia: 1.37 (1.24-1.50)               |                                                      | North America: 1.06 (1.05-1.07)                       | North America: 1.06 (1.05-1.07)                                                    |                                             |
|                                         | Europe: 1.10 (1.06-1.15)             |                                                      | MHT users: 1.01 (0.99-1.02) [Keum 2015]               | MHT users: 1.01 (0.99-1.02) [Keum 2015]                                             |                                             |
|                                         | North America: 1.10 (1.08-1.12)      |                                                      | MHT nonusers: 1.11 (1.08-1.13) [Keum 2015]            | MHT nonusers: 1.11 (1.08-1.13) [Keum 2015]                                         |                                             |
| Colon and rectum                        | 1.05 (1.03-1.07)                     | 1.02 (1.01-1.03)                                      | 1.02 (1.01-1.04)                                      | 1.04 (0.99-1.09) [Chen 2015]                                                      | Men: 1.18 (0.84-1.65) for BMI ≥27.5 to <19 kg/m², age 21 y [Zhang 2015] |
|                                         | Men: 1.08 (1.04-1.11)                | Men: NS                                               | Colon: 1.20 (1.09-1.32)                               | Men: 1.09 (1.01-1.18) [Chen 2015]                                                   | Women: 1.44 (1.06-1.95) for BMI ≥27.5 to <19 kg/m², age 18 y [Zhang 2015]    |
|                                         | Women: 1.05 (1.02-1.08)              | Women: 1.03 (1.02-1.04)                               | Rectum: NS                                           | Women: 1.01 (0.96-1.08) [Chen 2015]                                                 |                                             |
|                                         | Colon: 1.07 (1.05-1.09)              | Colon: 1.04 (1.02-1.06)                               |                                                      |                                                                                     |                                             |
|                                         | Rectum: 1.02 (1.01-1.04)             | Rectum: NS                                            |                                                      |                                                                                     |                                             |
|                                         | 1.50 (1.42-1.59)                     | 1.13 (1.08-1.18)                                      | 1.21 (1.13-1.29)                                      | 1.16 (1.10-1.22)                                                                  | 1.42 (1.22-1.66)                                                              |
|                                         | MHT users: 1.15 (1.06-1.25)          |                                                      | MHT users: 1.09 (1.02-1.16)                           | MHT users: 1.09 (1.02-1.16)                                                        |                                             |
|                                         | MHT nonusers: 1.73 (1.44-2.08)       |                                                      | MHT nonusers: 1.39 (1.29-1.49) [Keum 2015, Aune 2015] | MHT nonusers: 1.39 (1.29-1.49) [Keum 2015, Aune 2015]                                 |                                             |
| Esophageal adenocarcinoma                | 1.48 (1.35-1.62)                     | 1.34 (1.17-1.52)                                      | 1.38 (1.10-1.73)                                      |                                                                                     |                                             |
| Gallbladder                              | 1.25 (1.15-1.37)                     |                                                      |                                                      |                                                                                     |                                             |
|                                         | Men: 1.23 (1.13-1.33)                |                                                      |                                                      |                                                                                     |                                             |
|                                         | Women: 1.25 (1.07-1.46)              |                                                      |                                                      |                                                                                     |                                             |
|                                         | Asia: NS                              |                                                      |                                                      |                                                                                     |                                             |
|                                         | Europe: 1.32 (1.24-1.41)             |                                                      |                                                      |                                                                                     |                                             |
| Kidney                                  | 1.30 (1.25-1.35)                     | 1.11 (1.05-1.19)                                      | 1.26 (1.18-1.36)                                      |                                                                                     |                                             |
|                                         | Asia: 1.47 (1.26-1.72)               |                                                      |                                                      |                                                                                     |                                             |
|                                         | Europe: 1.27 (1.24-1.31)             |                                                      |                                                      |                                                                                     |                                             |
| Liver                                   | 1.30 (1.16-1.46)                     |                                                      |                                                      |                                                                                     |                                             |
|                                         | North America: 1.29 (1.20-1.39)      |                                                      |                                                      |                                                                                     |                                             |
| Meningioma                              | 1.21 (1.01-1.43)                     |                                                      |                                                      |                                                                                     |                                             |
|                                         | for BMI ≥25 to 18.5≤BMI<25 kg/m²      |                                                      |                                                      |                                                                                     |                                             |
|                                         | [Niedermaier 2015]                   |                                                      |                                                      |                                                                                     |                                             |
|                                         | 1.54 (1.32-1.79)                     | for BMI ≥30 to ≥18.5≤BMI<25 kg/m²                     |                                                      |                                                                                     |                                             |
|                                         | [Niedermaier 2015]                   |                                                      |                                                      |                                                                                     |                                             |

