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Obesity and Cancer

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Preface

The notion that obesity is associated with a higher risk of certain cancers has been known among cancer epidemiologists and nutritional epidemiologists for quite some time but only within the past decade became more widely distributed in the scientific community and lately in clinical practice. While organizations like the World Cancer Research Fund (WCRF) have put studying the impact of obesity on cancer occurrence and outcome as top research priority for several years now, it was only in 2013/2014 that the American Society of Clinical Oncology identified obesity as a strategic issue for the society, laid out key priorities, and published a position paper. The number of studies on obesity and cancer—and in parallel the number of cancers for which we now have sufficient evidence for a causal relationship to obesity—increased substantially during the past decade, and it seems that this increase is ongoing with accelerated pace. These developments make it more and more challenging to keep up-to-date with the current status that is achieved in this field. Having a book that comprehensively summarizes that status is therefore appealing. We were therefore more than happy when the Managing Editors and Springer Verlag invited us to become volume editors of a book on Obesity and Cancer.

The aim of this book is to provide a comprehensive and up-to-date review on the relation between obesity and cancer. It includes an introductory overview, followed by in-depth reviews on those cancers for which we have sufficient evidence of a causal relationship to obesity. The chapters address effects of obesity and body fat distribution on cancer incidence and cancer survival, effects of weight gain and weight loss, and of childhood and adolescent obesity. Potential biologic pathways are discussed from both an epidemiological and an experimental perspective. The book closes with a population perspective on the cancer burden due to obesity.

For each chapter, we have invited the leading experts in their field, and we are deeply grateful to the authors for their contribution to this book. We would also like to thank the Managing Editors, Prof. P.M. Schlag and Prof. H.-J. Senn, as well as the employers of Springer Verlag, Ms M. Stoeck, Ms D. Ignasy, and Ms B. Dhayalan, for their support in publishing this book. We believe this book is of particular value

to researchers and epidemiologists and is also of interest to public health workers and clinicians. We would welcome feedback from the readers on their perception of the book.

Berlin, Germany
September 2016

Tobias Pischon
Katharina Nimptsch

Contents

Obesity and Risk of Cancer: An Introductory Overview

Tobias Pischon and Katharina Nimptsch

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 needs to be addressed in future studies.

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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 m^2) [8, 9]. A BMI <18.5 kg/m^2 defines underweight, 18.5 to <25.0 kg/m^2 normal weight, 25.0 to <30 kg/m^2 overweight, and ≥30 kg/m^2 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 did not make their way into national or 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 shows 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 of 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/m^2 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 7000 relevant studies [24]. 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,

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

Strength of evidence	Cancer type
Convincing	• Colorectal cancer • Postmenopausal breast cancer • Endometrial cancer • Renal cell carcinoma • Esophageal adenocarcinoma • Pancreatic cancer • Liver cancer
Probable	•Ovarian cancer •Advanced stage prostate cancer •Gallbladder cancer •Gastric cardia cancer

[a]Based on evaluations by the World Cancer Research Fund (IARC) [24–29, 36, 39, 41, 43, 45]. 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

Latin America, and Eastern Europe, whereas in the high-income countries, rates tend to decrease in the USA, 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 20–40 % higher risk of 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 50–70 % higher risk of colon cancer and a 25–75 % higher risk of rectal cancer, while obese versus normal-weight women have a 10–25 % higher risk of colon cancer and a 2–40 % 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 [33, 34]. 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]. 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- to 2.0-fold higher risk of esophageal adenocarcinoma, while obesity is associated with an approximately 2.0- to 3.0-fold higher risk, compared to normal weight [40]. Likely mechanisms include gastroesophageal reflux disease, and Barrett's esophagus, 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 [32, 47]. 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/m^2 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/m^2, 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/m^2 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/m^2 [27]. The underlying mechanisms that may link obesity with gallbladder cancer are unclear and may include hormones like insulin and IGF 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/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 3 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 are 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 are 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, 44, 46, 51]. 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 needs to be addressed in future studies [4, 59].

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Obesity and Colorectal Cancer

Carmen Jochem and Michael Leitzmann

Abstract

There is strong evidence that modifiable lifestyle factors such as obesity play a key role in colorectal carcinogenesis. Epidemiologic data have consistently reported a positive association between obesity and colorectal cancer. The relative risk associated with general obesity (as assessed by BMI) is higher in men than in women and for cancer of the colon than for cancer of the rectum. Abdominal obesity (as assessed by waist circumference (WC) or waist-to-hip ratio) is associated with an increased risk of colorectal cancer in both sexes, with stronger associations for cancer of the colon than for cancer of the rectum. Plausible biological mechanisms include insulin resistance, hyperinsulinemia, chronic inflammation, altered levels of growth factors, adipocytokines and steroid hormones. In addition to its effect on colorectal cancer incidence, obesity may play a role in colorectal cancer recurrence, treatment outcomes and survival. Understanding the effects of childhood and adolescent obesity and weight change over the life course in relation to future risk of colorectal cancer is incomplete but essential for targeted preventive recommendations. This chapter summarizes the current evidence on the relationship between obesity and colorectal cancer and colorectal adenoma, a common precursor lesion.

Keywords

Obesity · Colorectal cancer · Epidemiology

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1 Introduction

Worldwide, colorectal cancer is the third[1] most common cancer in men and the second[2] leading malignancy in women, accounting for 10.0 and 9.2 % of all cancer cases, respectively [1]. In 2012, approximately 746,000 new colorectal cancer cases were diagnosed in men and 614,000 were diagnosed in women [1]. Age-standardized incidence rates (ASRs) vary widely across the world, and almost 55 % of all cases occur in economically more developed regions such as Australia/New Zealand (men: 44.8 per 100,000, women: 32.2), Europe (men: 37.3, women: 23.6) and Northern America (men: 30.1, women: 22.7) [1]. Incidence rates are lowest in economically less developed regions such as Africa (men: 7.0, women: 5.8) and South Central Asia (men: 7.0, women: 5.2) [1]. Colorectal cancer is the fourth[3] most common cause of death from cancer, contributing to 8.5 % of total cancer mortality worldwide (694,000 deaths per year in both sexes) [1]. Overall, colorectal cancer is among those cancers that contribute most to the global burden of cancer—in terms of incidence, mortality and disability-adjusted life years (DALYs) [2].

Higher rates of colorectal cancer in "westernized" countries suggest that environmental or lifestyle factors may play a key role in the etiology of colorectal cancer beyond genetic factors. Early migrant studies showed that individuals who originated from regions with relatively low incidences of colorectal cancer and their descendants tended to adopt the higher risk of the new host population [3]. In addition, an increase in colorectal cancer incidence in rapidly developing Asian countries such as Japan, Singapore and China during the past 20–50 years points to an etiologic role of dietary and lifestyle habits [4]. In addition, ecological data show high rates of colorectal cancers in countries with high obesity prevalence (Fig. 1).

Today, there is convincing evidence that lifestyle-associated risk factors such as abdominal[4] and general[5] obesity and nutritional factors such as red and processed meat and alcoholic beverages increase the risk of colorectal cancer, whereas physical activity and foods rich in dietary fiber decrease the risk [5]. Additionally, cigarette smoking and low vegetable and fruit consumption may be associated with an increased risk of colorectal cancer [6].

Whereas only approximately 5–10 % of colorectal cancer cases are hereditary in nature (with familial adenomatous polyposis and hereditary non-polyposis colorectal cancer as the two major forms), the vast majority are sporadic colorectal cancer cases (including approximately 20 % of familial colorectal cancer cases) with genetic and environmental causes [7].

[1]Following lung cancer and prostate cancer.

[2]Following breast cancer.

[3]Following death from cancer of the lung, liver and stomach.

[4]Defined as an increase in waist circumference (WC) or waist-to-hip ratio (WHR).

[5]Defined as a body mass index (BMI) $\geq$ 30 kg/m^2.

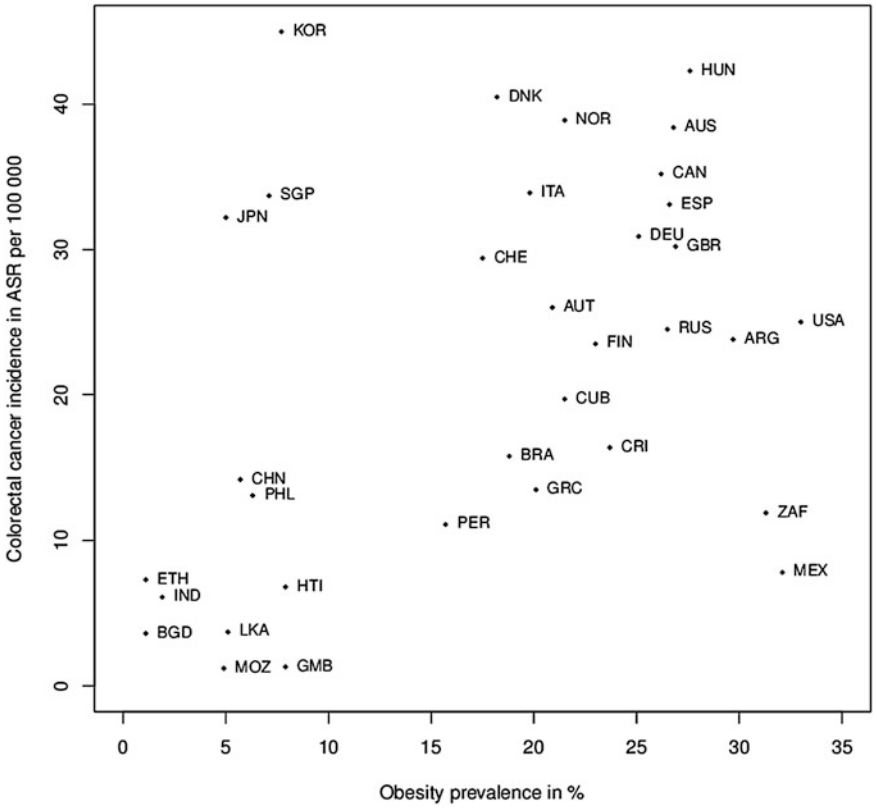

Fig. 1 Plot of age-standardized colorectal cancer incidence (ASR per 100,000) [84] versus obesity prevalence (%) [85] for 26 selected countries

The pathogenesis of colorectal tumorigenesis is based on the concept of the adenoma–carcinoma sequence (Fig. 2), which implies that mutations of oncogenes (such as K-*ras*) and tumor suppressor genes [e.g., adenomatous polyposis coli gene (APC)] together with other genetic abnormalities determine the stepwise progression from normal to dysplastic epithelium to invasive carcinoma [8].

Transition rates from advanced adenomas to colorectal carcinomas appear to be age dependent, with a 10-year cumulative risk of progression from 25 % at age 55 to approximately 40 % at age 80 [9].

This chapter outlines the association between obesity and colorectal cancer risk, and it highlights plausible underlying biological mechanisms. In particular, this chapter summarizes current evidence on the relations of general and abdominal obesity, weight change, childhood and adolescent obesity to risks of colorectal adenoma (as a precursor of colorectal cancer), colorectal cancer and colorectal cancer survival.

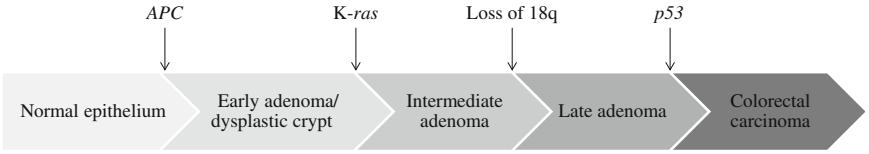

Fig. 2 Schematic representation of the adenoma–carcinoma sequence underlying colorectal carcinogenesis

2 Association Between Obesity and Colorectal Cancer Incidence

The relationship between general and abdominal obesity and colorectal cancer and its precursor—colorectal adenoma—has been investigated in numerous epidemiologic studies. Whereas several studies reported on the association between general obesity [as assessed by body mass index (BMI)] and colorectal cancer risk, others used WC or waist-to-hip ratio (WHR) to investigate the association between abdominal obesity and colorectal cancer risk.

2.1 General Obesity and Colorectal Cancer Risk

In the past 15 years, a number of systematic reviews and meta-analyses have summarized the findings from a large number of epidemiologic studies that investigated the relationship between general obesity, as assessed by BMI, and risk of colorectal cancer (Table 1).

In 2001, Bergström and colleagues were the first to quantitatively summarize the association between general obesity and risk of colon cancer from six studies and reported an overall RR for colon cancer of 1.03 (95 % CI 1.02–1.04) per 1 kg/m^2 higher BMI [10]. They estimated the risk of developing colon cancer to be 33 % higher in obese people compared to people with normal weight [10]. The analysis showed that approximately 11 % of colon cancer cases in 15 countries of the European Union are attributable to overweight and obesity [10].

In 2007, the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) quantified the relative risk of colorectal cancer per 1 kg/m^2 higher BMI in a meta-analysis including 28 cohort studies as 1.03 (95 % CI 1.02–1.04) [11]. In 2011, an expert panel of the Continuous Update Project (CUP) included the findings of 24 additional publications, of which 20 showed a positive association between obesity and colorectal cancer [5]. The updated overall risk estimate per 1 kg/m^2 higher BMI was again 1.03 (95 % CI 1.02–1.03) [5]. The association was stronger for

Table 1 Meta-analyses on the association between general obesity and colorectal cancer

Authors, year No. of studies included	Exposure category	Outcome	Sex	RR (95 % CI)
Bergström et al., 2001 [10]				
6 studies (4 cohort, 2 case–control)	Per 1 kg/m^2 higher BMI	CC	All	1.03 (1.02–1.04)
Dai et al., 2007 [19]				
15 cohort studies	Highest to lowest quantiles of BMI	CC	M F	1.59 (1.35–1.86) 1.22 (1.08–1.39)
		RC	M F	1.16 (0.93–1.46) 1.23 (0.98–1.54)
	BMI $\geq$ 30 versus BMI 18.5–24.9	CC	M F	1.71 (1.33–2.19) 1.10 (0.92–1.32)
		Prox. CC Dist. CC	All All	1.41 (0.66–3.01) 1.23 (0.80–1.90)
		RC	M F	1.75 (1.17–2.62) 1.12 (0.84–1.49)
Larsson and Wolk, 2007 [20]				
30 cohort studies	Per 5 kg/m^2 higher BMI	CC	M F	1.30 (1.25–1.35) 1.12 (1.07–1.18)
		Prox. CC Dist. CC	M F M F	1.29 (1.17–1.42) 1.35 (1.22–1.48) 1.13 (0.93–1.36) 1.14 (1.01–1.28)
		RC	M F	1.12 (1.09–1.16) 1.03 (0.99–1.08)
Moghaddam et al., 2007 [18]				
31 studies (23 cohort, 8 case–control)	BMI $\geq$ 30 versus BMI < 25	CRC	All M F	1.19 (1.08–1.30 1.40 (1.33–1.47) 1.07 (0.97–1.18)
		CC	All M F	1.21 (1.06–1.38) 1.53 (1.33–1.75) 1.09 (0.93–1.28)
		RC	All M F	1.12 (0.98–1.28) 1.27 (1.17–1.37) 1.02 (0.85–1.22)
	Per 2 kg/m^2 higher BMI	CRC	All	1.06 (1.03–1.09)
World Cancer Research Fund/American Institute for Cancer Research, 2007 [11]				
28 cohort studies	Per 1 kg/m^2 higher BMI	CRC	All	1.03 (1.02–1.04)
Renehan et al., 2008 [86]				
29 cohort studies	Per 5 kg/m^2 higher BMI	CC	M F	1.24 (1.20–1.28) 1.09 (1.05–1.13)
		RC	M F	1.09 (1.06–1.12) 1.02 (1.00–1.05)

(continued)

Table 1 (continued)

Authors, year No. of studies included	Exposure category	Outcome	Sex	RR (95 % CI)
Guh et al., 2009 [87]				
12 cohort studies	BMI $\geq$ 30 versus BMI < 30	CRC	M F	1.95 (1.59–2.39) 1.66 (1.52–1.81)
Harriss et al., 2009 [88]				
28 studies (25 cohort, 3 case–control)	Per 5 kg/m^2 higher BMI	CC	M F	1.24 (1.20–1.28) 1.09 (1.04–1.14)
		Prox. CC Dist. CC	M F M F	1.16 (0.99–1.37) 1.12 (0.97–1.37) 1.28 (1.18–1.39) 1.09 (0.95–1.24)
		RC	M F	1.09 (1.06–1.12) 1.02 (0.99–1.04)
Ning et al., 2010 [89]				
58 studies (44 cohort, 14 case–control)	BMI $\geq$ 30 versus BMI < 23	CRC	All M F	1.41 (1.30–1.53) 1.53 (1.44–1.62) 1.25 (1.14–1.37)
		CC	All M F	1.49 (1.35–1.63) 1.60 (1.53–1.69) 1.25 (1.12–1.39)
		RC	All M F	1.26 (1.17–1.37) 1.30 (1.17–1.43) 1.14 (1.02–1.27)
	Per 5 kg/m^2 higher BMI	CRC	All M F	1.18 (1.14–1.21) 1.25 (1.20–1.30) 1.12 (1.06–1.16)
		CC	All	1.21 (1.17–1.26)
		RC	All	1.11 (1.06–1.16)
World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project (CUP), 2011 [5]				
24 cohort studies identified during the CUP (January 2006–December 2009)	Per 1 kg/m^2 higher BMI	CRC	All M F	1.02 (1.02–1.03) 1.03 (1.03–1.04) 1.02 (1.01–1.03)
		CC	All M F	1.03 (1.03–1.04) 1.04 (1.03–1.05) 1.02 (1.01–1.03)
		Prox. CC Dist. CC	All M F All M F	1.03 (1.01–1.05) 1.06 (1.02–1.09) 1.02 (0.99–1.04) 1.04 (1.02–1.05) 1.05 (1.02–1.08) 1.03 (1.01–1.05)
		RC	All M F	1.01 (1.01–1.02) 1.02 (1.01–1.02) 1.01 (1.00–1.02)

