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Obesity and risk of cancer: an introductory overview

Tobias Pischon*, Katharina Nimptsch

1Molecular Epidemiology Research Group, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

*tobias.pischon@mdc-berlin.de
Abstract

The prevalence of obesity has increased substantially in the past in almost all countries of the world, and a further increase is expected for the future. Besides the well-established effects on type 2 diabetes and cardiovascular disease, there is convincing evidence today that obesity also increases the risk of several types of cancer, including colorectal cancer, postmenopausal breast cancer, endometrial cancer, renal cell carcinoma, esophageal adenocarcinoma, pancreatic cancer, and liver cancer. Obesity probably also increases the risk of ovarian cancer, advanced prostate cancer, gallbladder cancer, and gastric cardia cancer. For some cancer types there is also some evidence that weight gain during adulthood increases cancer risk, e.g., colorectal cancer, postmenopausal breast cancer, endometrial cancer, and liver cancer. However, for most cancers it is an open question as to whether vulnerability to weight gain in relation to cancer risk depends on specific life periods. There are a number of plausible mechanisms that may explain the relationship between obesity and cancer risk, including pathways related to insulin resistance, inflammation, and sex hormones. For most cancers there is only limited evidence that weight loss in adulthood decreases cancer risk, which is primarily due to the limited long-term success of weight loss strategies among obese individuals. There is limited evidence suggesting that obesity may also be associated with poor prognosis among patients with colorectal cancer, breast cancer, endometrial cancer, ovarian cancer and pancreatic cancer. Taken together, these findings support efforts to prevent weight gain on an individual level as well as on a population level. Whether and to what extent overweight or obese cancer patients benefit from weight loss strategies is unclear and a matter of debate.
1 Introduction

The prevalence of obesity has increased substantially in the past in almost all countries of the world, and a further increase is expected for the future [1]. According to recent estimates, the global age-standardized prevalence of obesity increased between 1975 and 2014 from 3.2% to 10.8% in men, and from 6.4% to 14.9% in women [1]. On a regional level, the highest obesity prevalence is observed for men in high income Western countries (27.2%) and for women in Central Asia, the Middle East and North Africa (31.4%) [1]. Obesity is a risk factor for a number of chronic diseases, most notably type 2 diabetes, hypertension, dyslipidemia and coronary heart disease [2]. In the past decade, it became more and more evident that obesity is also a risk factor for certain types of cancer [3]. In addition, more and more studies suggest that obesity may also increase the risk of poor prognosis for patients with certain cancers [4]. Cancer has traditionally primarily been viewed as a disorder of proliferation but has today been suggested to be also considered as a metabolic disease [5,6]. This suggestion was primarily based on the notion of cancer-associated metabolic changes on a tissue (tumor) level [6]. In this context it is interesting to note that within the past years it also became clear that there is likely some overlap in the potential mechanisms that may link obesity with cardiovascular-metabolic diseases such as type 2 diabetes or coronary heart disease on the one hand, and with cancer on the other hand [7]. Thus, cancer cannot only be considered as a metabolic disorder in terms of existing tumors but also in terms of cancer risk, at least for tumor progression. The current article provides an overview on the association of obesity and risk of cancer.