(Continued)
| CANCER SITE | RR PER 5 KILOGRAMS/M² IN BMI (95% CI) | RR PER 10 CENTIMETERS IN WAIST CIRCUMFERENCE (95% CI) | RR PER 0.1 UNIT IN WAIST-TO-HIP CIRCUMFERENCE (95% CI) | RR PER 5 KILOGRAMS ADULT WEIGHT GAIN FROM YOUNG ADULTHOOD, AGE 18 TO 25 YEARS (95% CI) | RR PER 5 KILOGRAMS/M² IN YOUNG ADULTHOOD, AGE 18 TO 30 YEARS (95% CI) |
|-------------|-------------------------------------|-----------------------------------------------|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Multiple myeloma | 1.12 (1.07-1.18) | — | — | 1.28 (1.12-1.47) [Marinac 2018] | — |
| Ovary | 1.06 (1.02-1.11) [Collaborative Group 2012] | 1.06 (1.02-1.11) [Collaborative Group 2012] | — | 1.02 (0.96-1.09) [Aune 2015] | — |
| Pancreas | 1.10 (1.07-1.14) | 1.11 (1.05-1.18) | 1.19 (1.09-1.31) | 1.40 (1.13-1.72) for BMI gain of >10 kg/m² to BMI change ≤2 kg/m² [Genkinger 2011] | 1.18 (1.11-1.25) [Genkinger 2015] |
| Stomach cardia | 1.23 (1.07-1.40) | — | — | — | — |
| Thyroid | 1.06 (1.02-1.10) [Kitahara 2016] | 1.03 (1.01-1.05) [Kitahara 2016] | — | 1.07 (1.00-1.15) [Kitahara 2016] | 1.13 (1.02-1.25) [Kitahara 2016] |
| Mouth, pharynx, and larynx | Nonsmokers: 1.15 (1.06-1.24) [Gaudet 2015] | Nonsmokers: 1.07 (1.01-1.14) [Gaudet 2015] | 1.07 (1.05-1.09) [Gaudet 2015] | — | — |
| Prostate, advanced | 1.08 (1.04-1.21) | 1.12 (1.04-1.21) | 1.15 (1.03-1.28) | Overall: 0.98 (0.94-1.02) [Moller 2013] | — |

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; Collaborative Group, Collaborative Group on Epidemiological Studies of Ovarian Cancer; MHT, menopausal hormone therapy; NS, nonsignificant; RR, relative risk; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research. Note that the reference for RR values is WCRF/AICR Report 2018 (WCRF/AICR 2018), unless specified. Adjusted for BMI. Cancers were determined to be causally associated with excess body weight by either the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR 2018) or the International Agency for Research on Cancer (IARC) [Lauby-Secretan 2016], but not by both organizations. Advanced high-grade and fetal prostate cancers.
sites. A substantial body of evidence has been generated for body fatness approximated by BMI, expressed as the relative risk associated with a 5-kg/m² increase in BMI, which corresponds to weight gains of approximately 15 kg (or 33 pounds) in a person with 173-cm height and 13 kg (or 28.6 pounds) in a person with 161-cm height. Evidence for associations of waist circumference, waist-to-hip ratio, adult weight gain, and BMI in early life with cancer risk also is presented whenever possible (Table 1). The estimates are consistent but are largely based on populations of European origin living in high-income countries.

Several studies have quantified the proportions of global cancer burden attributable to excess body weight using population-attributable fraction (PAF) estimates, which incorporate relative risks from meta-analyses of BMI and cancer incidence and country-specific prevalence of excess body weight by age and sex. In a recent study, Pearson-Stuttard et al estimated PAFs of cancer incidence for 12 cancer types in 175 countries and 9 worldwide regions, assuming a 10-year lag time between exposure and cancer development. Overall, approximately 544,300 cancer cases (or 3.9% of all cancers worldwide) in 2012 were attributable to excess body weight in 2002. The proportions attributed to excess body weight varied widely across countries, ranging from 0.4% to 8.2% (Fig. 5). The countries with the highest PAFs were Egypt (8.2%), Mongolia (8%), Puerto Rico (7.7%), Saudi Arabia (7.5%), Russia (7.3%), Fiji (7.2%), the Czech Republic (7.2%), the United States (6.9%), Jordan (6.9%), and 6 more nearby Middle Eastern and Northern African countries (all >6.5%). Countries with a PAF of 1% or less included Ethiopia (1.0%), India (0.9%), Uganda (0.8%), Bangladesh (0.7%), Malawi (0.4%), and 10 more countries, all in sub-Saharan Africa, South Asia, or South-Eastern Asia.