(continued)

Table 1 (continued)

Authors, year No. of studies included	Exposure category	Outcome	Sex	RR (95 % CI)
Matsuo et al., 2012 [13]				
8 cohort studies	BMI $\geq$ 30 versus BMI 23 $\leq$ 25	CRC	M F	1.24 (1.06–1.44) 1.17 (0.87–1.57)
		CC	M F	1.47 (0.99–2.18) 1.18 (0.83–1.68)
		Prox. CC Dist. CC	M F M F	1.61 (0.83–3.09) 1.26 (0.79–1.99) 1.77 (1.06–3.00) 1.42 (0.76–2.66)
		RC	M F	1.57 (0.97–2.53) 1.39 (0.81–2.39)
	Per 1 kg/m^2 higher BMI	CRC	M F	1.03 (1.02–1.04) 1.07 (1.05–1.08)
		CC	M F	1.04 (1.02–1.06) 1.03 (1.01–1.05)
		Prox. CC	M F	1.03 (1.00–1.06) 1.03 (1.01–1.06)
		Dist. CC	M F	1.05 (1.03–1.08) 1.02 (0.99–1.05)
		RC	M F	1.02 (0.99–1.04) 1.00 (0.97–1.03)
Ma et al., 2013 [12]				
41 cohort studies	Obese versus normal category of BMI	CRC	All M F	1.33 (1.25–1.42) 1.47 (1.36–1.58) 1.15 (1.08–1.23)
		CC	All M F	1.47 (1.35–1.60) 1.55 (1.47–1.63) 1.23 (1.10–1,37)
		Prox. CC Dist. CC	All All	1.30 (1.11–1.51) 1.37 (1.16–1.61)
		RC	All M F	1.15 (1.10–1.20) 1.24 (1.11–1.38) 1.07 (1.01–1.14)

Abbreviations: *BMI* body mass index; *CC* colon cancer; *prox. CC* proximal colon cancer; *dist. CC* distal colon cancer; *CI* confidence interval; *CRC* colorectal cancer; *F* females; *M* males; *RC* rectal cancer; *RR* relative risk

men than for women, with risk estimates for colorectal cancer of 1.03 (95 % CI 1.03–1.04) and 1.02 (95 % CI 1.01–1.02) per unit higher BMI, respectively [5]. Stronger associations were observed for colon than for rectal cancer [5].

The most recent systematic review came from Ma and colleagues (2013) and included 41 prospective studies on BMI and colorectal cancer, with a total of

8,115,689 individuals and 85,935 colorectal cancer cases [12]. They reported an overall RR for colorectal cancer of 1.33 (95 % CI 1.25–1.42) when comparing obese with normal categories of BMI [12]. The association was stronger for men than for women, for colon than for rectal cancer and for distal than for proximal colon cancer [12].

In order to examine the association between obesity and colorectal cancer in populations other than Caucasians, Matsuo and colleagues [13] conducted a pooled analysis of eight population-based prospective studies in Japan. Comparing the risk estimates of obese with normal-weight categories, stronger associations were shown for men than for women and for distal than for proximal colon cancer [13]. These findings extend the evidence of a positive association between general obesity and colorectal cancer risk from Caucasian to Asian populations.

Summing up the findings from published meta-analyses and systematic reviews, the overall risk of developing colorectal cancer is 20–40 % greater for obese than for normal-weight individuals, with stronger associations observed in men than in women. The risk of obese men for developing colon cancer is between 50 and 70 % higher than the risk of men with normal BMI. Obese women have a 10–25 % higher risk of developing colon cancer than women with normal BMI. The risk of developing rectal cancer is about 25–75 % higher for obese men and about 2–40 % higher for obese women than for their normal-weight counterparts. Furthermore, there is evidence for a dose–response relationship, with an increase in colorectal cancer risk by 2–3 % for each unit (1 kg/m^2) higher BMI.

2.2 General Obesity and Colorectal Adenomatous Polyps

According to the adenoma–carcinoma sequence, most colorectal cancer cases develop from colorectal adenomas. Thus, the relationship between general obesity (as assessed by BMI) and colorectal adenomas is of interest, and the heterogeneous findings from epidemiologic studies have been summarized in several meta-analyses. Compared to normal-weight individuals, obese people have a 32–47 % higher overall risk of colorectal adenoma [14–16]. The risk of colorectal adenoma is 2 % (95 % CI 0.99–1.03) per 1 kg/m^2 higher BMI, although that risk estimate is statistically nonsignificant [16]. A meta-analysis by Ben and colleagues showed that a 5-kg/m^2 higher BMI was associated with an increased risk of colorectal adenomas of 1.19 (95 % CI 1.13–1.26) [17]. There was no statistically significant difference between men and women. The risk was significantly increased for colon but not for rectal adenomas [17]. These findings show that there is consistent evidence for a statistically significant positive association between general obesity and colorectal adenoma risk.

2.3 Abdominal Obesity and Colorectal Cancer Risk

Several systematic reviews and meta-analyses investigated the association between abdominal obesity (as assessed by WC or WHR) and colorectal cancer and reported similar overall results (Table 2). The risk of colorectal cancer is about 45 % higher for those in the highest category of WC compared to those in the lowest category and is similar for men and women [12, 18]. The risk of developing colon cancer is approximately 50–70 % higher for men and about 45–50 % higher for women in the highest compared with the lowest gender-specific categories of WC [12, 19]. For rectal cancer, Dai et al. reported similar risk estimates for men and women, although they were not statistically significant [19]. Ma and colleagues showed an overall risk of rectal cancer of 1.35 (95 % CI 1.11–1.63) for the highest compared to the lowest category of WC [12]. When stratified by sex, the association was statistically significant only for women [12]. Further, risk estimates for the highest compared to the lowest category of WC were similar for proximal and distal colon cancer [12].

The WCRF/AICR expert panel analyzed the association between abdominal obesity and colorectal cancer and showed a 3–5 % higher risk of colorectal cancer per 2.5-cm higher WC [5, 11]. The CUP showed that the positive association was

Table 2 Meta-analyses on the association of abdominal obesity with colorectal cancer

Authors, year No. of studies included	Exposure category	Outcome	Sex	RR (95 % CI)
Dai et al., 2007 [19]				
7 cohort studies	Highest versus lowest quantiles of WC	CC	M F	1.68 (1.36–2.08) 1.48 (1.19–1.84)
		Prox. CC Dist. CC	All All	2.05 (1.23–3.41) 1.86 (1.05–3.30)
		RC	M F	1.26 (0.90–1.77) 1.23 (0.81–1.86)
6 cohort studies	Highest versus lowest quantiles of WHR	CC	M F	1.91 (1.46–2.49) 1.49 (1.23–1.81)
		Prox. CC Dist. CC	All All	1.66 (0.69–3.99) 1.79 (0.82–3.90)
		RC	M F	1.93 (1.19–3.13) 1.20 (0.81–1.78)
Larsson and Wolk, 2007 [20]				
3 cohort studies	Per 10-cm higher WC	CC	M F	1.33 (1.19–1.49) 1.16 (1.09–1.23)
		RC	M F	1.12 (1.03–1.22) 1.09 (0.99–1.20)
	Per 0.1-unit higher WHR	CC	M F	1.43 (1.19–1.71) 1.20 (1.08–1.33)
		RC	M F	1.22 (0.81–1.83) 1.15 (0.95–1.39)

(continued)

Table 2 (continued)

Authors, year No. of studies included	Exposure category	Outcome	Sex	RR (95 % CI)
Moghaddam et al., 2007 [18]				
8 cohort studies	Highest versus lowest category of WC	CRC	All	1.45 (1.31–1.61)
World Cancer Research Fund/American Institute for Cancer Research, 2007 [11]				
4 cohort studies	Per 2.5-cm higher WC	CRC	All	1.05 (1.03–1.07)
5 cohort studies	Per 0.1-unit higher WHR	CRC	All	1.30 (1.17–1.44)
Guh et al., 2009 [87]				
3 cohort studies	WC $\geq$ 102 cm versus WC < 102 cm (men) or WC $\geq$ 88 cm versus WC < 88 cm (women)	CRC	M F	2.93 (2.31–3.73) 1.55 (1.27–1.88)
World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project (CUP), 2011 [5]				
6 cohort studies identified during the CUP (January 2006–December 2009)	Per 2.5-cm higher WC	CRC	All	1.03 (1.02–1.04)
		CC	All M F	1.05 (1.03–1.06) 1.06 (1.04–1.08) 1.03 (1.02–1.04)
		RC	All	1.03 (1.01–1.04)
6 cohort studies identified during the CUP	Per 0.1-unit higher WHR	CRC	All	1.17 (1.09–1.25)
		CC	All	1.27 (1.15–1.41)
		RC	All	1.20 (1.07–1.34)
Ma et al., 2013 [12]				
13 cohort studies	Highest versus lowest category of WC	CRC	All M F	1.46 (1.33–1.60) 1.48 (1.30–1.68) 1.44 (1.30–1.60)
		CC	All M F	1.61 (1.42–1.84) 1.81 (1.46–2.24) 1.50 (1.25–1.79)
		Prox. CC Dist. CC	All All	1.87 (1.12–3.14) 1.94 (1.25–3.02)
		RC	All M F	1.35 (1.11–1.63) 1.28 (0.99–1.66) 1.50 (1.03–2.18)

Abbreviations: *CC* colon cancer; *prox. CC* proximal colon cancer; *dist. CC* distal colon cancer; *CI* confidence interval; *CRC* colorectal cancer; *F* females; *M* males; *RC* rectal cancer; *RR* relative risk; *WC* waist circumference; *WHR* waist-to-hip ratio

stronger for colon than for rectal cancer, and within colon cancer, the relation was stronger for men than for women [5]. Meta-analyses that quantified the association between WHR and colorectal cancer showed an overall risk of 17–30 % per 0.1-unit higher WHR [5, 11]. Whereas the CUP showed statistically significant risk estimates for colon as well as for rectal cancer [5], Larsson and Wolk reported a statistically significant association only for colon but not for rectal cancer [20].

In summary, there is consistent evidence that abdominal obesity is a strong risk factor for colorectal cancer in both sexes, with risk appearing to be more strongly associated with colon than with rectal cancer.

2.4 Abdominal Obesity and Colorectal Adenomatous Polyps

A meta-analysis conducted by Lee and colleagues included 12 studies and found that abdominal obesity was associated with an increased overall risk of colorectal adenomas (RR = 1.42; 95 % CI 1.30–1.56) [14]. A meta-analysis by Hong and colleagues showed that a 10-cm higher WC was associated with a RR of 1.23 (95 % CI 1.12–1.36) for developing colorectal adenomas, and the RR for the highest versus lowest level of WC was 1.39 (95 % CI 1.24–1.56), with similar risk estimates for men and women [21]. A 0.1-unit higher WHR was associated with an overall RR of 1.16 (95 % CI 1.06–1.26) [21]. Individuals in the highest WHR category had a 22 % greater colorectal adenoma risk compared with individuals in the lowest category of WHR (RR = 1.22; 95 % CI 1.10–1.35) [21].

2.5 Shortcomings of Existing Studies and Future Research Needs

The existing literature on the association between obesity and risk of colorectal cancer and adenoma has several shortcomings. First, between-study variation in the definitions of BMI and WC exposure categories represents a potential source of heterogeneity, resulting in less accurate risk estimates. Second, although studies usually adjusted for common confounders, problems with unknown confounding factors cannot be excluded. Third, findings on the association between obesity and colon cancer anatomic subsite are heterogeneous, which needs to be resolved. Fourth, in order to develop targeted public health prevention strategies, possible heterogeneity in risk across ethnicities should be investigated in more detail.

2.6 Summary on the Association Between Obesity and Colorectal Cancer

There is consistent evidence supporting a positive association between obesity and colorectal cancer. General obesity (as assessed by BMI) and abdominal obesity (as assessed by WC and WHR) are independently associated with higher colorectal cancer risk. For general obesity, the relative risks are stronger in men than in women, and they are more pronounced for cancers of the colon than of the rectum. For abdominal obesity, the association also appears to be stronger for colon than for rectal cancer, but sex differences are less clear. For both BMI and WC, there is evidence for a dose–response relationship with colorectal cancer risk. Both general

obesity and abdominal obesity seem to be associated with an increased risk of colorectal adenomatous polyps, a precursor of colorectal cancer.

3 Association Between Obesity and Colorectal Cancer Survival

In contrast to the considerable amount of published literature on obesity and colorectal cancer incidence, little data are available on the relation of obesity to colorectal cancer recurrence and survival. In the USA, 5-year relative colorectal cancer survival is 65 % and in 2012, an estimated 1,168,929 people were living with colorectal cancer [22]. Although survival rates differ across countries, the large number of people being diagnosed with colorectal cancer requires additional research on the relations of obesity and other lifestyle factors to colorectal cancer survival in order to provide adequate weight recommendations for colorectal cancer patients.

3.1 General Obesity and Mortality in Colorectal Cancer Patients

A recent meta-analysis by Lee and colleagues investigated the association between pre- and post-diagnostic BMI and colorectal cancer prognosis. That meta-analysis included 16 prospective cohort studies with a total of 58,917 colorectal cancer cases and follow-up periods between 4.9 and 20 years [23]. Pre-diagnostic obesity was associated with statistically significant increases in colorectal cancer-specific mortality and all-cause mortality, with risk estimates of 1.22 (95 % CI 1.003–1.35) and 1.25 (95 % CI 1.14–1.36), respectively [23]. However, post-diagnostic obesity was positively associated only with all-cause mortality (RR = 1.08; 95 % CI 1.03–1.13), but not with colorectal cancer-specific mortality [23]. Thus, a healthy weight may protect colorectal cancer patients against other causes of death such as cardiovascular disease but not against colorectal cancer recurrence. In subgroup analyses, Lee and colleagues showed that post-diagnostic obesity was statistically significantly associated with all-cause mortality in women (RR = 1.13; 95 % CI 1.05–1.21) but only borderline statistically significantly so in men (RR = 1.05; 95 % CI 0.99–1.23) [23]. When analyzed according to anatomic subsite, post-diagnostic obesity was positively associated with all-cause mortality in colon cancer patients (RR = 1.09; 95 % CI 1.05–1.15), but not in rectal cancer patients [23]. Other systematic reviews summarizing the association between general obesity and colorectal cancer survival revealed heterogeneous results [24, 25]. Thus, the association between general obesity and colorectal cancer survival remains unclear and more long-term studies are needed.

3.2 Abdominal Obesity and Mortality in Colorectal Cancer Patients

Several epidemiologic studies investigated the association between abdominal obesity and colorectal cancer survival. Some studies found that abdominal obesity was associated with a reduction in colorectal cancer-specific or overall survival [26, 27]. Haydon and colleagues showed that a 10-cm higher WC increased disease-specific mortality by 20 % (95 % CI 1.02–1.31) [26]. Findings from the Iowa Women's Health Study showed that women in the highest versus lowest tertiles of WC and WHR had 34–45 % greater risks of all-cause and colon cancer-specific mortality [27]. Another study demonstrated that there was no difference between overall survival of overweight (including obese) and normal-weight colorectal cancer patients [28]. However, there was a statistically nonsignificant borderline increase in risk of tumor recurrence in overweight (and obese) patients with resectable cancer [28]. Although the available evidence points to an adverse influence of abdominal obesity on colorectal cancer survival, more research is needed in this field.

3.3 Obesity and Treatment Outcomes in Colorectal Cancer Patients

Studies investigating the role of obesity on treatment outcomes in patients with colorectal cancer showed an increased risk of surgical and wound-related complications, such as wound infection and slow healing following colon cancer surgery [29], and anastomotic leak following proctectomy [30]. A meta-analysis on the outcomes of laparoscopic colorectal surgery showed that obesity was significantly associated with increased conversion rates (to open procedures), operating times and postoperative morbidity [31]. Furthermore, obesity may decrease the effect of drug treatment, such as bevacizumab (an antibody against vascular endothelial growth factor) [32]. However, other studies showed opposing findings, implying that further research is required to establish causal links between obesity and specific treatment outcomes and to draw appropriate conclusions regarding treatment options and therapeutic guidelines for obese colorectal cancer patients.

3.4 Summary and Recommendation on Weight Management in Colorectal Cancer Patients

The association between obesity and colorectal cancer survival remains unclear, but the sparse literature suggests that obesity may adversely influence the outcomes of surgical and chemotherapeutic treatments and colorectal cancer recurrence and survival. Based on the existing evidence, colorectal cancer patients should be recommended to maintain (or reach) normal weight in order to improve survival and to reduce all-cause mortality. Since pre-diagnostic BMI is strongly associated

with post-diagnostic BMI, it is preferable to maintain normal weight throughout the life span. In addition, adherence to other healthy lifestyle behaviors such as physical activity and a healthy diet should be recommended to colorectal cancer patients [33].