2 Definition and assessment of obesity

Current guidelines classify states of obesity still primarily based on the body mass index (BMI), which is body weight (in kg) divided by height squared (in m²) [8,9]. A BMI <18.5 kg/m² defines underweight, 18.5 kg/m² to <25.0 kg/m² normal weight, 25.0 kg/m² to <30 kg/m² overweight, and ≥30 kg/m² obesity. BMI is highly correlated with fat mass and morbidity and mortality, and it reflects obesity-related disease risk in a wide range of populations, but there are some well-known important limitations. First, for the same BMI older adults tend to have a higher body fat composition, and therefore risk assessment using BMI is less accurate in these individuals (>65 years of age)[10]. Second, current BMI cut-off points for overweight and obesity are suggested to be too high for Asian populations; this fact has been well-recognized more than 10 years ago [11]. For the definition of abdominal obesity in the context of the metabolic syndrome (see below), different cut-offs for waist circumference have been defined to acknowledge differences in ethnicities [12], but, surprisingly, such differences so far didn’t make their way in national and international guidelines to assess
obesity [13,14]. Third, and probably most important, the BMI does not assess body fat distribution. Obesity is conceptually defined as a condition of abnormal or excessive body fat accumulation to the extent that health may be impaired [8,9,15]. However, although BMI is correlated with the amount of fat, it is neither a specific marker of body fat nor a marker for abnormal fat accumulation. In this context, accumulation of visceral adipose tissue is of particular concern because it is metabolically more active and it secretes more cytokines and hormones that may be relevant for disease risk compared with subcutaneous adipose tissue [2], yet BMI is only a crude measure of visceral fat mass. Waist circumference or waist-hip ratio show much closer correlations with the amount of visceral fat, which may explain why they are more strongly associated with risk of metabolic diseases than BMI. Current obesity guidelines recommend to measure waist circumference as a marker of regional body fat distribution in Caucasian persons with a BMI between 25.0 and 34.9, and they propose cut-off points for waist circumference of 102 cm in men and 88 cm in women to define abdominal obesity and to identify persons at risk for disease [8,9]. The choice of these cut-offs is somewhat arbitrary and goes back to the observation that they largely correspond to a BMI of 30 kg/m² in men and women, respectively [16]. Results from the large European Prospective Investigation into Cancer and Nutrition (EPIC study) suggested that at any given BMI, an increase in waist circumference increases the risk of death, thus questioning the usefulness of thresholds for waist circumference [17]. Also, in contrast to current recommendations to measure waist circumference in overweight or obese persons only [8,9], results of the EPIC study also suggested that measurement of waist circumference could particularly be useful for persons with a BMI in the normal range [17].

Body fat distribution can also be determined by imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) scans, but these methods have not been used often in large-scale epidemiological studies, and may not readily be applicable in clinical practice [18].

3 Obesity and cancer – weighing the evidence: a historical perspective

The notion that obesity may be a risk factor for cancer goes back to the 1930s when – based on the observation that overnutrition is common in cancer patients – it was speculated that overabundant food consumption may be a cause of cancer [19]. Yet, the evidence for a causal role of obesity remained inconclusive. In 1997, the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) published a first report on the evidence for a causal relationship between diet and cancer, based on the evaluation of over 100 experts [20]. In 2002, the International Agency for Research on Cancer (IARC) published a monograph on the evaluation of cancer-preventive strategies, focusing on weight control and physical activity [21]. This was followed by a report by the
World Health Organization on diet, nutrition and the prevention of chronic diseases in 2003 [22].
Taken together, these were among the first steps to not only investigate the association of diet with cancer but also to evaluate the evidence of a causal relationship. Although slightly different in detail, at that time the overall evaluation was that there was convincing evidence for obesity to increase risk of colorectal cancer, postmenopausal breast cancer, endometrium cancer, renal cell carcinoma, and adenocarcinoma of the esophagus [22]. Yet, it was already clear that obesity may also be related to other cancers as well. Thus, in 2003, Eugenia Calle and colleagues published a seminal paper reporting that obesity was significantly associated with total cancer mortality in men and women [23]. Further, for specific cancers, they found in their study obesity associated with increased mortality from cancer of the breast, colorectum, endometrium kidney, esophagus, stomach, liver, gallbladder, pancreas, cervix, ovaries, and prostate, as well as to mortality from Non-Hodgkin’s lymphoma, multiple myeloma, and leukemia [23]. Although cancer mortality depends not only on incidence but also on survival, these data suggested that obesity may be causally related to other cancers as well. In 2007, the WCRF published a second report on diet and cancer, this time based on a thorough systematic literature review and meta-analysis of around 7,000 relevant studies [24].
Further, since then the WCRF has initiated the continuous update project (CUP), which is an ongoing program to update the evidence. Based on these reports, the list of cancers for which we currently have convincing evidence for a causal relationship due to obesity includes colorectal cancer, postmenopausal breast cancer, endometrial cancer, renal cell carcinoma, esophageal adenocarcinoma, pancreatic cancer, and liver cancer (Table 1) [24,25]. Obesity is probably also a cause of ovarian cancer, advanced stage prostate cancer, gallbladder cancer, and gastric cardia cancer [26-29]. Most recently, the IARC had convened a working group to reassess the relationship between obesity and cancer [30]. In their viewpoint, the working group concluded that there is sufficient evidence for a causal relationship between obesity and all of the above mentioned cancers with the exception of prostate cancer. The IARC working group also concluded that there is sufficient evidence for thyroid cancer, multiple myeloma, and meningioma.