Variation in Population-Attributable Fractions by Cancer Site, Sex, and Region

The PAF attributable to excess body weight differs substantially by cancer site (Fig. 6), reflecting the variation in relative risks associated with BMI. For example, among women, excess body weight accounted for approximately one-third of endometrial cancers (98,400 of 317,000 cases) and esophageal adenocarcinomas (2200 of 7300 cases), compared with only 4% of ovarian cancers (9100 of 235,000 cases). Among men, approximately 29% of esophageal adenocarcinoma cases were attributable to excess body weight compared with approximately 6% for cancers of the pancreas, colorectum, or thyroid.

The total number of cancer cases attributable to excess body weight was more than twice as high in women (368,500 cases) as in men (175,800 cases) (Fig. 7). Breast cancer was the largest contributor (114,800 cases or 31%) among women followed by endometrial cancer (98,400 cases).
cases or 27%) and colorectal cancer (42,300 cases or 12%). In contrast, the largest contributor among men was liver cancer (54,600 cases or 31%), followed by colorectal cancer (42,200 cases or 24%) and kidney cancer (37,400 cases or 21%).

Almost one-half of cancer cases attributable to excess body weight occurred in high-income Western countries (252,500 cases or 46%), reflecting both higher prevalence of excess body weight and higher incidence rates for many obesity-related cancers (Fig. 8). Despite a relatively low prevalence of excess body weight, the East and South-Eastern Asia region had the second largest share (87,600 cases or 16%) because of its large population and high burden of liver cancer. Central and Eastern Europe had the third largest share (77,700 cases or 14%), followed by Latin America and the Caribbean (9%), and Central Asia, the Middle East, and North Africa (6%).

Each region has a considerably different composition of cancer types contributing to the burden associated with excess body weight (Fig. 8). Female breast cancer was the top contributor in 5 of 9 regions, including South Asia (30%); sub-Saharan Africa (30%); Latin America and the Caribbean (26%); high-income Western countries (25%); and Central Asia, the Middle East, and North Africa (23%), whereas liver cancer contributed most in East and South-Eastern Asia (42%), Oceania (30%), and high-income Asia Pacific (22%). The contribution of female-specific cancers (eg, breast, endometrium, and ovary) was particularly high in Oceania (50%), sub-Saharan Africa (53%), and South Asia (51%) and was low in high-income Asia Pacific (22%) and East and South-Eastern Asia (26%).

### Cancers for Which Evidence Is Sufficient

#### Breast (postmenopausal)

Approximately 7% of all postmenopausal (aged 50 years and older) breast cancers (114,800 cases) in 2012 were attributable to excess body weight (Fig. 6). Each 5-unit increase in BMI is associated with an approximately 12% increased risk of postmenopausal breast cancer, and the risk is stronger for Asians (37%) compared with North Americans and Europeans (10%) (Table 1). The increased risk has been demonstrated consistently among women who never or previously used menopausal.

### Figure 6: Proportions and Numbers of Cancer Cases Attributable to Excess Body Weight (Body Mass Index ≥ 25 kg/m²) by Sex and Cancer Type in 2012

*Total percentage is calculated among the excess body weight–related cancers listed in the figure rather than among all cancers. Data source: Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M. Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol. 2018;6:e6–e15. Adapted with permission from the authors.*
hormone therapy (MHT) but not among current users. The associations have been consistent for hormone receptor (HR)-positive cancers but not for HR-negative or triple-negative cancers. Central adiposity measured by waist circumference is associated with increased risk of postmenopausal breast cancer (6% per 10-cm increase). Adult weight gain is also associated with increased risk (Table 1). In a study that followed women for up to 40 years, long-term weight gain of 20 kg (approximately 44 pounds) or more from age 18 years was associated with a 37% increased risk of postmenopausal breast cancer compared with stable weight. Paradoxically, increased weight during young adulthood (ages 18-30 years) has been inversely associated with the risk of postmenopausal breast cancer (18% decreased risk per 5-unit increase in BMI) (Table 1).