4 Weight Change in Adulthood and Risk of Colorectal Cancer

The vast majority of studies on obesity and colorectal cancer used one-time measurements of BMI, WC or WHR as exposure variables. However, anthropometric measures of individuals may change during the course of their lives. As colorectal tumorigenesis has a long latent period from tumor initiation to progression, changes in weight may play a role in the complex etiology of colorectal cancer. Therefore, it is of interest to examine whether dynamic exposure variables such as weight change (including weight gain and weight loss) are associated with colorectal cancer risk.

4.1 Weight Gain and Colorectal Cancer Risk

Four recently published meta-analyses summarized the relationship between weight gain during adulthood and colorectal cancer risk [34–37]. When comparing the largest weight gain group with those in the weight-stable reference group, all meta-analyses reported similar overall risk estimates and quantified the risk of colorectal cancer for those in the group with the highest weight gain as being 16–25 % higher than for those in the stable weight group [34–36]. Overall, the strength of the association was comparable across colorectal cancer anatomic subsites, and the relation was stronger in men than in women. The meta-analysis conducted by Karahalios and colleagues showed that the association was stronger in studies that assessed weight change from early adulthood to midlife compared with studies examining change from midlife to older age [36]. In line with this, Schlesinger and colleagues reported that body weight gain in early adult life was slightly more strongly associated with colorectal cancer risk than weight gain in midlife adulthood [34].

In dose–response meta-analyses, a weight gain of 5 kg was associated with a 3–5 % increased risk of colorectal cancer [34–36]. Schlesinger et al. and Chen et al. presented similar results, with increased risks of colorectal cancer of 8, 12–14 and 16–21 % for 10, 15 and 20 kg increases in weight, respectively [34, 35].

The studies included in the published meta-analyses used weight or BMI as body size measurements. However, it would be of interest to examine whether changes in WC during adulthood are associated with colorectal cancer risk. In addition, more prospective studies are needed to examine the time frames of weight change in more detail.

In conclusion, weight gain during adulthood, particularly from early adulthood to midlife, appears to be associated with an increased risk of colorectal cancer, regardless of cancer anatomic subsite.

4.2 Weight Loss and Colorectal Cancer Risk

Only one meta-analysis quantified the association between weight loss and the risk of colorectal cancer [36]. No association with risk of colorectal cancer was found when comparing weight loss with a weight-stable reference group (RR = 0.96; 95 % CI 0.89–1.05), regardless of the time frame during which weight loss occurred [36]. Since no information was available to distinguish between intentional and unintentional weight loss, reverse causation due to unintentional weight loss in colorectal cancer patients may be responsible for this finding. The association between weight loss after bariatric surgery and risk of colorectal cancer has been summarized by two meta-analyses [38, 39]. Bariatric surgery is the surgical treatment of obesity by gastric bypass or adjustable gastric banding, and it represents an effective means for weight loss in obese patients, reducing obesity-related comorbidities, even though risks of complications exist [40]. BMI loss within five years after bariatric surgery typically lies in the range of 12–17 kg/m^2 [40]. It was shown that weight loss after bariatric surgery was associated with a significantly reduced risk of colorectal cancer by 24–27 % [38, 39]. However, the evidence base is limited due to the small number of existing studies in this area.

4.3 Summary on the Effects of Weight Change on Colorectal Cancer Risk

There is increasing evidence that weight gain, particularly weight gain during early adulthood, is associated with an increased risk of colorectal cancer. The association is less clear for weight loss, although there is a significantly decreased risk of colorectal cancer in obese patients with weight loss after bariatric surgery. Nevertheless, based on the existing evidence, avoidance of weight gain during adulthood can be recommended in order to minimize the risk of colorectal cancer development.

5 Relations of Childhood and Adolescent Obesity to Risks of Colorectal Cancer and Colorectal Adenoma

The long latent period of colorectal cancer development suggests that certain exposures that lie in the past may play a role in its etiology. In particular, childhood and adolescence may represent critical time windows during which obesity may affect the future development of colorectal cancer.

In contrast to the well-studied association between adulthood obesity and colorectal cancer risk, the relations with childhood and adolescent obesity are less well known, and epidemiologic studies have yielded contrasting results, perhaps due to heterogeneous study designs and different exposure classifications.

The association between childhood obesity and colorectal adenoma was investigated in the Nurses' Health Study II [41]. Women who were in the highest versus lowest body fatness category at age 5 years had a 44 % greater risk of colorectal adenoma (RR = 1.44; 95 % CI 1.04–1.99), independent of adult BMI. A statistically nonsignificant positive association was seen for body fatness at age 10 years, and no association was apparent for body fatness at age 20 years [41]. Thus, in addition to obesity during adulthood, childhood obesity seems to be associated with an increased risk of colorectal adenoma, at least in women. Hormonal changes during adolescence may explain the null association with body fatness at age 20.

The relationship between obesity in childhood, adolescence and young adulthood and colorectal cancer was investigated in several cohort studies. The Nurses' Health Study included 75,238 women who were followed up over 22 years and showed positive relations of body fatness in childhood and adolescence to colorectal cancer risk [42]. Women in the highest body fatness category (as assessed by somatotypes) in childhood and adolescence had a 27–28 % greater risk of colorectal cancer compared to those in the lowest body fatness category, independent of adult BMI [42]. When comparing BMI categories ≥ 30 to <18.5 kg/m^2 in young adulthood (age 18 years), women in the highest BMI category had a 60 % greater risk of colorectal cancer than women in the lowest BMI category [42]. The association was stronger for rectal cancer (RR = 3.16; 95 % CI 1.40–7.08) than for other anatomic subsites [42].

In the Health Professionals Follow-up Study involving 34,544 men, a statistically nonsignificant positive association was seen between early-life body fatness and risk of colorectal cancer (RR = 1.04; 95 % CI 0.82–1.31) [42].

A large Israeli cohort comprising 1.1 million men showed that higher versus lower BMI during adolescence was associated with an increased risk of colon cancer but not rectal cancer [43]. Male adolescents in the highest BMI quintile had a 69 % higher risk of colon cancer compared to those in the lowest BMI quintile (95 % CI 1.24–2.29) [43].

A large Norwegian study showed that the risk of colorectal cancer mortality was higher in men and women whose BMI was $\geq$ 85th percentile compared to those with BMI within the 25–74th percentile during adolescence (age 14–19 years) [44]. The relative risks of colorectal cancer mortality were 2.1 (95 % CI 1.1–4.1) for men and 2.0 (95 % CI 1.3–3.5) for women [44].

The Harvard Alumni Health Study cohort showed that there was no statistically significant association between a higher BMI (by one standard deviation = 2.56 kg/m^2) in early adulthood and colorectal and colon cancer mortality [45].

Similarly, the Atherosclerosis Risk in Communities cohort found no statistically significant relations of early adulthood BMI to colorectal cancer incidence or mortality [46].

In conclusion, the existing literature on childhood and adolescent obesity and its relations to colorectal cancer risk is sparse. Studies differ substantially in their assessments and categorizations of exposures, and results are rather inconsistent. However, several studies found positive associations between obesity during childhood or adolescence and colorectal cancer. Although it is not clear how many colorectal cancer cases in adulthood might be prevented, there is some evidence that obesity in early life should be avoided.

6 Potential Biological Mechanisms Linking Obesity to Colorectal Cancer

Although there is convincing evidence linking obesity to colorectal cancer risk, the underlying biological mechanisms have not yet been fully elucidated. Obesity-induced insulin resistance, chronic inflammation, adipokines and sex hormones likely play a crucial role in the complex metabolic pathways in colorectal carcinogenesis.

6.1 Insulin Resistance, Hyperinsulinemia and Insulin-like Growth Factor

One of the main features of obesity is excess adipose tissue. Hypertrophic and dysfunctional adipocytes result in an increased release of free fatty acids (FFAs) [47]. By inhibiting insulin-stimulated glucose uptake (in skeletal muscle) and glycogen synthesis, elevated serum concentrations of FFAs lead to insulin resistance and hyperinsulinemia [48]. Tumorigenic effects of insulin may be direct through mediation of the insulin receptor (IR) in target cells, or indirect through influencing synthesis and biological availability of insulin-like growth factor 1 (IGF1) and sex hormones [49]. In vitro, both insulin and IGF1 have been shown to stimulate growth of both normal colorectal epithelial and carcinoma cells by promoting cell proliferation and inhibiting apoptosis [50].

Epidemiologic evidence has shown an increased risk of colorectal cancer in relation to clinical conditions associated with high levels of IGF1 (acromegaly) and insulin (type 2 diabetes mellitus) [51, 52]. For example, a meta-analysis reported a 21 % (95 % CI 1.02–1.42) increased risk of colorectal cancer in diabetic compared to non-diabetic individuals [51].

Supportive evidence also comes from serologic studies. A meta-analysis by Rinaldi and colleagues analyzed the findings from 10 prospective studies on IGF1 blood levels and colorectal cancer risk and showed that higher pre-diagnostic serum concentrations of IGF1 were modestly associated with risk of colorectal cancer [53]. Meta-analyses have consistently shown that higher levels of IGF, circulating

insulin and C-peptide (a marker for insulin production and hyperinsulinemia) were associated with an increased risk of colorectal cancer [53–55]. Similarly, higher levels of insulin and C-peptide have been shown to be associated with an increased risk of colorectal adenoma [56].

6.2 Chronic Inflammation

Obesity is considered a condition of chronic low-grade inflammation, and obesity-enhanced inflammation is mediated through adipose tissue macrophages that secrete pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and monocyte chemotactic protein 1 (MCP-1) [57]. Increased synthesis of acute phase proteins, such as C-reactive protein (CRP), and activation of pro-inflammatory pathways are further mechanisms related to obesity-induced inflammation [58]. For example, animal studies have shown that diet-induced obesity leads to an increase in colonic TNF-α and consecutively to an activation of the *Wnt* signaling pathway, which plays a critical role in colorectal carcinogenesis [59]. It has been shown that obesity is strongly associated with elevated levels of CRP in children and adults, whereby these associations were stronger in women than in men [60]. Similarly, IL-6 and TNF-α are positively associated with obesity [61]. Higher pre-diagnostic concentrations of CRP (a systemic marker of inflammation) have been found to be associated with elevated risk of colorectal cancer, particularly in men [62]. Furthermore, colorectal cancer patients have higher serum levels of IL-6 compared to healthy individuals [63], and higher IL-6 serum levels appear to be associated with increased tumor stage and size, greater metastasis and decreased survival [63].

The hypothesized association between chronic inflammation and colorectal carcinogenesis is supported by studies that investigated the relationship between chronic inflammatory bowel diseases (IBD)—Crohn's disease and ulcerative colitis—and colorectal cancer. There is strong evidence that individuals with IBDs have an increased risk of developing colorectal cancer compared to healthy individuals [64–66]. In addition, it has been shown that (long-term, low-dose and regular) use of aspirin (a nonsteroidal anti-inflammatory drug) is associated with a 20–26 % decreased risk of colorectal cancer [67].

6.3 Hypoadiponectinemia and Hyperleptinemia

Adipocytes secrete adiponectin and leptin—molecules that have been proposed to be involved in several steps of colorectal tumorigenesis.

Adiponectin is an adipose tissue-derived protein hormone which is expressed at high levels in healthy individuals and has several beneficial effects through

insulin-sensitizing, anti-angiogenic, anti-inflammatory and probably anti-carcinogenic properties [68]. Circulating adiponectin levels correlate inversely with BMI [69]. Animal and in vitro studies have shown that adiponectin reduces colon cancer cell proliferation, adhesion and invasion and directly inhibits angiogenesis [70].

Three meta-analyses have summarized the heterogeneous findings from epidemiologic studies and showed that adiponectin was inversely associated with risks of colorectal adenoma and colorectal cancer [71–73].

Leptin, a product of the *Ob* gene, is a hormone primarily produced by adipocytes, with higher serum concentrations in obese compared to normal-weight individuals [74, 75]. Leptin is involved in the regulation of energy homeostasis, neuroendocrine function, metabolism and immune function [76]. In vivo studies revealed proliferative and anti-apoptotic effects of leptin on cell growth [77].

The relationship between leptin concentrations and colorectal cancer risk in humans has been investigated in several epidemiologic studies, though with inconsistent results. Meta-analyses found no association between circulating leptin levels and colorectal cancer risk, but a positive association of serum leptin with colorectal adenoma was suggested [71, 78].

6.4 Sex Hormones

In an attempt to explain the apparent sex-specific discrepancies in the association between general obesity and colorectal cancer risk, differences in body composition between men and women and the influence of hormone status and hormone replacement therapy in postmenopausal women have been taken into consideration.

Epidemiologic studies investigating the relationship between endogenous estrogen levels with colorectal cancer risk showed inconsistent findings [79–81]. However, hormone replacement therapy (estrogen plus progestin) in postmenopausal women is related to decreased risk of colorectal cancer [82, 83]. Estrogen may act through genomic and non-genomic pathways, but its exact role in colorectal carcinogenesis remains unclear and further research is required.

6.5 Summary of Potential Biological Mechanisms

Although the exact mechanisms linking obesity with colorectal cancer development and progression are not completely elucidated, it appears biologically plausible that obesity-induced increased levels of insulin and IGF1 and obesity-associated chronic inflammation contribute to colorectal carcinogenesis. Furthermore, low levels of adiponectin and high levels of leptin may play a role in the complex pathways underlying colorectal cancer development. Other potential mechanisms such as the influence of estrogen are not understood in detail.

7 Summary and Future Research

The existing literature provides strong and consistent evidence that obesity is positively related to colorectal cancer. Both general obesity and abdominal obesity are associated with an increased risk of colorectal cancer development and with reduced survival among colorectal patients. In order to prevent obesity-associated colorectal cancer, the maintenance of normal weight and the avoidance of adult weight gain can be recommended to all individuals. The same holds true for colorectal cancer patients in order to improve treatment outcomes and survival.

Further research in this field is required in order to answer important questions such as the appropriateness of existing measures of obesity, the impact of obesity on colorectal cancer treatment outcomes, recurrence and survival, the effect of weight change throughout the life course and the role of childhood and adolescent obesity, the variation in risk according to sex and colorectal cancer anatomic subsite, and the underlying biological mechanisms.

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Obesity and Breast Cancer

Renée T. Fortner, Verena Katzke, Tilman Kühn and Rudolf Kaaks

Abstract

The relationship between adiposity and breast cancer risk and prognosis is complex, with associations that differ depending on when body size is assessed (e.g., pre- vs. postmenopausal obesity) and when breast cancer is diagnosed (i.e., pre- vs. postmenopausal disease). Further, the impact of obesity on risk differs by tumor hormone receptor status (e.g., estrogen (ER) and progesterone (PR) receptor) and, among postmenopausal women, use of exogenous hormones (i.e., hormone replacement therapy (HRT)). In the context of these complexities, this review focuses on associations between childhood and adolescent adiposity, general adiposity, weight changes (i.e., loss and gain), abdominal adiposity, and breast cancer risk and survival. Finally, we discuss potential mechanisms linking adiposity to breast cancer.

Keywords

Adiposity · Body fatness · BMI · Waist circumference · Waist hip ratio · Weight change · Somatotype · Breastcancer incidence · Breast cancer survival · Hormone receptor · Estrogen receptor · Progesterone receptor

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1 Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide (1.67 million new cases in 2012) and a leading cause of cancer mortality [1]. Age, age at menarche, first full-term pregnancy and menopause, parity, use of hormone replacement therapy (HRT), alcohol consumption, and postmenopausal obesity are among the established risk factors for disease. Obesity is a modifiable risk factor, but the relationship between adiposity and breast cancer risk is complex, and differs by tumor characteristics, menopausal status, and exogenous hormone use. We describe the association between body size, from childhood through post-menopause, and breast cancer risk and survival, and discuss the mechanisms linking adiposity to breast cancer risk.

2 Body Size Across the Life Course and Breast Cancer Risk

Higher adiposity has opposing effects on breast cancer risk, depending on a woman's menopausal status. Among premenopausal women, higher adiposity, in childhood or during adult life, is associated with decreased risk of breast cancer, while among postmenopausal women obesity increases risk [2, 3]. Interestingly, greater adiposity during childhood and adolescence is inversely associated with both hormone receptor-positive disease (i.e., tumors expressing estrogen (ER) and progesterone (PR) receptors) and receptor-negative disease. In contrast, obesity in adulthood has been found to be associated predominantly with ER+/PR+ breast cancer, and, in the case of postmenopausal obesity, with increased risk of ER+/PR+ disease only among women not using HRT. Of note, while the relationship between body size in pre- and postmenopausal women and subsequent breast cancer risk has been extensively investigated, it still remains somewhat uncertain until what point in the premenopausal period obesity is protective, and, similarly, from what point in the postmenopausal period obesity begins to show a deleterious effect.