3.1 Colorectal cancer

In terms of incidence, colorectal cancer is worldwide the third most common cancer in men (746,000 cases in the year 2012) and the second most common cancer in women (614,000 cases), accounting for 10.0% and 9.2% of all incident cancers in men and women, respectively [31]. There is substantial variation in the trends of colorectal cancer incidence: Incidence rates tend to increase in many parts of Asia, Latin America, and Eastern Europe, whereas in the high-income countries, rates tend to decrease in the United States, New Zealand, and France; to increase in Norway, Spain and Italy; and
to remain relatively stable in Australia and Canada [32]. The highest incidence of colorectal cancer is observed in Australia/New Zealand, and the lowest in Western Africa [31].

There is convincing evidence that higher body fatness is associated with a higher risk of colorectal cancer [24,25]. There is also substantial evidence that weight gain during adulthood increases colorectal cancer risk [25]. Overall, obese individuals have a 20% to 40% higher risk for colorectal cancer compared to normal weight persons, with stronger associations in men than women, and stronger associations for colon than for rectal cancer [33]. Thus, obese versus normal weight men have a 50% to 70% higher risk of colon cancer and a 25% to 75% higher risk of rectal cancer, while obese versus normal weight women have a 10% to 25% higher risk of colon cancer and a 2% to 40% higher risk of rectal cancer [33]. The reasons for the difference in the strength of the association of obesity with colon cancer risk between men and women have long been unclear. It was suggested that one potential reason is that men and women have different body fat distribution [34]. Thus, men are more likely to present with abdominal obesity, while women are more likely to have gluteofemoral obesity. Therefore, BMI may not accurately reflect the colon cancer risk that is associated with abdominal fat accumulation, at least in women. In fact, abdominal obesity is an almost equally-strong risk factor for colon cancer in men and women, although slight gender differences may remain [34,33]. Possible mechanisms for the association of obesity with colorectal cancer risk include insulin resistance, hyperinsulinemia, chronic inflammation, altered levels of growth factors, adipocytokines and steroid hormones [33]. Whether weight loss during adulthood decreases the risk of colorectal cancer is less clear [33]. The reason for the lack of evidence is primarily the limited success of long-term strategies to lose weight among overweight or obese individuals, which underscores the importance of avoiding weight gain in adulthood.

The association of obesity with survival among colorectal cancer patients is less clear. Most studies conducted so far suggest that obesity is associated with poorer survival among colorectal cancer patients, but it is less clear whether this is due to a higher mortality from colorectal cancer or from other causes [33]. Further, many of the studies conducted so far used pre-diagnostic instead of post-diagnostic BMI or have other limitations, which limit the interpretability to give evidence-based recommendations for colorectal cancer patients.

3.2 Breast cancer

Breast cancer is the most common cancer among women (1,677,000 cases in 2012), accounting for 25.2% of incident female cancer cases [31]. Breast cancer incidence varies substantially, with the highest rates in Northern America, Australia/New Zealand, and Northern and Western Europe, and
low rates in Africa and Asia [35]. Breast cancer incidence rates have increased in most countries of
the world over the past decades, although among western countries, the increases have slowed or
plateaued within the past 10 years [32].

The association of obesity with breast cancer risk is complex. There is convincing evidence that after
menopause, obesity increases the risk of breast cancer [36]. Further, weight gain in adulthood
probably also increases postmenopausal breast cancer risk. Conversely, before menopause, obesity
probably decreases breast cancer risk [36]. These opposing associations are most likely mediated via
endogenous sex hormones, primarily estradiol, which is likely to have tumor promoting activities.
After menopause, adipose tissue is the major source of estrogens, and obesity is associated with
higher estrogen concentrations, which may explain the higher breast cancer risk. Interestingly, the
higher risk of postmenopausal breast cancer associated with obesity is primarily seen for estrogen
and progesterone receptor positive disease, and it is limited to women not using hormone
replacement therapy, which gives indirect evidence to support the hypothesis that estrogens may be
the crucial link [37]. The inverse association between obesity and premenopausal breast cancer is
primarily thought to be due to reduced exposure to endogenous progesterone because of obesity-
induced ovarian hyperandrogenism [37]. There is limited evidence showing that among breast cancer
patients, obesity is related to poorer survival [38].