**Colon and rectum**

Seven percent of colorectal cancers in women (42,300 cases) and 6% in men (42,200 cases) worldwide in 2012 were attributable to excess body weight (Fig. 6). Each 5-unit increase in BMI is associated with a 5% increased risk of colorectal cancer. The association appears to be stronger for men (8% per 5-unit increase in BMI) than for women (5% per 5-unit increase in BMI) and for colon cancer (5%-8% per 5-unit increase in BMI) than for rectal cancer (2% per 5-unit increase in BMI). Each 0.1-unit increase in waist-to-hip ratio is associated with a 20% increased risk of colon cancer. In a study comparing various indices of adiposity, only visceral adipose tissue remained statistically significant as a determinant of colorectal neoplasia after adjusting for BMI, waist circumference, percentage body fat, and subcutaneous adipose. This suggests that the adverse metabolic consequences caused by increased visceral adipose may mediate the link between obesity and cancer risk. Adult weight gain is more strongly related to colorectal cancer risk among men than among women, whereas increased weight during childhood and young adulthood appears to be more strongly related among women than among men (Table 1).

**Endometrium**

Worldwide, excess body weight accounted for approximately 31% of endometrial cancers in 2012 (98,400 cases) (Fig. 6). Compared with normal-weight women, risk is increased linearly by 1.5-fold among those who are overweight (BMI ≥25 and <30 kg/m²), by 2.5-fold among those with class 1 obesity (BMI ≥30 and <35 kg/m²), by 4.5-fold among those with class 2 obesity (BMI ≥35 and <40 kg/m²), and by 7.1-fold among those with class 3 obesity (BMI ≥40 kg/m²).

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**FIGURE 7. Contribution of Each Cancer to Total Cancer Burden Attributable to Excess Body Weight (Body Mass Index ≥ 25 kg/m²) by Sex in 2012.** Data source: Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ, Ezzati M. Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. Lancet Diabetes Endocrinol. 2018;6:e6-e15. Adapted with permission from the authors.
Each 5-unit increase in BMI is associated with a 48% increased risk of esophageal adenocarcinoma after adjustment for smoking status. Among nonsmokers, the association is stronger, with a 62% increased risk per 5-unit increase in BMI. Central adiposity is associated with increased risk of esophageal adenocarcinoma by 34% per 10-cm increase in waist circumference and by 38% increased risk per 0.1-unit increase in waist-to-hip ratio.

**Gallbladder**

Approximately 13% of gallbladder cancers in women (13,000 cases) and 10% in men (7400 cases) worldwide in 2012 were attributable to excess body weight (Fig. 6). Each 5-unit increase in BMI is associated with a 25% increased risk of gallbladder cancer.

**Kidney**

Approximately 20% of kidney cancers (25,200 women and 37,400 men) worldwide in 2012 were attributable to excess body weight (Fig. 6). Each 5-unit increase in BMI is associated with a 30% increased risk of kidney cancer. Central adiposity is associated with risk of kidney cancer by 11% per
10-cm increase in waist circumference and by 26% per 0.1-unit increase in waist-to-hip ratio.\textsuperscript{7}

**Liver**
Approximately 10% of liver cancers in men (54,600 cases) and 14% in women (30,200 cases) worldwide in 2012 were attributable to excess body weight (Fig. 6).\textsuperscript{8} Each 5-unit increase in BMI is associated with a 30% increased risk of liver cancer.\textsuperscript{7} The association appears to be stronger among Europeans (59% per 5-unit increase in BMI) than among Asians (18% per 5-unit increase in BMI) (Table 1).

**Meningioma**
Meningioma is one of the most common primary central nervous system tumors, representing approximately 36% of cases worldwide.\textsuperscript{89} Compared with normal-weight individuals, the risk of meningioma is increased by 20% among overweight individuals and by 50% among obese individuals.\textsuperscript{90,91} The fraction of meningioma attributable to excess body weight has not been reported.

**Multiple myeloma**
Worldwide, excess body weight accounted for 7% (4500 cases) of multiple myeloma cases in women and 9% (4400 cases) in men in 2012 (Fig. 6).\textsuperscript{8} Each 5-unit increase in BMI is associated with a 12% increased risk of multiple myeloma.\textsuperscript{92} A pooled analysis of 3 large prospective cohort studies found that each 5-unit increase in BMI at ages 18-30 years is associated with a 28% increased risk.\textsuperscript{93}

**Ovary**
Approximately 4% (9100 cases) of ovarian cancers worldwide in 2012 were attributable to excess body weight (Fig. 6).\textsuperscript{8} Each 5-unit increase in BMI is associated with a 6% increased risk of ovarian cancer.\textsuperscript{7} Similar to breast and endometrial cancers, the association appears to be confined to women who have never used MHT (Table 1). A few studies have suggested that higher BMI increases the risk only for less common subtypes (eg, endometroid and mucinous carcinomas)\textsuperscript{94,95}; however, further studies are needed to confirm these subtype associations.