2.1 Childhood Body Size

In several prospective cohort studies, larger recalled body size in childhood and adolescence has been found to be inversely associated with subsequent breast cancer risk, independently of current body mass index (BMI, kg/m^2) [3]. In the largest and most comprehensive study to date, Baer et al. investigated recalled childhood body size (ages 5 and 10 years; Fig. 1) and breast cancer risk among 188,860 women in the Nurses' Health Studies [4]. Women reporting larger body size in childhood had lower risk of breast cancer regardless of menopausal status at diagnosis and tumor hormone receptor status (e.g., RRs per 1-unit higher body size at age 5, premenopausal: 0.94 [0.90–0.97], postmenopausal: 0.93 [0.91–0.95]; RRs per 1-unit higher body size in adolescence: ER+/PR+: 0.92 [0.89–0.95], ER−/PR−: 0.85 [0.80–0.90]); results were essentially unchanged after controlling for BMI at age 18 or BMI at baseline

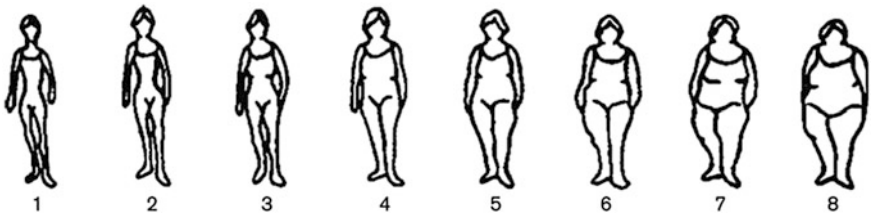

Fig. 1 Somatotype pictogram to assess body shape at different ages. Reproduced from Stunkard et al. [94]

recruitment (e.g., RRs per 1-unit higher body size at age 5, not adjusted for BMI at older ages RR: 0.93 (0.92–0.95), adjusted for current BMI, RR: 0.93 [0.91–0.95]), adjusted for BMI at age 18, RR: 0.95 [0.94–0.97]. Similar inverse associations have been observed in other prospective studies [3].

2.2 General Adiposity in Adulthood and Breast Cancer

2.2.1 BMI and Premenopausal Breast Cancer Risk

Consistent with larger childhood body size, obesity in adulthood is associated with lower breast cancer risk in premenopausal women [3], though this inverse association is observed only for hormone receptor-positive disease. For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, a 5 kg/m^2 higher BMI was associated with a 20 % decreased risk of ER+/PR+ breast cancer (RR: 0.80 [0.69–0.93]) among premenopausal women (age ≤ 49 years), but showed no association with ER−/PR− disease (RR: 0.90 [0.71–1.13], p heterogeneity = 0.44) [5]. Similar observations were made in the Nurses' Health Study II (RRs, per 1-unit higher BMI, ER+: 0.91 [0.84–0.99]; ER−: 1.03 [0.91–1.15]) [6].

2.2.2 Premenopausal BMI and Postmenopausal Breast Cancer Risk

The protective effect of larger body size in early adulthood persists into the postmenopausal period [4, 7–10]. In the most recent prospective investigation, Fagherazzi et al. [7] observed a 14 % decrease in risk of postmenopausal breast cancer for women reporting larger body sizes at age 20–25 years (RR, ≥4 vs. 1 on pictogram: 0.86 [0.74–1.00]). These results are in line with findings from another large cohort using the somatotype pictogram [4] and prospective investigations evaluating breast cancer risk and BMI at age 18 [8–10]. The protective effect of premenopausal BMI on postmenopausal breast cancer risk is likely strongest for ER+/PR+ tumors; however, risk differences by hormone receptor status are not well characterized.

Of note, Fagherazzi et al. observed no association between later premenopausal body size (ages 35–40 years) and postmenopausal breast cancer risk (RR, ≥4 vs. 1 on pictogram: 0.98 [0.82–1.18]). Further data in prospective settings are required to clarify until what point larger premenopausal body size is inversely associated with postmenopausal breast cancer risk.

2.2.3 Postmenopausal BMI and Breast Cancer Risk

In contrast to the inverse association between larger early adult body size and breast cancer risk, higher postmenopausal BMI increases risk, though this association appears to be limited to ER+/PR+ disease among women not using HRT [5, 8, 10–12]. This differential effect by HRT use has been consistently observed across studies, with few exceptions [13]. In the EPIC cohort, risk was 28 % higher for every 5 kg/m^2 higher BMI in women who had never used HRT, with no association observed among current HRT users (RRs ER+/PR+, HRT never users: 1.28 [1.18–1.38]; past users: 1.47 [1.26–1.72]; current users: 1.01 [0.91–1.12]). Further, in analyses cross-classified by both BMI and HRT use, higher BMI was associated with increased risk in a stepwise fashion among both never and past-HRT users, while risk of ER+/PR+ disease was more than twofold higher among current HRT users, regardless of BMI (all relative to HRT never users with BMI ≤ 22.5 kg/m^2; Fig. 2).

Fat-derived estrogens are widely considered the principal mechanism through which postmenopausal obesity impacts breast cancer risk. Adipose tissue expresses high levels of aromatase and represents a major source of endogenous estrogens in the postmenopausal period. In turn, postmenopausal endogenous estrogens, as well as exogenous hormones (i.e., HRT), increase breast cancer risk [14–16]. It is plausible that fat-derived endogenous estrogens are only etiologically relevant for breast cancer in the context of the lower estrogen environment experienced by postmenopausal women not using HRT, and that obesity, and its actions via endogenous estrogens, is not etiologically relevant in the context of exogenous hormone use.

On balance, data to date do not support a relationship between BMI and ER−/PR− disease [5, 11, 13, 17]. In the EPIC cohort, BMI > 25.9 versus ≤22.5 kg/m^2 was associated with an increased risk of ER−/PR− disease, but only among never HRT users (RR: 1.59 [1.08–2.34]) [5]. However, the impact of BMI on postmenopausal ER−/PR− disease is not fully understood, with few other studies examining risk of ER−/PR− disease by HRT use [12]. Possibly, some breast tumors presenting as receptor-negative tumors at diagnosis were still receptor-positive and hormone–response reflects earlier stages of development. There are limited prior data on obesity by other tumor classifications based on molecular phenotype [18], though existing

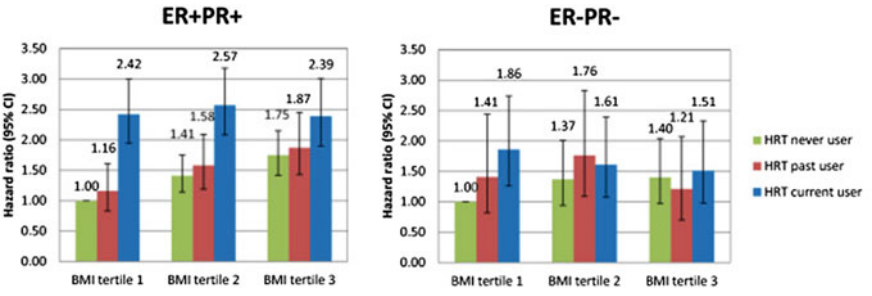

Fig. 2 BMI and risk of ER+ PR+ and ER− PR− tumors across HRT use categories, among postmenopausal women. HRT never users in BMI tertile1 serve as the reference category. BMI tertile cutpoints: T1: ≤22.5 kg/m^2; T2: 22.6–25.8 kg/m^2; T3: ≥25.9 kg/m^2 [5]

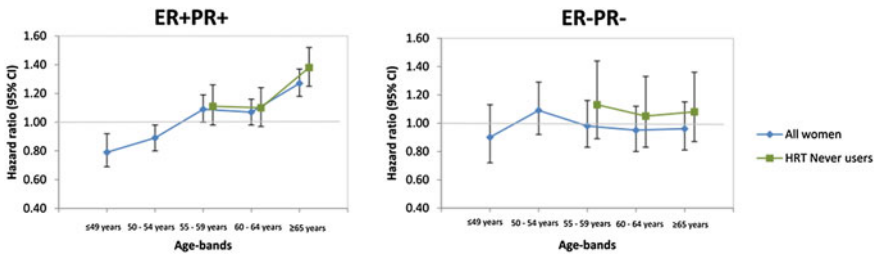

Fig. 3 Hazard ratios of ER+ PR+ and ER− PR− tumors for increases in BMI across age bands. All models are for a 5 kg/m^2 increase in BMI and were stratified by age at recruitment and study center [5]

data suggest obesity impacts androgen receptor (AR)-positive and androgen receptor-negative tumors similarly [19].

To date, it remains unclear precisely when in the postmenopausal period higher BMI begins to increase risk. Data from the EPIC cohort suggest BMI may become a relevant risk factor especially for breast cancer diagnosed at a more advanced, postmenopausal age. [5] evaluated risk in 5-year age bands (e.g., women 55–59 or 60–64 for both BMI assessment and diagnosis) to address the issue of timing (Fig. 3). In this investigation, higher BMI was significantly related to higher risk of ER+/PR+ disease among women aged 65 or older, but not significantly related to risk among women earlier in menopause (i.e., ages 55–64) [5].

These results suggest that it may take several years after the onset of menopause before the inverse association of excess adiposity with breast cancer risk among premenopausal women is offset, and gradually turned into a positive association. The findings by [5]. are in agreement with a pooled analysis of prospective cohort data by van den Brandt et al. which suggested postmenopausal BMI increases breast cancer risk after age 65 [20], but contrast with findings in the Women's Health Initiative which suggested stronger positive associations among younger postmenopausal women [10].

3 BMI and Breast Cancer-Specific Survival

Higher BMI is associated with poorer breast cancer-specific survival. A recent meta-analysis showed that overweight (25–29.99 kg/m^2) and obese (≥30 kg/m^2) women were at higher risk of breast cancer-specific mortality than normal weight women (18.5–24.99 kg/m^2) (RRs, overweight: 1.11 [1.06–1.17]; obese: 1.35 [1.24–1.47]), whether BMI was assessed before diagnosis, within one year after diagnosis, and at least 12 months after diagnosis [21]. In contrast to investigations on BMI and breast cancer risk, studies on BMI and breast cancer survival generally do not suggest strong heterogeneity by menopausal status or tumor hormone receptor status [21].

4 Weight Changes

Independently of BMI, adult weight gain has been found to increase breast cancer risk in many epidemiologic studies. In addition to the possible independent effect of weight gain on risk, this observation underscores the importance of maintaining a healthy weight, or minimizing weight gain [22].

4.1 Weight Gain and Risk of Premenopausal Breast Cancer

Data with respect to weight gain and premenopausal breast cancer risk are sparse and results are inconsistent. In a recent meta-analysis of three prospective studies, weight gain was not associated with premenopausal breast cancer risk [22]. In contrast, weight gain was associated with increased risk of premenopausal breast cancer in two subsequent evaluations in the EPIC cohort and the Nurses' Health Study (e.g., EPIC: RR, ≥0.83 kg/year weight gain vs. stable weight: 1.37 [1.02–1.85]) [23], and these associations persisted after adjustments for current [23] or average [24] BMI. In the Nurses' Health Study, weight gain was only associated with PR− tumors (i.e., ER+/PR−, ER−/PR−) and not with ER+/PR+ disease [24]; in the EPIC study, analyses by hormone receptor status among the premenopausal women were not reported.

Both studies investigated whether the impact of weight gain differed by baseline BMI at the time of recruitment into the cohort, with contradictory results. In EPIC, results were similar regardless of baseline BMI (RR ≥ 0.83 kg weight gain vs. stable weight, BMI < 25 kg/m^2: 1.23 [0.87–1.72]; BMI ≥ 25 kg/m^2: 1.42 [0.76–2.65]; p for heterogeneity >0.05) [23]. In the Nurses' Health Study, by contrast, weight gain was related to higher risk only among women leaner at baseline (RR per 11 kg weight gain, BMI < 25 kg/m^2: 1.65 [1.35–2.02]; BMI ≥ 25 kg/m^2: 1.02 [0.83–1.25]; p for heterogeneity <0.001) [24].

4.2 Weight Gain and Postmenopausal Breast Cancer Risk

As with overall postmenopausal obesity, adult weight gain is associated with postmenopausal breast cancer risk among women not using HRT (RRs per 5 kg increase, HRT nonusers: 1.11 [1.08–1.13]; HRT users: 1.01 [0.99–1.02]) [22] and according to recent meta-analyses appears to be more strongly associated with ER+/PR+ disease (RR: 2.33 [2.05–2.60]) than with ER−/PR− disease (RR: 1.34 [1.06–1.63]) [25]. However, it should be noted that two subsequent prospective analyses observed similar results regardless of HRT use and for both ER+/PR+ and ER−/PR− tumors [23, 24]. In most prospective studies, weight gain was associated with postmenopausal breast cancer risk irrespective of body size at baseline [24, 26–29], though three large studies, including recent analyses in the EPIC cohort and

Women's Health Initiative, reported stronger associations among women leaner at baseline [13, 23, 30].

4.3 Weight Loss and Breast Cancer Risk

Data to date do not support a relationship between weight loss and breast cancer risk, with most investigations observing no association [13, 23, 24, 26, 28, 31], or risk reductions only in subgroups of postmenopausal women (i.e., >10 kg weight loss after menopause and only in never HRT users (RR: 0.43 [0.21–0.86] [30]); >1 kg weight loss between ages 45–55 years (RR: 0.5 [0.3–0.9] [29]).

4.4 Weight Change and Breast Cancer-Specific Survival

Weight gain after breast cancer diagnosis is common [32, 33], but whether weight gain impacts breast cancer-specific survival is not fully understood. Weight gain of >10 % body weight was suggestively associated with increased risk of breast cancer-specific mortality in a recent meta-analysis (RR: 1.17[1.00–1.38]) [32]; it remains to be determined whether the effect of weight gain differs depending on baseline BMI. Clinical trials are underway to assess the effect of post-diagnosis weight loss on disease-free survival [34].

5 Visceral Adiposity: Waist Circumference/Waist-Hip Ratio

While imaging studies suggest that BMI is a valid parameter of general adiposity, it does not reflect the visceral fat compartment well [35]. Waist circumference (WC) and waist–hip ratio (WHR) provide measures of body fat distribution and are proxy measures of abdominal subcutaneous fat and of visceral adiposity. Independent of BMI, higher WC and WHR increase risk of several chronic diseases including other cancers, cardiovascular disease, and all-cause mortality [36–38] and accumulating evidence suggests WC and WHR may be risk factors for breast cancer [2, 39]. Whether the relationship between WC and WHR and breast cancer risk differs by tumor hormone receptor subtype has not been thoroughly explored in prior studies, though limited data to date suggest heterogeneity by tumor subtypes.

5.1 WC/WHR and Risk of Premenopausal Breast Cancer

On balance, data support a positive association between WHR and premenopausal breast cancer risk. Each 0.1 unit higher WHR was related to 8 % higher risk of

premenopausal breast cancer in a recent meta-analysis of 12 studies [40]. Few studies have investigated WC and WHR and premenopausal breast cancer by hormone receptor subtype, and results are conflicting. After adjusting for BMI, WC and hip circumference (HC) were not associated with premenopausal ER+/PR+ or ER−/PR− breast cancer in the EPIC cohort [5], whereas higher WC, HC, and WHR was related to higher risk of ER−breast cancer risk in the Nurses' Health Study II (e.g., WC ≥ 87 cm vs. <69 cm, RR: 2.75 [1.15–6.54], multivariable models including adjustment for BMI) [41]. Consistent with the results from EPIC, in the Nurses' Health Study no association was observed for premenopausal ER+/PR+ disease.

5.2 WC/WHR and Risk of Postmenopausal Breast Cancer

Prospective investigations suggest higher WC and WHR increase postmenopausal breast cancer risk. A meta-analysis restricted to cohort studies observed a 5 % increase in risk with each 8 cm higher WC (RR: 1.05 [1.00–1.10]) and a 19 % increase in risk of with each 0.1 unit higher WHR (RR: 1.19 [1.10–1.28]) [2]. However, data to date are not consistent [5, 9, 10, 26, 42–46].

Investigations on the relationship between WHR and WC with postmenopausal breast cancer classified by hormone receptor subtype are limited [5, 44, 45, 47]. In the largest study to date, from the EPIC cohort, larger WC was not associated with ER+/PR+ or ER−/PR− breast cancer risk in BMI-adjusted models (ER+/PR+, n = 3586; ER−/PR−, n = 1021); WHR was not included in this investigation [5]. In contrast, higher WC was related to higher risk of ER+ breast cancer, but not triple negative disease (i.e., ER−/PR−/HER2−), in the Women's Health Initiative (RRs WC $\geq$ 95 vs. <76 cm, ER+: 1.34 [1.09–1.64] n = 2610 cases; triple negative: 0.66 [0.37–1.20], n = 307 cases; after adjustment for BMI); WHR was not associated with either subtype [47]. Other prospective studies [44, 45] observed no association between WHR and WC and postmenopausal breast cancer by ER status. While there is some evidence that the association between WC and breast cancer risk may differ by HRT use [5, 47], this is not well characterized.

5.3 WC and WHR and Breast Cancer-Specific Survival

The impact of abdominal adiposity on survival after a breast cancer diagnosis is not established; however, data to date do not support an association between WC and breast cancer-specific mortality [48, 49], and the evidence for WHR is weak (e.g., RR, ≥0.867 vs. <0.763: 1.27 (0.98–1.65), p_{trend} = 0.04; n = 11,351 breast cancer cases) [48].