3.3 Esophageal cancer

Esophageal cancer is the sixth most common cancer in men and the twelfth most common cancer in
women, accounting worldwide for 323,000 cases (4.3%) in men and 133,000 cases (2.0%) in women
in the year 2012 [31]. The highest incidence rates for esophageal cancer are found in Eastern Asia
and in Eastern and Southern Africa, while low rates are found in Western Africa [35]. There are two
main types of esophageal cancer: Squamous cell carcinoma and adenocarcinoma. Squamous cell
carcinoma is the predominant type of esophageal cancer, especially in developing countries [35]. Risk
factors include alcohol consumption, smoking, high-temperature-beverage-drinking, low
consumption of fruits and vegetables, and poor nutritional status. Esophageal adenocarcinoma is
more common in developed countries, and the incidence rates are increasing in these areas [32].
There is convincing evidence that obesity increases the risk of esophageal adenocarcinoma [39].
Overweight is associated with an approximately 1.5-2.0-fold higher risk of esophageal
adenocarcinoma, while obesity is associated with an approximately 2.0-3.0-fold higher risk,
compared to normal-weight [40]. Likely mechanisms include gastro-oesophageal reflux disease, and
Barrett’s oesophagus, which are more prevalent among obese persons [40]. There are only a limited
number of studies that have investigated whether obesity influences survival among esophageal cancer patients, and these studies have found conflicting results [40].

3.4 Kidney cancer

Kidney cancer accounted for 214,000 incident cancer cases (2.9%) in men and for 124,000 cancer cases (1.9%) in women worldwide in the year 2012 [31]. The highest rates of kidney cancer are found in Northern America, Australia/New Zealand, and Europe, while lowest rates are observed in Africa and the Pacific Islands [31]. There are two major types of kidney cancer: renal cell cancer, which arises from the renal tubules, and renal pelvis cancer. Renal cell cancer accounts for 80–90% of adult kidney cancer. There is convincing evidence that obesity increases the risk of renal cell cancer [41]. Overweight persons have approximately a 30% higher risk of renal cell cancer, and obese persons approximately an 80% higher risk compared to normal weight persons [42]. Some studies report slightly stronger risks of renal cell cancer associated with obesity in women than in men [42]. Possible mechanisms for the association of obesity and kidney cancer include the insulin-like growth factor (IGF) pathway, sex steroid hormones, and other hormones such as adiponectin [42]. Whether weight gain in adulthood is related to risk of renal cell cancer has been examined in only a few studies. It is unclear whether obesity has an effect on survival among kidney cancer patients [42].

3.5 Pancreatic cancer

Pancreatic cancer accounted for 178,000 incident cancer cases (2.4%) among men, and for 160,000 cancer cases (2.4%) among women worldwide in the year 2012 [31]. The highest incidence rates are observed in Asia and Europe, whereas the lowest rates are observed in Africa and Oceania [31]. There is convincing evidence that obesity increases the risk of pancreatic cancer [43]. Compared to normal weight persons, overweight as well as obese individuals have a 20% higher risk to develop pancreatic cancer [44]. Possible mechanisms for the association of obesity with pancreatic cancer risk include insulin resistance and associated hyperglycemia/hyperinsulinemia, inflammatory and immune pathways, and sex steroid hormones [44]. There are only few studies that have examined whether weight gain during adulthood is associated with pancreatic cancer [44]. Among pancreatic cancer patients, preliminary evidence suggests that obese persons have poorer survival compared to normal-weight individuals [44].
3.6 Endometrial cancer