**Pancreas**
Worldwide, excess body weight accounted for approximately 6% (10,300 cases) of pancreatic cancer cases in men and 7% (11,200 cases) in women (Fig. 6).\textsuperscript{5} Each 5-unit increase in BMI is associated with a 10% increased risk of pancreatic cancer.\textsuperscript{7} Central adiposity, measured as waist circumference (11% per 10 cm) or waist-to-hip ratio (19% per 0.1 unit), is also associated with increased risk.\textsuperscript{7} Excess body weight during young adulthood (ages 18-21 years) appears to be associated with increased risk of pancreatic cancer later in life (Table 1).\textsuperscript{96,97}

**Stomach cardia**
Approximately 9% (6400 cases) of stomach cardia cancers among men and 11% (2900 cases) among women in 2012 were attributable to excess body weight (Fig. 6).\textsuperscript{8} Body fatness increases the risk of stomach cancer that develops in the cardia, which comprises approximately 27% of stomach cancers worldwide,\textsuperscript{98} but it has not been associated with noncardia stomach cancer.\textsuperscript{99,100} Each 5-unit increase in BMI is associated with a 23% increased risk of stomach cardia cancer.\textsuperscript{7}

**Thyroid**
Excess body weight accounted for 7% (14,800 cases) and 6% (3900 cases) of thyroid cancer among men and women, respectively, in 2012 (Fig. 6).\textsuperscript{8} Each 5-unit increase in BMI is associated with a 6% increased risk of thyroid cancer.\textsuperscript{101} Excess body weight in early adulthood (ages 18-30 years) appeared to be associated with increased risk of thyroid cancer in later life (13% per 5-unit increase in BMI).\textsuperscript{101}

**Cancers for Which Evidence Is Probable**

**Mouth, pharynx, and larynx**
There is growing evidence that body fatness may increase the risk of cancers of the mouth, pharynx, and larynx. A pooled analysis that included 20 cohort studies demonstrated that each 5-unit increase in BMI was associated with a 15% increased risk of these cancers among nonsmokers.\textsuperscript{102} However, central adiposity measured by waist circumference (4% per 5 cm) or waist-to-hip ratio (7% per 0.1 unit) was associated with increased risk among both smokers and nonsmokers. The fraction of these cancers attributable to excess body weight has not been reported.

**Prostate (advanced)**
Accumulating evidence indicates that body fatness may increase the risk of advanced, high-grade and fatal prostate cancer.\textsuperscript{7} Each 5-unit increase in BMI was associated with an 8% increased risk of advanced stage of prostate cancer. Both waist circumference (12% per 10 cm) and waist-to-hip ratio (15% per 0.1 unit) were associated with increased risk.\textsuperscript{7} The fraction of advanced prostate cancer attributable to excess body weight has not been reported.

**Smoking-Related Cancers**
Inverse associations have been reported between excess body weight and cancers of the lung\textsuperscript{104-106} and esophagus (squamous cell carcinoma).\textsuperscript{107} However, the inverse association is likely accounted for by reverse causation or by residual confounding or effect modification by smoking,\textsuperscript{105,106,108,109} because smokers tend to have a lower BMI than nonsmokers, and patients with smoking-related chronic illnesses (eg, chronic obstructive pulmonary disease) often experience
weight loss.\textsuperscript{110} Furthermore, smoking may also increase visceral fat accumulation and insulin resistance, both of which increase the risk of cancer development.\textsuperscript{111,112} A study using genetic variants associated with BMI as a proxy for body fatness to assess the possible causal association demonstrated that genetically predicted BMI is positively associated with an increased risk of lung cancer overall and of squamous cell lung cancer in particular, suggesting that the observed inverse association is not causal.\textsuperscript{113} A case-control study using recalled body size from youth, which is purported to be less likely prone to reverse causation, reported an association of very obese body size with an increased risk of esophageal squamous cell carcinoma.\textsuperscript{114}