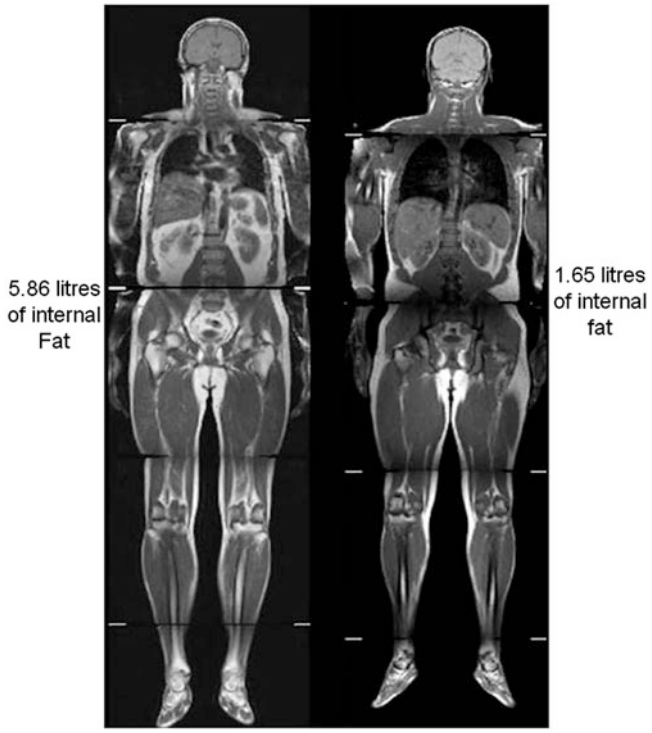

Fig. 4 Individuals with similar age, gender, BMI and same % body fat. Reproduced from Thomas et al. [95]

Body fat distribution versus general adiposity: Limitations of anthropometric exposure assessments

While general adiposity is well reflected by BMI, imaging data show that this is not the case for visceral adiposity (Fig. 4) [35, 50]. The use of alternative anthropometric parameters more directly reflecting visceral adiposity (e.g., WC and WHR) may not fully resolve this issue; however, anthropometric measures of adiposity in most large prospective investigations are limited to BMI, WC, and WHR.

An additional pitfall with the use of anthropometric parameters, especially in studies on breast cancer survival, is that muscle mass is not sufficiently captured [51]. It is plausible that sarcopenic adiposity, characterized by reduced muscle mass and abdominal fat accumulation, rather than overall adiposity, is related to worse prognosis in breast cancer patients [51, 52]. Although there is a lack of prospective patient trials, studies on other cancer types clearly indicate that both visceral fat accumulation and sarcopenic adiposity may be much more relevant for cancer progression than general adiposity [51]. Imaging studies to assess the effects of visceral and sarcopenic adiposity in breast cancer patients, as well as in the general population, are needed to achieve a better understanding of the role of different types of adiposity in cancer development and to facilitate a more precise quantification of risk estimates.

6 Potential Biologic Mechanisms

6.1 Endogenous Sex Hormones

Numerous observations document the relationships between breast cancer development and endogenous sex hormone metabolism. Cancer registry data worldwide show that before the average age at menopause of about 50 years breast cancer incidence rates increase more strongly with age than after the age of 50 [53]. Also, an older age at menopause, indicative of a longer cumulative period of premenopausal steroid hormone levels, is associated with increased risk of breast cancer; this is more strongly the case for ER+ than for ER− tumors [54]. These observations point to tumor-enhancing effects of ovarian sex hormones, notably estradiol, and possibly progesterone. Anti-estrogenic pharmacologic treatments with selective estrogen receptor modulators (SERMs) [55] or aromatase inhibitors (AIs) reduce the risk of ER+ breast tumor recurrences among cancer patients, and have also been shown to reduce first occurrence of breast tumors among high-risk women [56]. Conversely, the postmenopausal use of hormone replacements—especially combined estrogen-plus-progestin regimens, but to a lesser extent also regimens based on estrogen only—increases the risk of breast cancer, and this increase in risk consistently has been found to be stronger among women who are comparatively leaner and have a lower endogenous synthesis of estrogens [5, 47, 57].

Especially in postmenopausal women, the impact of adiposity on concentrations of circulating sex steroid hormones likely represents the main mechanism linking adiposity and breast cancer risk. Aromatase is a key enzyme in the synthesis and metabolism of sex steroid hormones (Fig. 5).

Aromatase activity is well known to be upregulated in the context of obesity, and adipose tissue is a major source of estrogens in postmenopausal women [58, 59]. Adiposity is consistently associated with higher concentrations of estradiol and estrone (e.g., estradiol, BMI ≥ 30 kg/m^2: 54.9 pmol/L; BMI < 22.5 kg/m^2: 30.0 pmol/L; [60]) in postmenopausal women [60–64]. Beyond total estrogen concentrations, obesity is associated with lower sex hormone-binding globulin (SHBG) (e.g., BMI ≥ 30 kg/m^2: 29.6 nmol/L; BMI < 22.5 kg/m^2: 52.8 nmol/L) [60], resulting in higher concentrations of bioavailable estradiol, as well as bioavailable testosterone, unbound to SHBG.

Prospective epidemiologic investigations have consistently documented direct associations between circulating endogenous estrogens (i.e., estradiol, estrone) and

Fig. 5 Synthesis of sex steroid hormones

postmenopausal breast cancer risk [14–16]. In a pooled analysis of eight cohort studies (total of 624 incident cases of breast cancer), the Endogenous Hormones and Breast Cancer Collaborative Group evaluated the mediation effect of postmenopausal sex steroid hormones on the association between BMI and postmenopausal breast cancer. In this analysis, which included only women not using HRT at the time of blood donation, a 5 kg/m^2 unit higher BMI was associated with a 18 % increase in breast cancer risk (RR: 1.18 [1.06–1.16]) before adjusting for hormone concentrations. This increase in risk was attenuated and no longer statistically significant after adjusting for estrogens, with the strongest attenuations observed for estradiol and free estradiol (e.g., RRs, after estradiol adjustment: RR: 1.07 [0.95–1.20]; after free estradiol adjustment: RR: 1.02 [0.89–1.17]) [60]. Very similar findings were noted in a study within the EPIC cohort (613 incident cases of breast cancer), again in support of a mediation effect of estradiol and free estradiol on the association between other anthropometric measures and breast cancer risk [61].

With regard to premenopausal breast cancer, the mechanisms underlying the inverse associations between childhood and adult life overall adiposity and risk are less well understood. One postulated mechanism [65] refers to reductions in ovarian progesterone synthesis, especially among more obese women, as consequence of obesity-induced ovarian hyperandrogenism [66]. This hypothesis gains some support from epidemiologic observations that, among postmenopausal women, use of combined estrogen-plus-progestin HRT induces a stronger increase in breast cancer risk than the use of estrogen-only formulations [57]. However, prospective studies have not observed significant associations between higher serum progesterone levels and increased breast cancer risk among premenopausal women [67, 68], although in the same studies a significant reduction in progesterone levels was observed for women with BMI > 30 kg/m^2 [67]. For estrogens, prospective studies among premenopausal women have shown a positive association between higher circulating estrogen levels and breast cancer risk [67, 68], as well as a weak inverse association between BMI and circulating total, but not bioavailable (calculated free, estradiol concentrations) [67].

Besides estrogens, prospective studies have shown increases in breast cancer risk among both pre- and postmenopausal women who have higher blood concentrations of androgenic steroid hormones, including androstenedione and testosterone [67–69]. Like estrogens, blood levels of androgens also show positive associations with BMI, among both pre- and postmenopausal women.

6.2 Insulin

Obesity and visceral adiposity are associated with insulin resistance, resulting in hyperinsulinemia and the metabolic syndrome [70], and insulin has been implicated in breast cancer due to its mitogenic and anti-apoptotic effects as a growth factor [70–73]. High insulin levels, furthermore, lead to increased levels of bioactive (free) IGF-I due to downregulation of IGF-binding proteins −1 and −2, and also lead to

increased blood levels of bioavailable testosterone and estradiol by downregulating the hepatic synthesis and blood concentrations of SHBG. Finally, in at least a subgroup of susceptible women, hyperinsulinemia can cause overstimulation of ovarian androgen synthesis, which in a small percentage (3–5 %) of premenopausal women can result in anovulatory menstrual cycles coupled with impaired progesterone synthesis (polycystic ovary syndrome; PCOS) [66, 74].

The above various observations have led to speculations that, in addition to alterations in estrogen metabolism, hyperinsulinemia could provide a major physiologic link between excess adiposity and breast cancer development [73, 75]. Prospective studies, however, have yielded somewhat conflicting results regarding the relationship between insulin levels and risk of breast cancer [76–80]. A study within the EPIC cohort (1141 cases, 2204 matched controls), which included only women who did not use any exogenous hormones (i.e., oral contraceptives; HRT) at the time of blood donation, found a variable, age-dependent association of breast cancer risk with C-peptide, a marker for pancreatic insulin secretion, and breast cancer risk [78]. Elevated serum C-peptide levels were associated with a reduced risk of breast cancer diagnosed up to the age of 50 years, but with an increase of breast cancer risk among women above 60 years of age, mimicking the age-dependent association of breast cancer risk with BMI [78]. A study within the Women's Health Initiative cohort (835 cases, 816 controls) showed a positive association of serum insulin concentrations with breast cancer risk among postmenopausal women not using HRT (top vs. bottom quartile, RR: 2.48 [1.38–4.47]), but no association among HRT users (e.g., estrogen and progesterone HRT, RR: 1.15 [0.34–3.84]), again mimicking associations observed between breast cancer risk and BMI [76]. Further, within this subgroup, insulin was most strongly associated with ER+ disease (top vs. bottom quartile, RR for ER+: 3.23 [1.62–6.49], $p_{trend} = 0.001$; ER−: 1.37 [0.57–3.25], $p_{trend} = 0.99$). Finally, a study within the Nurses' Health Studies (1084 cases, 1785 controls) showed an approximately 50 % increase in risk of invasive breast cancer for the top versus bottom quartile of serum C-peptide; associations were similar after adjustment for free estradiol and sex hormone-binding globulin [79]. In this latter study, however, the association was stronger for ER− disease (RR: 2.0 [1.2–3.6]) than ER+ disease (RR: 1.4 [1.0–2.0]), contrary to the associations observed in the WHI cohort. Furthermore, in contrast to data from the EPIC cohort, associations were similar for breast cancers diagnosed before and after menopause (top vs. bottom quartile, RR, postmenopausal women: 1.4 [0.79–2.5]: premenopausal women: 1.5 [1.1–2.0]). Taken together, while experimental evidence supports growth promoting effects of insulin on breast cancer cells [72], epidemiologic associations between serum insulin or C-peptide and breast cancer risk are inconsistent with regard to menopausal status, users and nonusers of HRT, and tumor ER status. Thus, at present the evidence for insulin as an independent physiologic link between adiposity and breast cancer development, further to estrogens, remains limited.

6.3 Insulin-like Growth Factor 1 (IGF-1)

IGF-I is a peptide with high structural homology to insulin, and plays a central role in regulating anabolic (growth) processes as a function of available energy and elementary substrates, particularly amino acids. IGF-I has well-documented effects on cell proliferation, differentiation, and apoptosis. Further, higher IGF-I may both increase sex steroid hormone synthesis and decrease SHBG concentrations, resulting in higher concentrations of circulating free estradiol and free testosterone [81].

Epidemiologic investigations support a role for IGF-I in breast cancer risk. A pooled analysis of nested case–control data from 17 prospective cohorts, including a total of 4790 incident cases of breast cancer and 9428 matched controls, showed a modest positive association of breast cancer risk with blood levels of IGF-I (top vs. bottom quintiles, RR: 1.28 [1.14–1.44], $p < 0.0001$). This association did not vary significantly by menopausal status at blood collection, but was restricted to ER+ (RR: 1.38 [1.14–1.68]). No association was seen for ER-negative tumors (RR: 0.80 [0.57–1.13]) (p for heterogeneity = 0.007) [82, 83]. A complementary study within the EPIC cohort (938 breast cancer cases and 1394 matched controls) observed similar findings (top vs. bottom quartiles, IGF-I and ER+ disease, RR: 1.41 [1.01–1.98]), and no association for ER− tumors [83]. These observations suggest synergism between IGF-I and estrogens in promoting breast tumor development—an interpretation that is in line with experimental findings [84]. Epidemiologic data, however, did not indicate any clear evidence for interaction between IGF-I and BMI, or between IGF-I and serum estrogen levels, among either post- or premenopausal women [82, 83].

Although the association of higher IGF-I with higher risk of ER-positive breast tumors is well documented, this association can provide only a marginal explanation for the observed epidemiologic relationships of breast cancer risk with adiposity. First of all, the association of IGF-I with breast cancer risk is relatively weak. More importantly, however, the relationship between BMI and serum total IGF-I concentration is nonlinear and shows modest increases in IGF-I with BMI increasing from less than 18 to about 26 kg/m^2, followed by a progressive drop in IGF-I concentrations as BMI levels increase further [82, 83, 85]. A more direct, linear relationship may exist between BMI and serum levels of free IGF-I, a small fraction (1–2 %) of circulating IGF-I that is unbound to IGF-binding proteins, rather than with total IGF-I [81, 86], and one might anticipate a stronger association of free IGF-I with breast cancer risk. However, due to complexities associated with assays for free IGF-I only few prospective studies on the relationship of free IGF-I with breast cancer risk have been conducted so far, and did not document any clear association [76].

6.4 Chronic Inflammation

Obesity has been characterized as a condition of low-grade chronic inflammation [87]. To a large extent, the inflammation is the result of increased macrophage

infiltration of adipose tissue. Adipocytes and macrophages synergize to increase the production of inflammatory mediators, including the pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [88]. The pro-inflammatory cytokines contribute to the development of obesity-related insulin resistance and hyperinsulinemia [89], and also play a key role in upregulating aromatase expression and activity [90].

Recent studies have shown that overweight and obesity-associated aromatase expression and activity (i.e., hormone alterations) correlate with inflammation in the breast tissue of women, and, additionally, that increased levels of cyclo-oxygenase-2 (COX2) and its product prostaglandin E2 (PGE2) contribute to elevated aromatase expression in inflamed breast tissue of obese women [91]. The inflammation was strongly related to the presence of crown-like structures, formed by macrophages around large, lipid-filled adipocytes which are present in the breasts of obese women, and the severity of breast inflammation, defined as the CLS-B (crown-like structure) index, was found to correlate with both body mass index and adipocyte size [92]. COX2 is also frequently expressed in breast tumors and correlates with tumor size and a worse disease-free interval. Observations suggest that PGE2 produced by the tumor directly increases aromatase activity in immediately surrounding adipose tissue [90]. The local production of estrogens, in turn, can further stimulate proliferation of the tumorous breast epithelium. Besides increasing aromatase activity and estrogen synthesis in breast tissue, the inflammatory response in adipose tissue also causes the systemic increase in circulating estrogen levels observed in obese women.

6.5 Summary: Biologic Mechanisms

Taken together, epidemiologic, clinical and experimental data indicate a dominant role of estrogens in the development of ER+ breast cancer, the breast tumor subtype most clearly associated with adiposity. Overweight and obesity may drive breast cancer development by increasing estrogen synthesis in adipose tissue. This increase is largely the result of an inflammatory response of adipose tissue, which is characterized by macrophage infiltration and the production of pro-inflammatory cytokines and PGE2. Recent findings suggest that the obesity–inflammation–aromatase axis is present in the breast tissue of most overweight and obese women, and is likely to contribute to the increased risk of hormone receptor-positive breast cancer and the worse prognosis of obese patients with breast cancer. In addition to increasing aromatase activity and estrogen synthesis in breast tissue, the inflammatory response in adipose tissue also causes the systemic increase in circulating estrogen levels observed in obese women. Increased circulating levels of insulin and bioactive IGF-I may contribute to breast tumor development by increasing bioavailable estrogen levels, or directly as growth factors (Fig. 6).

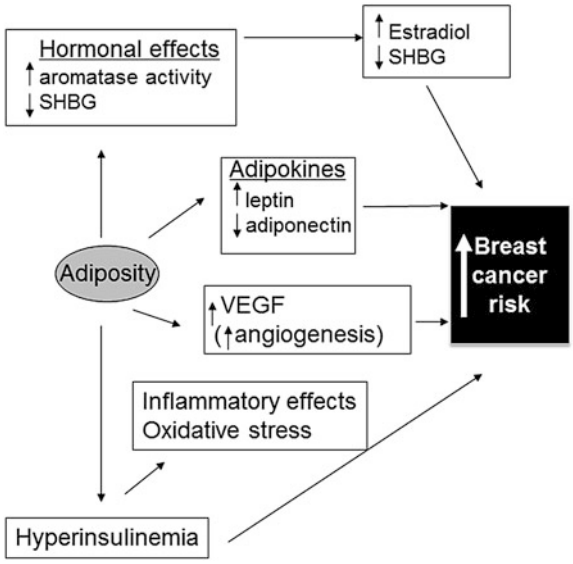

Fig. 6 Mechanisms linking adiposity and breast cancer

7 Summary and Conclusions

Higher adiposity has opposing effects on breast cancer risk, depending on the window of exposure (Table 1). Among premenopausal women, higher adiposity, in childhood or during adult life, is associated with decreased risk of both hormone receptor-positive and hormone receptor-negative disease. Conversely, postmenopausal obesity increases risk of hormone receptor-positive disease, though only among women not using HRT. It still remains uncertain until what point in the premenopausal period obesity is protective, and, similarly, from what point in the postmenopausal period onwards obesity begins showing a deleterious effect. Higher BMI is associated with poorer breast cancer-specific survival, irrespective of menopausal status or hormone receptor status of the tumor. As with postmenopausal BMI, weight gain increases risk of postmenopausal disease, though these effects may be limited to women not using HRT and appear to be predominantly impact risk of ER +/PR + disease. Data to date support a weak but significant positive association between WHR and pre- and postmenopausal breast cancer risk, with suggestive heterogeneity by tumor subtypes.