Worldwide, endometrial cancer is the sixth most common cancer type in women, accounting for 320,000 incident cancers (4.8%) in the year 2012 [31]. The highest rates are observed in Northern America, and Northern and Western Europe, while low rates are observed in South-Central Asia and Africa [31]. There is convincing evidence that obesity increases the risk of endometrial cancer [45]. This relationship is particularly strong. Thus, obesity is associated with a 2.6-fold higher risk of endometrial cancer compared to normal weight [46]. Similarly, weight gain during adulthood is associated with a higher risk [46]. Potential mechanisms for the observed association primarily include endogenous sex steroid hormones, but also insulin resistance, chronic inflammation and adipokines. There are only a few studies that have investigated whether the association of obesity with survival among women with endometrial cancer, and these studies suggest that obesity is related to poorer survival [46].

3.7 Liver Cancer

Liver cancer is the fifth most common cancer in men and the ninth most common cancer in women, accounting for 554,000 incident cancer cases (7.5%) in men and 228,000 incident cancer cases (3.4%) in women worldwide in the year 2012 [31]. High incidence rates of liver cancer are observed in less developed countries, and lower rates in more developed countries [31]. Incidence rates of liver cancer have increased over the past years in developed countries of Western Europe, North America, and Oceania, but decreased in the highest risk areas of Asia [47,32]. The major form of liver cancer is hepatocellular carcinoma, which accounts for 70-90% of liver cancer. Established traditional risk factors for liver cancer include chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infection, exposure to toxins, such as aflatoxin, and excessive alcohol consumption [48]. However, there is now also convincing evidence that obesity increases the risk of liver cancer, which may explain to some extent the increasing incidence rates in developed countries [25,32]. Thus, every 5 kg/m² higher BMI is associated with a 30% higher risk of liver cancer [25]. Studies suggest that weight gain during adulthood is also associated with liver cancer [49]. Potential mechanisms for the higher risk include the development of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, which are often observed in obese persons and are risk factors for liver cancer [49]. There are only a limited number of studies that have investigated whether obesity is associated with prognosis in liver cancer patients [49].
3.8 Prostate cancer

Prostate cancer is the second most common cancer in men, accounting for 1.112.000 incident cases (15.0% of all cancers) worldwide in the year 2012 [31]. Incidence rates vary substantially; the highest rates are found in Australia/New Zealand, Northern America, and in Western and Northern Europe, whereas low rates are observed in Asian populations [31]. The association of obesity with prostate cancer risk is complex. There is probable evidence that obesity increases the risk of advanced prostate cancer (and most likely also fatal prostate cancer) [28]. For every 5 kg/m² there is a 1.09-fold higher relative risk of advanced prostate cancer [50]. In contrast, obesity is not (or even inversely) related to total or non-advanced prostate cancer [50]. The biological mechanisms for the association of obesity with advanced prostate cancer risk are speculative and include insulin and IGF axis pathways, sex steroid hormones, and alterations in metabolism. The inverse association of obesity with local prostate cancer is likely due to methodological issues, including detection bias, since obesity is associated with less PSA screening, lower PSA levels, and lower accuracy of digital rectal examination in obese men [50]. There are only a few studies on weight gain and prostate cancer risk, which found no significant association with total, local or advanced prostate cancer risk [50].

3.9 Ovarian cancer

Ovarian cancer is the seventh most common cancer among women, and accounted for 239.000 cases (3.6%) of incident cancers worldwide among women in the year 2012 [31]. Incidence rates are highest in developed regions, and lower in less developed regions [31]. Obesity probably increases the risk of ovarian cancer [26]. The association with obesity is weaker than for other types of cancer. Thus, each 5-unit higher BMI is approximately associated with a 7% higher risk of ovarian cancer [51]. One reason for this weaker association may be that ovarian cancer is a heterogeneous disease, and studies suggest that the strength of the association with obesity may differ according to type of tumor [51]. Potential mechanisms for the association of obesity with ovarian cancer include inflammatory pathways and hormonal factors, including androgens. Current evidence does not allow definite conclusions about whether adult weight gain is associated with ovarian cancer risk [51]. A few studies have investigated the association of obesity with mortality among ovarian cancer patients, and these studies suggest that obesity is associated with poor prognosis among these patients [51].