Population-Attributable Fractions Are Likely Underestimated

The published PAFs using BMI are likely to be underestimates of the true impact of excess body weight on cancer burden because of several methodologic limitations of key components of the PAF calculation.\textsuperscript{108,115,116} Foremost, the relative risks used in PAF calculation are likely to be underestimates of the true strength of the association between body fatness and cancer risk, because they relied on a one-time measurement of BMI, the measure usually available in cohort studies. As mentioned above, BMI is an indirect measure of body fatness; therefore, direct measures of central adiposity or visceral adipose tissue may strengthen the associations and yield higher estimates of PAFs. Although BMI tracks the body weight of an individual well over time in general, a single measurement of BMI in midlife or later is not sufficient to represent the impact of adiposity in early life or of weight change during key periods in life.\textsuperscript{117} As described previously, emerging evidence suggests that excess body weight in early life is associated with increased risk of several cancers, including colorectal,\textsuperscript{118,119} endometrial,\textsuperscript{120–122} pancreatic,\textsuperscript{97} and thyroid cancers\textsuperscript{101} as well as multiple myeloma.\textsuperscript{93} Nevertheless, most studies assumed a 10-year lag period between excess body weight and cancer occurrence,\textsuperscript{8,75} which is a likely underestimate of the latency period required for the multistage carcinogenesis process. Moreover, those who have been exposed to excess body weight from their early life (ie, those who were affected by the obesity epidemic in the 1980s or later) have not yet entered the peak ages for cancer diagnosis. Insufficient consideration of lifetime exposure could lead to substantial underestimations of excess body weight to the global burden of cancers, especially given the rapid increase in the prevalence of excess body weight among children.\textsuperscript{115} In addition, using the traditional cutoff for BMI (25 kg/m\textsuperscript{2}) may fail to account for the linear association between BMI and cancer risk, which often starts below 25 kg/m\textsuperscript{2}, and thus may neglect the contribution of higher BMI within the normal category to cancer burden.

In the presence of strong effect modifiers such as smoking, estimated PAFs based on the entire population need cautious interpretation.\textsuperscript{108,116} Because smoking profoundly alters the effect of excess body weight on cancer risks, the associations are different between smokers and nonsmokers, especially for cancers causally associated with both smoking and obesity.\textsuperscript{123} Moreover, the spectrum of cancer burden among smokers is different from that among nonsmokers because of the preponderance of smoking-related malignancies. To account for smoking status correctly, stratified analysis by smoking status is critical.\textsuperscript{108} The importance of stratification by smoking status in estimating PAFs attributable to excess body weight is well illustrated in several studies. For example, the PAF of pancreatic cancer because of excess body weight is much higher among never-smokers and past smokers (range, 3%-26%) than among current smokers (range, 0%-8%).\textsuperscript{75} In the Cancer Prevention Study II, a nationwide cohort study begun in 1982 in the United States, the PAF of total cancer mortality caused by excess body weight was 4.2% in men and 14.3% in women for the entire population, but it was 14.2% and 19.8%, respectively, among never-smokers.\textsuperscript{124}

Mechanisms Relating Excess Body Weight to Cancer Risk

Various mechanisms have been proposed to explain how body fatness affects cancer risk. Alterations in hormonal systems—both peptide metabolic hormones and sex steroid hormones—and chronic inflammation are the most studied hypotheses.\textsuperscript{29,116,125} Effects of adiposity on metabolic hormones are thought to affect multiple types of cancers, whereas effects on steroid hormones are thought to be more specific to hormone-sensitive cancers. Local inflammation has been linked to some specific cancers.

Excess adiposity induces insulin resistance and, subsequently, hyperinsulinemia.\textsuperscript{125} Induced hyperinsulinemia suppresses hepatic production of insulin-like growth factor (IGF)-binding proteins, which, in turn, increases concentrations of circulating insulin and bioavailable IGF-1. The activation of insulin receptor and IGF-1 receptor triggers intracellular signaling cascades, which favor tumor development and spread.\textsuperscript{126} It was postulated that hyperinsulinemia may act primarily through enhancing the bioavailability of IGF-1, rather than through direct ligand activity.\textsuperscript{116} A large volume of epidemiological studies examining C-peptide (a marker of insulin secretion) and circulating IGF-1 levels support findings...
that the insulin and/or IGF-1 pathways are particularly relevant to cancers of the colorectum, prostate, breast, and endometrium.\(^{127,128}\) Genetically predicted higher fasting insulin levels have been associated with elevated risks for certain cancers, such as those of the pancreas\(^{129}\) and endometrium,\(^{130}\) supporting a causal role of higher insulin levels in the etiology of these cancers. Obesity is a strong risk factor for both insulin resistance and type 2 diabetes. Some cancers develop more commonly in persons with diabetes than those without diabetes. The relative risks associated with diabetes are greatest (approximately 2-fold or higher) for cancers of the liver, pancreas, and endometrium, and lower (approximately 1.2-fold to 1.5-fold) for cancers of the colorectum, breast, and bladder.\(^{131}\) It is plausible that common factors could drive the relationships of both obesity and diabetes with cancer. However, it is not clear whether the association of diabetes with cancer risk is indirect because of common risk factors, such as obesity and obesity-related metabolic changes (eg, insulin resistance and hyperinsulinemia), or is direct (eg, because of hyperglycemia).\(^{131}\)