While the strengths of risk associations with respect to postmenopausal breast cancer risk may seem modest, it has been argued that approximately 10 % of all postmenopausal breast cancer cases worldwide, and up to 14 % of cases in North America and Europe, can be attributed to high BMI, given the high global

Table 1 Summary of anthropometric measures and breast cancer risk by menopausal status of exposure and at diagnosis

	Breast cancer risk		Mortality[a]
	Premenopausal	Postmenopausal	
Premenopausal exposures			
Childhood body size	↓[d]	↓[d]	[c]
BMI	↓ ER+/PR+	↓[d]	↑
Weight gain	↑[b]	↑ER+/PR+	[c]
WC and WHR	↑ ER−/PR−	[b]	[c]
Postmenopausal exposures			
BMI	*n.a.*	↑ HRT nonusers	↑
Weight loss	*n.a.*	↓[c, e]	[c]
Weight gain	*n.a.*	↑[e, d]	↑
WC and WHR	*n.a.*	↑[e] ER+/PR+	[c]

[a]Reflects associations for breast cancer-specific mortality among pre- and postmenopausal women
[b]Differences by ER/PR status not observed or not well established
[c]Not established
[d]Associations evident in both ER+/PR+ and ER−/PR−
[e]Effect may differ depending on HRT status

prevalence of adiposity [93]. These observations underscore the relevance of maintaining a healthy weight, or minimizing weight gain, as a strategy for modulating breast cancer risk.

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Obesity and Oesophageal Cancer

Katharina Nimptsch, Annika Steffen and Tobias Pischon

Abstract

A substantial increase in the incidence of oesophageal adenocarcinoma has been observed in Western countries during the past 30 years, which may be related to the parallel rise of the obesity prevalence. On the other hand, incidence rates of oesophageal squamous cell carcinomas, the other major histological type of oesophageal cancer, have remained relatively stable. Epidemiological research of the past decades has identified obesity as risk factor for oesophageal adenocarcinoma. Studies investigating general obesity as assessed by body mass index (BMI) provide evidence for a strong positive association with oesophageal adenocarcinoma. Studies investigating abdominal obesity in relation to oesophageal adenocarcinoma observed also positive associations, which may be independent of general obesity. Some studies indicate that early life obesity is also associated with higher risk of oesophageal adenocarcinoma, but it is as to date unclear whether these associations are independent of adult obesity. Part of the positive association between obesity and oesophageal adenocarcinoma may be explained through obesity-related mechanical promotion of gastroesophageal reflux disease, which is one of the main risk factors for oesophageal adenocarcinoma. Other lines of evidence point to an independent role of metabolic pathways modulating cell proliferation, apoptosis and cell growth

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such as pro-inflammatory cytokines, adipokines and insulin resistance, the role of which in oesophageal carcinogenesis is, however, as to date insufficiently understood. Studies investigating obesity in relation to squamous cell carcinoma observed inverse relationships, but the underlying mechanisms remain unclear.

Keywords
Obesity · Oesophageal cancer · Oesophageal adenocarcinoma · Gastro-oesophageal reflux disease

1 Introduction

Oesophageal cancer is ranked as ninth most common incident cancer and sixth most common cancer death by the Global Burden of Disease Cancer Collaboration [1]. With a five-year survival rate between 15 and 25 %, oesophageal cancer poses an immense burden of disease globally [2, 3]. Unlike many other common types of cancer, oesophageal cancer occurs more frequently in developing countries than in developed countries. Global incidence rates differ up to 20-fold, with highest observed incidence rates in countries in East and Central Asia and southern sub-Saharan Africa. There is a male predominance of oesophageal cancer, which occurs globally 2–3 times more often in men than in women [4]. Two major histopathological types of oesophageal cancer can be distinguished, i.e. squamous cell carcinoma and adenocarcinoma, which differ in aetiology and risk factors. Worldwide, squamous cell carcinoma is the predominant type of oesophageal cancer while adenocarcinoma is less common [3]. During the last 30 years, a substantial increase in the incidence of oesophageal adenocarcinoma has been observed in Western Europe, North America, and Australia, making it the most rapidly growing cancer in developed countries [5]. Although this rise may be partly related to better diagnostic techniques [6], the parallel rise in the obesity prevalence has been suggested as a possible explanation. Incidence rates of oesophageal squamous cell carcinomas on the other hand did not face substantial changes in incidence rates [5]. Tobacco use and alcohol consumption are the main risk factors for squamous cell carcinoma of the oesophagus [3], which together may account for half of squamous cell carcinoma cases [7]. Tobacco use is also a risk factor for oesophageal adenocarcinomas, but observed relative risks (RR) are weaker. Gastrooesophageal reflux disease (GERD), Barrett's oesophagus and obesity are the best-established and strongest risk factors for oesophageal adenocarcinoma [8]. Barrett's oesophagus is a pre-malignant lesion that may develop as a consequence of long-term GERD and is considered a precursor of oesophageal adenocarcinoma. Since GERD is more prevalent in obese than non-obese individuals, it has been suggested that obesity is positively related to Barrett's oesophagus and oesophageal adenocarcinoma mainly through GERD. On the other hand, several lines of evidence also

observed an association between obesity and oesophageal adenocarcinoma independent of GERD, suggesting that also indirect mechanisms such as alterations in obesity-related biomarkers may play an aetiologic role [9].

In the following chapter, the current epidemiologic evidence on the association between obesity and risk of oesophageal adenocarcinoma will be summarized, with special emphasis on the distinction between general obesity and body fat distribution and the role of obesity during early life. We will further review current knowledge on the impact of pre-diagnostic obesity on survival among oesophageal cancer patients. Finally, we will give an overview on the current knowledge on the biological mechanisms underlying the positive association between obesity and oesophageal adenocarcinoma. Furthermore, we will give an overview on the current knowledge on the association of obesity and squamous cell carcinoma.

2 Association Between Obesity and Oesophageal Adenocarcinoma Incidence

A number of epidemiological studies have investigated the association between obesity and risk of oesophageal adenocarcinoma. There are abundant studies investigating general obesity represented by body mass index (BMI), while fewer studies have investigated abdominal obesity, for instance represented by waist circumference or waist-to-hip ratio. The definition of the outcome varies from study to study: some studies report results on oesophageal adenocarcinoma alone, while others report results for oesophageal adenocarcinoma and the anatomically related gastric cardia adenocarcinoma combined.

2.1 General Obesity

A positive association between BMI and risk of oesophageal adenocarcinoma has been observed in a number of case–control and cohort studies, and several meta-analyses and pooled analyses have been conducted to summarize the existing evidence (Table 1). The first comprehensive meta-analysis was published in 2006 and investigated the association between BMI and adenocarcinomas of the oesophagus or gastric cardia [10] combining data from 2 cohort and 12 case–control studies. In this data synthesis, being overweight or obese (BMI $\geq$ 25 kg/m^2) was associated with a 1.7-fold (odds ratio (OR) 1.7, 95 % confidence interval (CI) 1.6, 1.9) higher risk of oesophageal adenocarcinoma (including studies that combined oesophageal and gastric cardia adenocarcinomas). When studies using a combined endpoint were excluded (leaving 1 cohort and 5 case–control studies for analysis), the association was slightly stronger (OR 2.1, 95 % CI 1.7, 2.4) and indicated a linear relationship. In a systematic review summarizing the evidence from epidemiological studies published between this first meta-analysis and May 2010, obesity (BMI $\geq$ 30 kg/m^2) was associated with a significantly higher risk of

oesophageal adenocarcinoma in all studies [6], with RR ranging from 2.5 to 11.3. Another meta-analysis on the association of BMI with oesophageal and gastric adenocarcinoma was published in 2013 and included 22 studies (12 case–control, 10 cohort studies) [11]. The results of this meta-analysis are generally in line with the previous meta-analysis: a positive association between overweight and obesity and risk of oesophageal or gastric cardia adenocarcinoma combined was observed (RR for overweight 1.71, 95 % CI 1.50, 1.96; RR for obesity 2.34, 95 % CI 1.95, 2.81). Risk estimates were higher when pooling data from case–control as compared with cohort studies, but associations were statistically significant for both study designs. No substantial sex differences were observed. Similar to the previous meta-analysis, the positive association with BMI was stronger for oesophageal adenocarcinoma (RR for overweight 1.87, 95 % CI 1.61, 2.17; RR for obesity 2.73, 95 % CI 2.16, 3.46) than for gastric cardia adenocarcinoma. In this meta-analysis, also a dose-response meta-analysis was conducted, estimating a 13 % higher risk of

Table 1 Summary of pooled analyses and meta-analyses on the association between overweight and obesity and risk of oesophageal adenocarcinoma

Publication	Data synthesis type	Number and design of included studies	Findings for oesophageal adenocarcinoma
Lindkvist et al. (2014)	Pooled analysis	7 prospective cohorts	Compared with BMI 18.5–25.0 kg/m^2 BMI 25.0–29.9 kg/m^2: RR 2.32 95 % CI 1.51, 3.57 BMI $\geq$ 30 kg/m^2: RR 3.29, 95 % CI 1.82, 5.95
Hoyo et al. (2012)	Pooled analysis	10 case–control studies, 2 prospective cohorts	Compared with BMI < 25.0 kg/m^2 BMI 25.0–29.9 kg/m^2, RR 1.54 95 % CI 1.26, 1.88 BMI 30.0–34.9 kg/m^2, RR 2.39, 95 % CI 1.86, 3.06 BMI 35.0–39.9 kg/m^2, RR 2.79, 95 % CI 1.89, 4.12 BMI $\geq$ 40 kg/m^2: RR 4.76, 95 % CI 2.96, 7.66
Turati et al. (2013)	Meta-analysis	12 case–control studies, 10 prospective cohorts	Compared with BMI < 25.0 kg/m^2 BMI 25.0–29.9 kg/m^2: RR 1.87 95 % CI 1.61, 2.17 BMI $\geq$ 30 kg/m^2: RR 2.73, 95 % CI 2.16, 3.46
Kubo et al. (2006)	Meta-analysis	12 case–control studies, 2 prospective cohorts	Compared with BMI < 25.0 kg/m^2 BMI 25.0–29.9 kg/m^2: RR 1.9 95 % CI 1.5, 2.4 BMI $\geq$ 30 kg/m^2: RR 2.4, 95 % CI 2.0, 2.8

Abbreviations: *RR* relative risk; *CI* confidence interval

oesophageal adenocarcinoma associated with 5 kg/m^2 higher BMI. However, the meta-analysis also revealed potential publication bias, which may indicate an overestimation of the true association. Adjustment for publication bias resulted in lower, but still statistically significant estimates for overweight and obesity.

In a pooled analysis using individual participant data from 12 epidemiological studies (10 case–control and 2 cohort studies), the association between BMI and oesophageal and oesophagogastric junction adenocarcinoma was investigated with special regard to potential effect modification by GERD or sex [9]. With respect to oesophageal adenocarcinoma, a strong positive dose-response association with BMI was observed, with risk estimates increasing linearly across BMI categories, up to an almost fivefold risk for a BMI $\geq$ 40 kg/m^2 (compared with BMI < 25 m/^{2}). These findings were multivariable adjusted for age, sex, smoking and study-specific adjustment variables and remained unchanged after additional adjustment for GERD in the five studies that collected information on GERD symptoms. Furthermore, the positive association between BMI and risk of oesophageal adenocarcinoma was similar in individuals with and without history of GERD symptoms. These observations suggest that also indirect metabolic pathways may explain part of the association between obesity and risk of oesophageal adenocarcinoma beyond the pathway via GERD. However, an analysis testing for interaction found evidence for synergism between BMI and GERD with respect to oesophageal adenocarcinoma risk, i.e. the joint effect of both exposures had a greater effect on the risk than would be expected from their independent effects. Similar associations between BMI and oesophageal adenocarcinoma were observed after stratification by sex, but there was some indication that sex may modify the association between BMI and oesophageal adenocarcinoma in individuals without GERD symptoms, which, considering the sex-specific differences in fat distribution, especially differences in the amount of metabolic active visceral fat, also points to a role of indirect metabolic pathways. BMI was also positively associated with adenocarcinoma of the oesophagogastric junction in a dose-response manner, but associations were less pronounced than with oesophageal adenocarcinoma. Compared with the study-level meta-analyses, this pooled analysis used individual-level data and harmonized variables and statistical models enabling targeted investigation of confounding, effect modification and interaction. However, the pooled studies had some limitations in common, which may also influence pooled findings. For instance, most of the pooled studies were case–control studies lacking the ability to investigate the time-sequence between obesity and oesophageal adenocarcinoma. In addition, BMI was derived from self-reported adult height and weight in all pooled studies, which may introduce misclassification bias. However, a positive association between BMI and risk of oesophageal adenocarcinoma was also observed in a consortium of seven prospective cohort studies from Austria, Norway and Sweden, in all of which weight and height weight were measured at baseline [12]. In the pooled analysis adjusted for sex, age and smoking status, overweight at baseline was associated with more than twofold higher (RR 2.32, 95 % CI 1.51, 3.57) and obesity with more than threefold (RR 3.29, 95 % CI 1.82, 5.95) higher risk of oesophageal adenocarcinoma compared with normal weight.

2.2 Abdominal Obesity

It has been suggested that abdominal obesity, reflecting the amount of metabolically active visceral fat, may be more important for the risk of Barrett's oesophagus and oesophageal adenocarcinoma than general obesity [13]. In particular, it has been proposed that abdominal obesity may be associated with Barrett's oesophagus and oesophageal adenocarcinoma independent of BMI and GERD. In a meta-analysis from 2013, abdominal obesity measured by waist circumference, waist-to-hip ratio or visceral fat determined by abdominal computed tomography (CT) was associated with risk of Barrett's oesophagus independent of BMI [14]. In addition, abdominal obesity was associated with risk of Barrett's oesophagus independent of GERD, while no association was observed with general obesity after adjustment for GERD symptoms. The association between both general and abdominal obesity and risk of oesophageal and gastric adenocarcinoma was investigated in the EPIC study [15]. In this prospective study with measured anthropometry at baseline, general obesity represented by BMI as well as abdominal obesity represented by waist circumference or waist-to-hip ratio were strongly positively associated with risk of oesophageal adenocarcinoma. After mutual adjustment, BMI was no longer associated with oesophageal adenocarcinoma, whereas both waist circumference and waist-to-hip ratio remained strongly positively associated (RR 3.76, 95 % CI 1.72, 8.22 and RR 4.05, 95 % CI 1.85, 8.87, respectively). On the other hand, in the large prospective NIH-AARP Diet and Health Study, where both general and abdominal obesity were associated with higher risk of oesophageal adenocarcinoma [16], the association with abdominal obesity (waist-to-hip ratio) was attenuated but not eliminated by simultaneous adjustment for BMI, while the association with BMI was only slightly attenuated. In a meta-analysis on the association between waist circumference and risk of oesophageal adenocarcinoma, five studies including findings from the NIH-AARP Study [16] and an earlier investigation of EPIC [17] were summarized [14]. This meta-analysis concluded that abdominal obesity is associated with higher risk of oesophageal adenocarcinoma, although substantial heterogeneity was present.

2.3 Association Between Obesity During Early Life and Risk of Oesophageal Cancer

Because carcinogenesis is a long process that may take several decades, it is possible that not only obesity during adulthood, but also earlier in life may impact cancer risk. There is some evidence from epidemiological studies that overweight and obesity during early childhood or adolescence are related to later risk of cancer, such as colorectal neoplasia [18, 19], independent of adult obesity. Also for oesophageal adenocarcinoma, early life body fatness may be of importance, since there is epidemiologic evidence that high BMI in children is associated with GERD [20]. So far

only few studies have investigated whether BMI during childhood or adolescence is related to later risk of oesophageal adenocarcinoma. In a study from Israel, more than one million men whose weight and height were measured during an obligatory medical board examination to assess their suitability for military service were followed for cancer incidence including oesophageal and gastroesophageal junction adenocarcinomas by data linkage with the National Cancer Registry [21]. Adolescent overweight (BMI $\geq$ 25 kg/m^2; mean age at examination was 17 years) was associated with more than twofold higher combined risk of oesophageal and gastroesophageal junction adenocarcinomas. In Denmark, the association between BMI during childhood (ages 7–13 years) and risk of oesophageal adenocarcinoma were investigated by linking the Copenhagen School Health Records Register with the Danish Cancer Registry [22]. Authors observed a linear positive association between childhood BMI and later risk of oesophageal adenocarcinoma, in particular for BMI from ages 10 years onwards. For example, per one unit higher BMI z-score at age 13 years, the risk of oesophageal adenocarcinoma during adulthood was 31 % higher (RR 1.31, 95 % CI 1.13, 1.51). It is a downside of both these studies that follow-up measures of BMI were not available. Thus, it could not be evaluated whether these associations are independent of adult overweight or obesity. Although tracking rates of early life overweight into adulthood appear to be moderate [23], the distinct effect of obesity throughout the life course should be addressed in long-term cohort studies with repeated anthropometry measurement.