3.10 Gallbladder Cancer
Worldwide, gallbladder cancer accounted for 77,000 incident cancer cases (1.0%) in men and 101,000 cancer cases (1.5%) in women in the year 2012 [31]. The highest incidence rates are observed in South America and Eastern Asia. There is probable evidence that obesity increases the risk of gallbladder cancer [27]. When estimated on a linear scale, every 5 kg/m² higher BMI is associated with a 1.25-fold higher risk of gallbladder cancer [27]. However, there is some evidence for non-linearity, indicating that the risk increases only at BMI levels higher than or equal to 24 kg/m² [27]. The underlying mechanisms that may link obesity with gallbladder cancer are unclear and may include hormones like insulin and insulin-like growth factor 1 [27]. Another possible link is the presence of gallstones, which is a risk factor for gallbladder cancer and may be caused by obesity [27]. It is unclear whether weight gain in adulthood is associated with an increase in gallbladder cancer risk. It is also not clear whether obesity affects prognosis among patients with gallbladder cancer.

4 Potential mechanisms and pathways for the association of obesity with cancer risk

The exact mechanisms that link obesity with cancer risk are not entirely clear and may differ by cancer type. Obesity is associated with a number of metabolic abnormalities, and several of these have been proposed as a link to cancer risk. They can broadly be classified into three major pathways: the insulin resistance/insulin-like growth factor (IGF) pathway, the inflammatory pathway, and the sex hormone pathway [52]. Notably, this classification is somewhat artificial since there is a high degree of overlap between these pathways. Insulin resistance in liver, muscle, and adipose tissue is a hallmark of obesity, and it is also a central feature of the metabolic syndrome (MetS), which is clinically defined as a minimum of 2 out of 5 metabolic abnormalities, including abdominal obesity, elevated blood glucose levels, elevated blood pressure levels, low high-density-lipoprotein (HDL) cholesterol levels and high triglyceride levels [2,12]. Insulin resistance leads to hyperinsulinemia, which in turn leads to elevated levels of free bioavailable IGF-1 concentrations, and both, insulin and IGF-1, purportedly have anti-apoptotic and cell proliferative effects, which may promote tumor development [52,53]. Insulin resistance is also closely related to (and probably partly caused by) abnormal production of adipose tissue derived cytokines and hormones, including leptin, adiponectin, and tumor necrosis factor (TNF) alpha. There are several lines of evidence that indicate that some of these cytokines and hormones, as well as clinical features of the metabolic syndrome, may be a link for obesity-related cancer risk [53]. The insulin resistance/IGF pathway may be particularly relevant for colorectal cancer, pancreatic cancer, and, potentially, prostate cancer. Obesity is also closely related to chronic subclinical inflammation, as reflected by elevated concentrations of pro-inflammatory cytokines and acute phase proteins, including TNF-alpha,
interleukin-6 (IL-6), and C-reactive protein (CRP). Inflammation plays a critical role in tumor progression [54] and may therefore be a critical link to obesity-related cancers [55]. The inflammatory pathway is probably particularly important for colorectal cancer, which is supported by the observation that patients with inflammatory bowel disease have higher colorectal cancer risk and that aspirin use decreases colorectal cancer risk [52]. Obesity also has profound effects on sex hormone metabolism. Thus, as indicated above, before menopause, obesity-induced ovarian hyperandrogenism may lead to reduced ovarian progesterone synthesis, whereas after menopause, obesity may lead to higher levels of bioavailable estradiol and testosterone, and these hormones purportedly reduce apoptosis and increase cell proliferation, which may promote tumor development. The sex hormone pathway is probably particularly relevant for breast cancer and endometrial cancer [52].

There are of course also other potential pathways for the obesity-cancer link. One specific example is obesity induced gastroesophageal reflux that predisposes to esophageal adenocarcinoma, as described further above.