Adipose tissue, as an endocrine organ, influences the synthesis and bioavailability of sex hormones. Adipose tissue expresses aromatase enzymes, which convert androgens to estrogens and converts less active forms of these hormones (androstenedione, estrone) to more active forms (testosterone, estradiol).\(^{116}\) In addition, hyperinsulinemia and increased IGF-1 bioactivity result in reduced hepatic synthesis and blood concentrations of sex-hormone–binding globulin, which, in turn, increases bioavailable free estradiol and testosterone. Sex-steroid hormones are thought to mediate the link of adiposity to risks of breast and endometrial cancers and, possibly, to the risk of prostate and colorectal cancer.\(^{116}\) In postmenopausal women, the rate of conversion of androgens to estrogens is elevated among women with obesity.\(^{132}\) In a large pooled analysis combining 8 prospective studies, the association of BMI with postmenopausal breast cancer risk was explained almost entirely by the increase in estradiol levels with increased BMI.\(^{133}\) In men, however, the etiologic role linking sex hormones to advanced prostate cancer is not completely understood.\(^{134}\) Obese men are known to have increased serum estradiol and decreased androgen levels.\(^{135}\) Because androgens play important roles in normal prostate epithelial cell growth and differentiation, one hypothesis suggests that lower bioavailable testosterone specifically may promote more advanced prostate cancer.\(^{134,136}\) Indeed, at least 2 prospective studies have shown that lower prediagnostic circulating androgen levels were associated with risk of high-grade, more poorly differentiated prostate cancer.\(^{137,138}\)

Adiponectin is the most studied adipokine in the context of cancer risk.\(^{29,139}\) Serum adiponectin levels are negatively correlated with BMI because of several mediators (eg, insulin, tumor necrosis factor \(\alpha\), estrogen) that suppress its transcription.\(^{140}\) Adiponectin may have indirect effects on tumor development by sensitizing cells to insulin or through anti-inflammatory actions. Adiponectin also may exert antitumor effects directly by regulating metabolic, inflammatory, and cell cycle signaling pathways.\(^{141}\) Evidence from experimental studies strongly supports the role of adiponectin in many types of cancers, including those of the breast, colorectum, kidney, liver, pancreas, thyroid, myeloma, stomach, esophagus, and prostate.\(^{141}\) However, observational studies on the relationship of prediagnostic circulating adiponectin levels with the risk of several cancers have reported mixed results.\(^{142-145}\)

Adipose tissue produces and secretes a wide range of proinflammatory molecules, including tumor necrosis factor \(\alpha\) and interleukin-6, which may cause local inflammation in adipose tissue and systemic effects on other organs.\(^{29,116}\) Low-grade chronic inflammation, which is often identified in obese individuals, predisposes to certain types of cancer by creating a tissue environment that generates oxidative stresses, stimulates DNA damage, increases cellular proliferation, and suppresses apoptosis. Several examples of local inflammation linked to cancer risks include the association of nonalcoholic fatty liver disease with liver cancer,\(^{29,146}\) chronic acid reflux and the development of Barrett esophagus and esophageal adenocarcinoma,\(^{147,148}\) and the association of chronic cholecystitis and cholecystitis with gallbladder cancer.\(^{149,150}\)

### The Effect of Weight Loss on Cancer Risk

The association between weight loss and subsequent cancer risk has not yet been established.\(^{151,152}\) Observational studies of weight loss and cancer risk are often limited because of the small numbers of individuals who successfully maintain weight loss and the lack of information on intentionality of weight loss.\(^{152,153}\) In a recent systematic review based on 34 studies examining different types of weight loss (intentional, nonintentional, cause undefined), 16 studies found a significant reduction in the risk of incident cancer associated with weight loss, most of which were in women for postmenopausal breast cancer and endometrial cancer.\(^{152}\) Intentional weight loss (with or without bariatric surgery) resulted in reductions from 24% to 78%
in the overall incidence of cancer, mainly driven by women and obesity-related cancers, in most but not all studies. Despite inconclusive data, achieving healthy body weight might extend life expectancy and is sensible, given the health harms associated with excess body weight.2