3 Association Between Obesity and Squamous Cell Carcinoma

A number of studies have also investigated obesity in relation to squamous cell carcinoma, observing either no association or inverse relationships. A meta-analysis summarizing evidence from 7 case–control and 3 cohort studies estimated linear inverse associations (RR per 5 kg/m^2 higher BMI 0.49, 95 % CI 0.44, 0.55 for case–control; RR 0.69, 95 % CI 0.69, 0.75 for cohort studies) [24]. Overweight and obesity were also strongly inversely associated in a pooled analysis of prospective studies (RR for BMI $\geq$ 25 vs. 18.5–25.0 0.64, 95 % CI 0.47, 0.87) [12]. It has been discussed whether the consistently observed inverse association with obesity may be real or due to residual confounding, for instance by smoking, which is a strong risk factor for squamous cell carcinoma. In line with this hypothesis, a significant inverse association with obesity was only observed in smokers, but not in former or never smokers in the pooled analysis [12]. The biological mechanisms that could explain the inverse association remain unclear.

4 Association Between Obesity and Oesophageal Cancer Survival

Because oesophageal cancer is often diagnosed at advanced stages, the prognosis is generally poor with 5-year survival rates around 15 % [3]. The predominant determinants of survival from oesophageal cancer are the pathologic stage and tumour grade at the time of diagnosis [25]. Some studies have investigated whether risk factors of oesophageal cancer including obesity are also associated with survival, independent of clinicopathologic factors [26]. The studies investigating pre-diagnostic BMI in relation to survival among oesophageal cancer patients were heterogeneous, in particular with respect to the time of when BMI measures were determined or recalled: the definition of pre-diagnostic BMI varied from usual BMI [27] to BMI one year [28] or 20 years prior to diagnosis [29]. The first study investigated the association between usual BMI and survival in oesophageal adenocarcinoma patients and observed longer survival associated with usual overweight but not obesity [27]. In a nationwide Swedish study in oesophageal adenocarcinoma patients, overweight or obesity 20 years before diagnosis was associated with a tendency of better survival compared with normal weight [26, 29]. On the other hand, BMI one year prior to diagnosis was not associated with oesophageal adenocarcinoma survival in a study conducted in Australia [28]. A meta-analysis summarizing these studies concluded that pooled results were suggestive of pre-diagnostic overweight or obesity being associated with longer survival in oesophageal adenocarcinoma patients, although there was substantial heterogeneity among studies [26]. Authors of the meta-analysis also observed a suggestive association between overweight or obesity and better survival among oesophageal squamous cell carcinoma patients, summarizing evidence from four studies that also showed heterogeneity. A better survival associated with pre-diagnostic overweight or obesity is contrary to what is observed for other obesity-related types of cancer such as breast cancer [30] and colorectal cancer [31]. Although most studies adjusted for tumour stage, residual confounding by clinicopathological characteristics cannot be excluded. In addition, it could be speculated that the observed survival benefits are due to a higher likelihood of early diagnosis in obese individuals, since a higher BMI is associated with GERD and Barrett's oesophagus, both of which increase the likelihood of undergoing endoscopic examination which increases the chance of early detection and better survival. Finally, the observed association between pre-diagnostic obesity and better survival among oesophageal cancer patients may be consistent with a phenomenon commonly termed the "obesity paradox", which has also been observed for cardiovascular and metabolic diseases and may be related to reverse causation or a special form of selection bias, but could also indicate a true association [32].

5 Potential Mechanisms for the Association of Obesity with Oesophageal Adenocarcinoma

The mechanisms underlying the positive association between obesity and higher risk of oesophageal adenocarcinoma are not fully elucidated. The major hypotheses include mechanical effects of (abdominal) obesity promoting GERD on the one hand, and GERD-independent metabolic pathways on the other hand.

5.1 Pathways Related to Gastroesophageal Reflux Disease (GERD)

GERD is more common in obese individuals due to mechanically increased intra-abdominal pressure [6]. GERD is the main cause of Barrett's oesophagus, which is considered a precursor of oesophageal adenocarcinoma. It has been hypothesized that the obesity-related development of oesophageal adenocarcinoma follows a stepwise process leading from obesity-related GERD to Barrett's oesophagus and eventually to oesophageal adenocarcinoma [13]. Support for this hypothesis comes from the observation that BMI about two decades before cancer diagnosis is more strongly associated with risk of oesophageal adenocarcinoma than BMI closer to diagnosis [33, 34]. On the other hand, studies showing that the positive association between obesity and risk of oesophageal adenocarcinoma persisted after adjustment for GERD symptoms, and was observed in individuals with and without GERD symptoms, are in favour of the hypothesis that obesity and GERD are independent risk factors [9]. Further support for a GERD-independent pathway comes from a Mendelian Randomization study showing that a genetic risk score for obesity was unrelated to gastroesophageal reflux symptoms, but was associated with higher risk of Barrett's oesophagus and oesophageal adenocarcinoma [35]. Taken together, these observations suggest that an indirect metabolic pathway may link obesity with oesophageal adenocarcinoma in addition to GERD-related mechanisms.

5.2 Metabolic Pathways

Adipose tissue, in particular visceral adipose tissue, results in altered concentrations and/or bioavailability of a variety of endogenous hormones such as insulin, proinflammatory cytokines and adipokines such as leptin and adiponectin. These metabolic factors may influence carcinogenicity by modulating cell proliferation, apoptosis and cell growth [36]. In particular, obesity can be considered a state of chronic low-grade inflammation due to the production of pro-inflammatory cytokines such as TNF-alpha or IL-6, which may exert systemic as well as local mediating effects [37]. It has been suggested that these pro-inflammatory processes may promote oesophageal metaplasia and carcinogenesis independently or

synergistically with GERD symptoms [14]. Such a synergistic effect may be explained by an exacerbating effect of a pro-inflammatory environment on local inflammation due to reflux-related gastric acid exposure at the oesophagogastric junction, which may then lead to metaplasia and development of oesophageal adenocarcinoma [37].

Compared with other obesity-related types of cancer such as colorectal cancer or postmenopausal breast cancer, high-quality epidemiologic evidence relating obesity-related metabolic markers to risk of oesophageal adenocarcinoma is scarce. However, several studies have investigated the association between metabolic biomarkers and risk of Barrett's oesophagus, which is considered a precursor lesion of oesophageal adenocarcinoma. For instance, a case–control study among individuals undergoing oesophagogastroduodenoscopy showed that circulating leptin and pro-inflammatory cytokines were positively associated with Barrett's oesophagus [38]. In addition, it has been observed that among individuals with GERD symptoms high concentrations of the anti-inflammatory low-molecular weight adiponectin are associated with lower risk of Barrett's oesophagus [39]. Findings from another case–control study suggest that blood concentrations of leptin and adiponectin mediate part of the positive association between obesity and risk of Barrett's oesophagus [40]. There is also some evidence for the insulin and insulin-like growth factor-1 (IGF-1) axis playing a role in obesity-related development of oesophageal adenocarcinoma [41–43]. However, there is an urgent need of well-designed epidemiological studies, for instance nested case–control studies of prospective cohorts in order to clarify the role of obesity-related metabolic biomarkers in the development of oesophageal adenocarcinoma.

6 Summary and Outlook

Epidemiological research of the past decades has provided strong evidence for overweight and obesity as risk factors for oesophageal adenocarcinoma. Thus, the latest scientific evidence up to today remains in line with the 2007 report of the World Cancer Research Fund and the American Institute for Cancer Research, in which the evidence for body fatness as risk factor for oesophageal adenocarcinoma was judged as "convincing" [44]. Recent epidemiological studies have extended previous evidence by indicating the importance of abdominal obesity for oesophageal cancer risk. The association of abdominal obesity with oesophageal adenocarcinoma may be even independent of general obesity, as has been demonstrated in recent analyses from large prospective cohort studies.

Part of the positive association between obesity, in particular abdominal obesity, and oesophageal adenocarcinoma may be explained through obesity-related mechanical promotion of GERD, which is one of the main risk factors for oesophageal adenocarcinoma. On the other hand, the observed GERD-independent positive association between obesity and risk of oesophageal adenocarcinoma points to metabolic pathways modulating cell proliferation, apoptosis and cell

growth such as pro-inflammatory cytokines, adipokines and insulin resistance. The specific role of obesity-related biomarkers in oesophageal cancer development, however, is as to date insufficiently understood and deserves further attention in future research. In particular, there is a need of prospective investigations of a large variety of obesity-related biomarkers, in order to study the complex interrelations of potentially mediating pathways in oesophageal adenocarcinoma risk. Furthermore, the role of overweight and obesity throughout the life course, and in particular the association between early life independent of adult overweight and obesity should be addressed in long-term prospective investigations monitoring anthropometric measures throughout the life course. Also a potentially protective role of weight loss in relation to oesophageal adenocarcinoma risk should be addressed in well-designed studies.

In conclusion, the state-of-the-art epidemiological knowledge suggests a strong association of general obesity and in particular abdominal obesity with risk of oesophageal adenocarcinoma. These associations support the hypothesis that at least part of the increase in oesophageal adenocarcinoma incidence rates that has been observed particularly in Western countries may be due to the parallel increase in obesity prevalence. On the other hand, incidence rates of squamous cell carcinoma of the oesophagus have remained relatively stable. There are still aspects in the role of obesity in relation to oesophageal cancer that remain to be elucidated in well-designed future epidemiological studies. These investigations may pave the way for targeted prevention of oesophageal cancer through lifestyle or medical interventions.

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Obesity and Kidney Cancer

Kathryn M. Wilson and Eunyoung Cho

Abstract

Renal cell cancer (RCC) is the major type of kidney cancer with increasing incidence. Obesity is one of the well-established risk factors for RCC. Meta-analyses including multiple cohort and case–control studies have found a consistent positive association between obesity and RCC. The association appeared to be independent of other RCC risk factors including hypertension and has been often stronger in women, although a positive association has also been observed in men. Obesity has been largely measured as body mass index (BMI). Studies which evaluated other measures of obesity including waist circumference (WC), waist-to-hip ratio (WHR) as well as increase in weight have reported similar positive associations with RCC. Although the mechanisms by which obesity influences renal carcinogenesis have been under-explored, insulin resistance and certain growth factors including insulin-like growth factor (IGF-1), sex steroid hormones, and biochemical markers such as adiponectin may be involved. The positive association with obesity has been observed with

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the clear cell type of RCC, which is the major histological subtype. On the other hand, the association between obesity and RCC survival appears to be much more complex. An apparent inverse association between obesity at time of diagnosis and RCC survival has been observed in some studies, generating speculation of an "obesity paradox" hypothesis. However, this "paradox" may be due to reverse causation, selection bias, or other forms of bias rather than a true biological association.

Keywords
Obesity · BMI · Renal cell carcinoma · Cancer survival · Obesity paradox

1 Introduction

In 2012, there were an estimated 338,000 new cases of kidney cancer worldwide and 144,000 deaths due to kidney cancer [1]. Kidney cancer is made up of renal cell cancer (RCC), which arises from the epithelium of the renal tubules, and cancer of the renal pelvis. Cancers of the renal pelvis appear to have more in common with bladder cancer. Only RCC, which comprises 80–90 % of adult kidney cancers, will be addressed in this chapter.

RCC is itself comprised of multiple histological subtypes including clear cell (75–80 % of cases), papillary (10–15 % of cases), chromophobe, and collecting duct as the most common histological subtypes [2]. While there is some indication that risk factors for these subtypes may differ, few studies have had sufficient case numbers of non-clear cell type RCC to examine them separately.

RCC does not usually show symptoms (pain, hematuria, or constitutional symptoms) until the tumor is relatively large. Locoregional and distant metastatic spread are common at the time of diagnosis. Furthermore, 30–40 % of patients treated with surgery experience relapse with distant metastases. Incidence of RCC has been rising in the USA [3]. Although incidental detection by increased abdominal imaging for many different medical conditions (e.g., hypertension, diabetes) might have contributed to the rising incidence, increase in incidence of all stages of RCC suggests that other factors may also contribute to the increase in incidence [4, 5].

Well-established RCC risk factors include smoking, obesity, and hypertension [6]. Other risk factors relatively recently identified include parity, alcohol consumption, history of diabetes, and use of analgesics. RCC is also more common in men than women [7]. Overweight and notably obesity are well-established risk factors for RCC in both women and men. The proportion of all cases of RCC attributable to overweight and obesity has been estimated to about 40 % in the USA and up to about 30 % in European countries [8, 9].

The majority of epidemiological studies have used body mass index (BMI) as a measure of obesity, though some studies have used WC and/or WHR. Studies have varied in terms of dealing with possible confounding by hypertension and smoking, two other well-established risk factors for RCC; however, the association with obesity appears fairly consistent in spite of differences in study designs and statistical analyses.

The relationship between obesity and survival among RCC patients is much less clear. Many studies have found that obesity measured around the time of diagnosis or treatment is associated with improved survival. The observation of an increased risk of disease but improved survival with obesity has been called an "obesity paradox;" such paradoxes have been described in multiple diseases, including type 2 diabetes [10] and congestive heart failure [11]. However, this "paradox" may be due to reverse causation, selection bias, or other forms of bias rather than a true biological association.

In this chapter, we will review the evidence on obesity and both incidence and survival in RCC and will also discuss possible mechanisms and important methodological issues involved in the study of obesity and RCC.

2 Body Mass Index and Risk of RCC

A 2014 meta-analysis of 21 cohort studies with 15,144 cases and 9,080,052 participants was the most recent and comprehensive meta-analysis of BMI and RCC. The study found increased risks of RCC associated with higher BMI [12]. The pooled relative risk of overweight (BMI 25 kg/m^2 ≤30 kg/m^2) was 1.28 (95 % CI 1.24–1.33) and of obese (BMI ≥ 30 kg/m^2) was 1.77 (95 % CI 1.68–1.87) [12]. There was no evidence of heterogeneity across studies. The Egger's test to test for publication bias showed a possibility of publication bias (p = 0.001), although the Begg's test, another test for publication bias, was not significant (p = 0.16). Relative risks were somewhat stronger for women than for men (RR for obesity of 1.63, 95 % CI 1.50–1.77 for men; 1.95, 95 % CI 1.81–2.10 for women) [12]. The association was also slightly stronger among Asian studies than those conducted in North America or Europe. Although most of the included studies adjusted for age and smoking status, many of the studies did not adjust for some potentially important confounders including hypertension, physical activity, and alcohol consumption. The meta-analysis also omitted a few prospective studies including Rapp et al. (137 cases from Austria) [13], Somanic 2006 (820 cases from Sweden) [14], Kuriyama et al. (5 cases from Japan) [15], and Tulinius et al. (58 cases from Iceland) [16]. An earlier meta-analysis of 17 prospective studies evaluated BMI and incidence of cancer overall. RCC was evaluated as part of it. Many of the studies included overlapped with the 2014 meta-analysis. The three studies omitted in the 2014 meta-analysis were included in this meta-analysis. The meta-analysis found that a 5 unit higher BMI was associated with a 24 % increase in RCC risk for men (95 % CI 15–34 %) and a 34 % increase in risk for women (95 % CI 25–43 %)

[17]. Among the 6 studies that included both men and women, the increase in risk per 5 unit higher BMI was 18 % (95 % CI 8–29 %) in men and 35 % (95 % CI 29–42 %) in women, a statistically significant difference by sex (p value = 0.004) [17]. On the other hand, a dose–response meta-analysis in the American Institute of Cancer Research Continuous Update Project kidney cancer report combined 17 studies (both case–control and cohort) and found a 29 % increased risk for men and a 28 % increase for women associated with a 5 unit higher BMI [18]. Therefore, there was a consistent positive association between BMI and RCC risk in studies conducted in North America, Europe, and Asia in all 3 of the meta-analyses often with dose–response manner. The analyses also consistently reported stronger association in women than in men. The population attributable risks attributable to excess BMI were 11.2 % in men and 17.1 % in women based on data from 30 European countries based on Globocan 2002 [19]. Using the same data, the estimated incident cancer burden attributable to excess BMI (BMI ≥ 25 kg/m^2) was 4520 cases in men and 3786 cases in women.

3 Waist Circumference, Weight Change, and Risk of RCC

WC and WHR provide an estimate of abdominal or central obesity, a powerful contributor to metabolic abnormalities such as insulin resistance and hyperinsulinemia. Several studies have examined WC, WHR, and risk of RCC and found positive associations. [20–24] Four of these studies also examined WC or WHR with adjustment for either BMI or body weight to examine independent effects. In women, two studies found that WHR was significantly associated with RCC risk independent of body weight [20, 23], whereas one study found that WHR was no longer associated with risk upon adjustment for body weight [21]. In men, WHR but not WC was associated with RCC risk in one study, and the WHR associated was independent of body weight [21]. In another study, WC was associated with RCC risk both with and without adjustment for BMI [24]. The AICR Continuous Update Project report meta-analysis combined 3 studies [21, 23, 24] for a relative risk of 1.11 (95 % CI 1.05–1.19) for a 10 cm higher WC [25].