5 Burden of Cancer Attributable to Obesity on a Population Level

The burden of cancer attributable to obesity is usually expressed as the population attributable fraction (PAF), which can be interpreted as “the proportion of disease cases over a specified time that would be prevented following elimination of the exposures, assuming the exposures are causal.” [56]. The PAF depends on the prevalence of exposure and on the relative risk estimates. Both, the relative risk estimates for the association of obesity with cancer, as well as the prevalence estimates for obesity include substantial uncertainty; therefore, estimates for the fraction of cancer that is attributable to obesity have to be interpreted carefully. It was recently estimated that worldwide, among men, 33.3% of esophageal adenocarcinoma, 13.0% of colon cancer, 6.2% of rectal cancer, 8.4% of pancreatic cancer, 16.6% of kidney cancer, and 11.9% of all obesity-related cancers is attributable to overweight and obesity [57,58]. Among women, 33.8% of esophageal adenocarcinoma, 7.6% of colon cancer, 3.6 of rectal cancer, 32.3% of gallbladder cancer, 7.8% of pancreatic cancer, 10.2% of postmenopausal breast cancer, 34.0% of endometrial cancer, 4.0% of ovary cancer, 25.9% of kidney cancer, and 13.1% of all obesity-related cancers is attributable to overweight and obesity [57]. There is substantial worldwide variation in these estimates, which is mainly due to the substantial variation in the prevalence of obesity. For example, the PAF for colon cancer due to obesity is 21.0% in North America but 5.0% in Sub-Saharan Africa [57]. The largest PAF is usually observed for endometrial cancer, which is mainly due to the relatively strong relative risk
estimates. For example, in North America, almost half (47.8%) of endometrial cancer is attributable to overweight and obesity [57]. Taken together, these data indicate that for some cancer sites, a substantial proportion could be prevented.

6 Conclusions

Besides the well-established effects on type 2 diabetes and cardiovascular disease, there is convincing evidence today that obesity also increases the risk of several types of cancer, including colorectal cancer, postmenopausal breast cancer, endometrial cancer, renal cell carcinoma, esophageal adenocarcinoma, pancreatic cancer, and liver cancer [24,25]. Obesity probably also increases the risk of ovarian cancer, advanced prostate cancer, gallbladder cancer, and gastric cardia cancer [26-28]. It is likely that this list of obesity-related cancers will increase in the future. Thus, a recent statement by the IARC added thyroid cancer, multiple myeloma, and meningioma to this list [30]. For some cancer types there is also some evidence that weight gain during adulthood increases cancer risk, e.g., colorectal cancer, postmenopausal breast cancer, endometrial cancer, and liver cancer [33,37,46,49]. However, for most cancers it is an open question as to whether vulnerability to weight gain in relation to cancer risk depends on specific life periods. There are a number of plausible mechanisms that may explain the relationship between obesity and cancer risk, including pathways related to insulin resistance, inflammation, and sex hormones [52,53]. For most cancers there is only limited evidence that weight loss in adulthood decreases cancer risk. This is primarily due to the limited long-term success of weight loss strategies among obese individuals. There is limited evidence suggesting that obesity may also be associated with poor prognosis among patients with colorectal cancer, breast cancer, endometrial cancer, ovarian cancer and pancreatic cancer [33,37,46,51,44]. Taken together, these findings support efforts to prevent weight gain on an individual level as well as on a population level. Whether and to what extent overweight or obese cancer patients benefit from weight loss strategies is unclear and a matter of debate [4,59].
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### Tables

**Table 1** Cancers for which there is convincing or probable evidence that they are caused by obesity*

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<thead>
<tr>
<th>Strength of evidence</th>
<th>Cancer type</th>
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<td>Convincing</td>
<td>• Colorectal cancer</td>
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<td>• Postmenopausal breast cancer</td>
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<td>• Endometrial cancer</td>
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<td>• Esophageal adenocarcinoma</td>
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<td>• Pancreatic cancer</td>
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<td>• Liver cancer</td>
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<td>Probable</td>
<td>• Ovarian cancer</td>
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<td>• Advanced stage prostate cancer</td>
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<td>• Gallbladder cancer</td>
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<td>• Gastric cardia cancer</td>
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*Based on evaluations by the World Cancer Research Fund (IARC) [24,36,43,45,26,28,25,27,41,39,29]. A recent report of a working group by the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence for a causal relationship between obesity and the cancers listed above, with the exception of prostate cancer [30]. In addition, the working group concluded that there is sufficient evidence for thyroid cancer, multiple myeloma, and meningioma.