Excess Body Weight and Cancer Survival

The association of excess body weight with cancer survival has not been well established mainly because of methodological challenges in evaluating the association regarding reverse causation (ie, cancer causing weight loss) and confounding by obesity-related comorbidities and differences in diagnosis or treatment.116,160 However, a growing body of evidence suggests that excess body weight portends less favorable outcomes for several cancers.161 The most consistent evidence has been generated from studies among breast cancer survivors.162–164 A meta-analysis that included 82 studies concluded that increased body fatness is associated with poorer overall and breast cancer–specific survival for both premenopausal and postmenopausal women regardless of when BMI was ascertained. Each 5-unit increase in BMI before, <12 months after, and 12 months after diagnosis increased risk by 17%, 11%, and 8%, respectively, for total mortality, and by 18%, 14%, and 29%, respectively, for breast cancer mortality.163 The data for the association between BMI and survival are fairly consistent for HR-positive breast cancer, with less consistent results reported for HR-negative tumors.165 A recent study using genetic variants associated with BMI as a proxy for body fatness supported a possible causal association between increased BMI and reduced breast cancer survival in women with estrogen receptor–positive cancers, but not in those with estrogen receptor–negative cancers.166 Postdiagnosis weight gain predicted worse survival in most but not all studies. A recent study using clinically acquired computed tomography scans from patients with stage II or III breast cancer demonstrated that those who had sarcopenia and high total adipose tissue had the highest mortality and that BMI alone did not optimally identify patients who were at higher risk of death because of variation in body composition.171 Similarly adverse associations with excess body weight before or at the time of diagnosis have been reported for cancers of the prostate, colorectum, pancreas, and ovary.172–178 For some cancers including lung, esophagus, and kidney, excess body weight has been associated with better outcomes. However, the possibility of reverse causation cannot be ruled out.

Policies and Actions to Prevent and Control Excess Body Weight

Halting the rise in obesity among adults and children is one of the WHO’s nine targets in an effort to address the growing global burden of noncommunicable diseases, including cancer.183 However, given the current pace of increasing and existing challenges, achieving this goal appears unlikely.184 Isolated attempts in some countries have provided important evidence that progress against obesity is feasible.185 There is emerging consensus on evidence-based and cost-effective strategies to prevent and control obesity, focusing on promoting a healthy diet and physical activity through policy and system approaches.183,185–189

In particular, concerted action by governments and stakeholders (eg, nongovernmental organizations, private sector) has been suggested to address the strong commercial forces seeking to profit from the overconsumption of palatable foods.185,186,187,188,190 More specifically, Swinburn suggests that: 1) governments should play a strong leadership role in reinforcing the importance of addressing the obesity problem; 2) multisector (ie, government, industry, civil society, and public sector) solutions should be sought; 3) funds should be allocated specifically to change the environment to one that promotes healthy eating and an active lifestyle; and 4) policy-level approaches aimed at preventing an obesogenic environment should be sought, implemented, and monitored.190 Moreover, Roberto et al similarly indicate that environmental factors exploiting human vulnerabilities (eg, at the psychological and physiologic levels) to eat unhealthy food need to be addressed by government and industry alike to bring about meaningful change.185

In a recent update of the Global Action Plan for the Prevention and Control of Noncommunicable Diseases, 2013 to 2020, which was released in September 2017, the WHO provided high-priority strategies that should be adopted by governments, industries, and civil societies.186 These high-priority actions include population-wide, policy-led interventions to rectify the production, distribution, and marketing of unhealthy foods and changes in the built environment to promote adequate levels of physical activity (Table 2).186 Interventions aimed at motivating behavioral changes include setting-based (preschools, schools, workplaces, religious settings, and hospitals) health promotion and education programs, mass media campaigns, social marketing to improve the knowledge and skills of the community and individuals, and routine primary health care and counseling to facilitate obesity prevention and management. The Global Action Plan proposes that countries consider using economic tools that are justified by evidence, which may include taxes and subsidies. According to national circumstances and local settings,
considerations should be given to the effectiveness, affordability, implementation capacity, and impact on health equity of interventions, and the combination of population-wide policy interventions and individual interventions.186,191

Finally, whereas population-level efforts should be an area of focus, they should be matched with enhancing access to health care interventions for weight management, including screening for and management of excess body weight, as a means of secondary intervention. These interventions should focus on education and opportunities for sustainable lifestyle change (ie, healthful eating and health-enhancing physical activity).
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