Weight change has been examined in four studies. One study among postmenopausal women found that those who gained weight during the study period were at nonsignificantly increased risk of RCC (adjusted RR 1.3, 95 % CI 0.9–1.8) [23]. In addition, women who gained and lost more than 4.5 kg were at increased risk (adjusted RR 1.5, 95 % CI 1.1–2.0), with increased relative risks for those with more episodes of weight fluctuations [23]. A population-based case–control study also found an association between 2 or more weight loss periods and risk of RCC among women, but not among men [26]. A large cohort study of men and women found that weight gain in early adulthood (18–35 years) and mid-adulthood (35–50 years) was associated with increased risk of RCC, whereas weight gain after age 50 was not related to risk [22]. A population-based case–control study found that weight gain was a risk factor for RCC among women, but not among men [27].

4 Interpretation and Possible Mechanisms for Risk Associations

The findings for BMI and risk of RCC are remarkably consistent. The AICR Continuous Update Project found 21 studies including 30 relative risk estimates for BMI and kidney cancer risk; of these, 28 showed a positive association between BMI and risk, and 14 were statistically significant [25]. The findings for WC and weight change are also quite consistent. While each of these measures has limitations, the consistency across measures suggests a true underlying association between obesity and RCC risk.

It is somewhat difficult to separate the effects of obesity from related risk factors for RCC, particularly hypertension. However, the 2014 meta-analysis found similar associations with obesity among 7 studies that adjusted for hypertension and 14 studies that did not [12]. The relative risk of obesity among studies with adjustment for hypertension was 1.93 (95 % CI 1.74–2.16) and among studies without adjustment was 1.72 (95 % CI 1.62–1.83) [12]. Associations were also consistent across studies with and without adjustment for alcohol intake, smoking, and physical activity. Thus, the association between obesity and RCC appears to be independent of these other RCC risk factors.

The mechanisms by which obesity influences renal carcinogenesis are not clear, but several plausible explanations exist. RCC has been described as a "metabolic disorder" [28]. The genes associated with kidney cancer are all associated with cells' ability to sense oxygen, nutrients, and energy. In addition, type 2 diabetes and hypertension—both of which are also related to metabolic syndrome—are associated with risk of RCC [29]. This suggests a role of insulin along with the interrelated hormonal systems of insulin-like growth factor (IGF) axis, sex hormones, and adipokines.

Obesity is associated with insulin resistance and increased levels of growth factors such as insulin-like growth factor (IGF)-I. It is also related to decreased levels of sex hormone-binding globulin and progesterone and to anovulation in women. The IGF pathway may be especially important for clear cell RCC which is strongly related to the von Hippel–Lindau (VHL) tumor suppressor gene, which in turn helps regulate IGF-I-mediated cell signaling [30]. The VHL tumor suppressor gene leads to an autosomal dominant familial syndrome called VHL syndrome, which is characterized by multiple RCCs. VHL is a critical player in renal carcinogenesis, especially for clear cell type. The VHL gene is directly related to IGF-I-mediated cell signaling, which in turn is inhibited in the presence of the wild-type VHL gene. Sex steroid hormones may affect renal cell proliferation and growth by direct endocrine receptor-mediated effects, by regulation of receptor concentrations, or through paracrine growth factors such as epidermal growth factor. Adiponectin, an adipokine involved in regulating glucose and fatty acid metabolism, has been associated with RCC risk in case–control studies [31, 32] and in a prospective nested case–control study among male smokers [33].

5 Obesity and RCC Subtypes

The association between obesity and histological subtypes of RCC has been examined in only a few studies. An analysis of two case–control studies of RCC, one from the USA and one from Europe, found that BMI was associated with increased risk of clear cell (OR 1.2, 95 % CI 1.1–1.3 per 5 kg/m^2 higher BMI) and chromophobe (OR 1.2, 95 % CI 1.1–1.4) but not papillary RCC (OR 1.1, 95 % CI 1.0–1.2, p value for difference from clear cell = 0.006) [34]. Combined there were 1524 clear cell cases, 207 papillary cases, and 50 chromophobe cases. The US study was a population-based case–control study, and the European study was a hospital-based case–control study. Hospital-based case–control studies of body size measures are difficult due to the wide range of conditions associated with obesity, making selection of controls difficult. However, results were similar when the 2 studies were analyzed separately.

An Italian hospital-based case–control study also found a suggestion that higher BMI at age 30 was more strongly associated with clear cell than with non-clear cell histology (p value for interaction = 0.08) [35]. There were 398 clear cell cases and 147 non-clear cell, of whom 34 % were papillary, 7 % were chromophobe, and 59 % were unclassified. Only 3 of the non-clear cell cases were in the BMI ≥ 30 group at age 30, limiting statistical power in this group. In an analysis of WHR at the time of the study, there were similar positive associations between WHR and RCC risk of both clear cell and non-clear cell subtypes. As this was also a hospital-based case–control study, again the difficulty of appropriately selecting controls for studies of obesity or body size should be noted.

Several clinical cohorts of patients treated surgically for localized RCC have examined the cross-sectional association among cases of obesity at the time of diagnosis and histological subtypes. Among 706 patients surgically treated for localized RCC in Korea, abdominal obesity as measured by visceral adipose tissue percent (VAT%) (measured by CT scan) was associated with relatively more clear cell and chromophobe cases and fewer papillary cases [36]. However, a study of 285 patients found an increased risk associated with higher visceral adiposity of clear cell and papillary, but not chromophobe RCC [37].

Thus, obesity seems to be related to clear cell RCC; this is not surprising given that clear cell is the most common subtype, so it plays a major role in driving the overall association between obesity and RCC risk. The relation of obesity and the less common subtypes is less certain at this point.

6 Obesity and Stage and Grade at Diagnosis of RCC

The American Joint Committee on Cancer (AJCC) TNM staging for RCC, last updated in 2010, stages RCC based on primary tumor size, involvement of adjacent structures (adrenal gland, renal vein, vena cava), involvement of lymph nodes, and distant metastasis for anatomic staging [38]. Stage is a strong predictor of

prognosis; 5-year relative survival is 92 % among those with localized disease, 65 % among those with regional spread, and 12 % with distant metastasis [39].

Multiple grading systems have been suggested in RCC. Fuhrman grade, a four level nuclear grading system put forward in 1982, is the commonly used. It is now used only in clear cell and papillary subtypes and is a prognostic factor for those subtypes independent of stage [40, 41].

Obesity is significantly or suggestively associated with lower stage of disease at diagnosis in most clinical studies that have examined this question [42–50]. While obesity is not always significantly associated with lower T stage, it is almost always associated with less N1 or M1 disease. Several studies also found that obesity was associated with lower risk of presenting with symptoms [42, 45, 48, 49], while only one study found no association between obesity and symptoms at presentation [43], suggesting that obese patients may be more likely to be diagnosed incidentally in the course of other imaging studies.

Obesity is associated with lower grade, though this association is weaker than that seen for stage. Of seven clinical cohorts examining the cross-sectional association between obesity and Fuhrman grade, obesity was associated with significantly lower grade in three studies [42, 45, 47], a suggestive but nonsignificant chance of lower grade disease in three studies [44, 48, 49], and no suggestion of an association with grade in one study [43].

It should be noted that almost all of these studies are of surgically treated patients, so there is some possibility of selection bias if obesity is related to the likelihood of undergoing surgery with curative intent as the primary treatment.

7 Obesity and RCC Survival

Two cohort studies have examined kidney cancer mortality as an outcome, with a combined 1427 deaths [25]. The pooled relative risk per 5 unit higher BMI was 1.32 (95 % CI 1.01–1.71). This was almost identical to the relative risk of kidney cancer incidence of 1.30 found across 21 studies [25]. Unlike these cohort studies of kidney cancer mortality, multiple clinical cohorts of patients treated for RCC have found that in case-only analyses, obesity measured at the time of diagnosis or treatment was associated with improved survival [49, 50]. This has given rise to an "obesity paradox" which stipulates that while obese people are more likely to be diagnosed with RCC, they appear less likely to die of the disease.

A meta-analysis [49] of 15 studies of BMI and cancer-specific mortality found a pooled relative risk of 0.66 (95 % CI 0.53–0.81) for a five unit higher BMI. Almost all of the included studies adjusted for age and stage, and most also adjusted for grade. However, most studies did not adjust for hypertension, and only one adjusted for smoking. There was evidence of significant heterogeneity across studies and evidence of publication bias. The heterogeneity may be partially explained by geographical differences, with a stronger association in Asian compared to European and American studies, and to adjustment for the presence of symptoms at

diagnosis, with a stronger association in studies that adjusted for the presence of symptoms. The association was weaker (less protective) in studies that adjusted for histological subtype. Sex does not appear to have been examined as a source of heterogeneity in the meta-analysis. However, a Japanese study of 435 patients surgically treated for RCC found that obesity was associated with better prognosis in men, but not in women [51].

7.1 Visceral Adiposity

Several clinical studies have assessed survival based on visceral adiposity measured by CT scan around the time of diagnosis. Visceral, or intra-abdominal, fat is more metabolically active and has been associated with poorer health outcomes compared to subcutaneous fat. Two studies of visceral fat area (VFA), an absolute measure of fat mass, found conflicting results. A study of over 2000 patients treated with nephrectomy found that VFA below the median was associated with worse cause-specific and overall survival, independent of stage and grade, among those with stage T3/T4 disease, but not T1/T2 disease [52]. A smaller study of 285 surgically treated non-metastatic RCC patients found that lower VFA was associated with worse survival in T1/T2 disease and in clear cell RCC, but not in the full cohort of T1–T4 disease and across histological subtypes [37]. One other smaller study of 220 clear cell RCC patients found no associations between VFA and overall survival, though as in other studies, BMI was associated with improved survival [53].

A study of 706 surgically treated patients found a U-shaped relation between VAT%—i.e., the proportion of visceral to total adipose tissue—and RCC recurrence, with greater risk among those in the bottom and top quartiles of VAT% [36].

7.2 Histological Subtypes and Survival

A study of 2769 patients surgically treated for non-metastatic RCC in Korea found that higher BMI was associated with significantly improved cancer-specific survival in clear cell RCC, with significantly worse cancer-specific survival in chromophobe RCC, and was not associated with survival in papillary RCC [54]. The lack of association with papillary RCC is consistent with the observations for incidence, as well.

7.3 Interpretation of Associations with Survival Among RCC Patients

It has been hypothesized that obese patients develop a biologically less aggressive disease. Supporting this, a study in a subset of 126 patients from a clinical cohort

surgically treated at Memorial Sloan-Kettering Cancer Center who had data available from The Cancer Genome Atlas Project found significantly lower gene expression of fatty acid synthase (*FASN*) in obese patients [50]. *FASN* expression, in turn, is associated with increased cancer-specific mortality in clear cell RCC. It is worth noting that in this study, obesity was not significantly associated with survival after adjustment for stage and grade at diagnosis. In addition, obese patients in this study and several others were less likely to present with symptoms at the time of diagnosis and were more likely to be diagnosed incidentally (as discussed above). Thus, is it possible that the observed association between obesity and improved survival is because obesity is associated with the increasing trend toward incidental diagnosis of RCC during imaging studies for other medical problems.

In addition, there are several methodological problems that may explain the "obesity paradox," most of which have not been considered in the literature. *Reverse causation* is a major concern, given that the evidence comes from clinical cohorts with measures of obesity at the time of diagnosis or treatment. At that point, there may have been weight loss due to undiagnosed disease, which likely correlates with disease severity. In addition, these clinical cohorts likely suffer from *selection bias*, as they tend to be based among surgically treated RCC patients, rather than among all patients diagnosed with RCC, regardless of treatment strategy. Finally, another form of selection bias is a methodological problem in studies of disease survival when the exposure of interest is also a risk factor for disease incidence. This may arise in case-only survival analysis studying the association between BMI, a risk factor for the disease, and mortality. Because the analysis is done only among people with the disease, this conditioning on disease status can induce a statistical association between BMI and mortality that is not, in fact, a causal association. This form of bias is less intuitive than some of the other possible sources of bias discussed here; it has been explored in the literature with respect to other "obesity paradoxes" in heart disease and type 2 diabetes using methods on causal inference and directed acyclic graphs (DAGs) [55–57].

Given these limitations, the association between obesity and prognosis in RCC should be examined in settings that can include all incident RCC cases, rather than those undergoing a particular primary treatment and with multiple measures of obesity over time. Additional molecular epidemiological studies of tumor markers associated with obesity may also shed light on this issue.

8 Conclusion

Obesity is clearly associated with risk of RCC and particularly with the clear cell subtype. The positive association is seen for both BMI and WC. The association with non-clear cell subtypes is less clear. Possible mechanisms linking obesity and kidney cancer may include IGF-1, sex steroid hormones, and other hormones such as adiponectin. Additional studies of biomarkers and molecular markers in tumors are needed to better understand the relevant mechanisms. An inverse association

between obesity and survival among RCC patients has been observed fairly consistently in clinical cohorts; however, numerous methodological issues make the interpretation of these findings difficult, and more work is needed in this area.

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Obesity and Pancreatic Cancer

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Abstract

Pancreatic cancer has few known risk factors, providing little in the way of prevention, and is the most rapidly fatal cancer with 7 % survival rate at 5 years. Obesity has surfaced as an important risk factor for pancreatic cancer as epidemiological studies with strong methodological designs have removed important biases and solidified the obesity associations. Moreover, studies indicate that obesity early in adulthood is strongly associated with future risk of pancreatic cancer and that abdominal obesity is an independent risk factor. There is increasing evidence suggesting long-standing diabetes type 2 and insulin resistance are important etiological factors of this disease, providing a strong mechanistic link to obesity. The challenge remains to determine whether intended weight loss in midlife will reduce risk of pancreatic cancer and to elucidate the complex underlying pathways directly involved with risk.

Keywords

Pancreatic cancer · Pancreas · Abdominal obesity · Early life obesity · Diabetes

1 Introduction

Pancreatic cancer is the fourth leading cause of cancer deaths in developed countries [1]. Pancreatic cancer incidence rates increase with age and are higher in men than women [2]. In addition, incidence rates vary by racial groups; in the USA,

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blacks have higher incidence rates than whites [2]. Countries with the three highest incidence rates of pancreatic cancer are China, the USA and Japan [3]. Survival for pancreatic cancer patients is very low; 93 % of cases die within the first five years after diagnosis [4]. The dismal prognosis requires more attention to prevention of this disease; cigarette smoking, obesity, long-standing diabetes and chronic pancreatitis are well-established *modifiable* risk factors for pancreatic cancer. Other established risk factors that are not modifiable include age, race, family history and genetic susceptibility. Most pancreatic cancers originate in the exocrine pancreas (96 %), and most of these are adenocarcinomas (95 %). The remaining pancreatic tumors originate in endocrine pancreas and have very different behaviors and characteristics from exocrine tumors, consequently most epidemiological studies typically restrict analyses to exocrine tumors.

2 Epidemiology of Obesity and Pancreatic Cancer Risk

The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) 2007 Report on the prevention of cancer classified "body fatness" as a convincing cause of pancreatic cancer [5]. Although now widely accepted as a major risk factor for pancreatic cancer, obesity was only recently recognized as a risk factor for pancreatic cancer. In 2002, the International Agency for Research on Cancer (IARC) publication on "*Weight Control and Physical Activity*" concluded that the evidence was too limited for any firm conclusion to be made on the association between obesity and pancreatic cancer [6]. Most of the cohort studies on obesity and pancreatic cancer, reporting positive associations, were published in the past 15 years; in contrast, most results from case–control studies, published earlier on, were null. The discrepancy between the two study designs can be explained by three major limitations in case–control studies that resulted in bias toward the null: (1) weight at diagnosis for cases did not reflect lifetime weight given severe weight loss commonly associated with pancreatic cancer, (2) obesity is associated with lower pancreatic cancer survival [7], such that cancer cases included in case–control studies, unless identified through rapid case ascertainment, were likely to be those that had survived longest and would have been less overweight, and (3) earlier studies did not adjust adequately for smoking status (which is inversely associated with weight). Cohort studies do not have the first two limitations, as weight is ascertained prior to disease diagnosis, often many years prior to diagnosis, and all cancer cases are included, regardless of survival. Furthermore, cohort studies typically have very accurate smoking data and adjust for this confounder in the analyses.

Several meta-analyses and pooled analyses of prospective cohort studies have been published on body mass index (BMI) and pancreatic cancer [8–11]. Similar associations for weight and pancreatic cancer have been reported in these summary analyses. In the largest meta-analysis, which included twenty-three prospective studies and 9504 pancreatic cancer cases, a 10 % increase in risk was reported for

each 5-unit higher BMI (RR 1.10, 95 % CI 1.07–1.14) [8]. In a large pooling study, an 18 % increase in risk (RR 1.18, 95 % CI 1.03–1.35) was estimated for overweight (25–29.9 kg/m^2) individuals, and a 20 % increase (RR 1.20, 95 % CI 1.00–1.44) for those who were obese (30–34.9 kg/m^2), compared with those with a healthy weight (18.5–24.9 kg/m^2) [9]. A 55 % increase in risk was observed in those who were morbidly obese ($\geq$35 kg/m^2; RR 1.55, 95 % CI 1.16–2.07) [9]; associations are not linear [8]. For these analyses, weight at time of recruitment into the cohorts was used to estimate BMI (i.e., over 40 years old in most studies).

In the largest meta-analysis [8], associations with obesity and pancreatic cancer were similar in men and women and by geographical region, but stronger among never smokers, as previously reported in a large pooling study [9]. Similar associations have been reported in African-Americans [12]. In contrast, obesity does not appear to be related to pancreatic cancer mortality in Asian populations [13, 14].

Abdominal obesity (measured using waist circumference or waist-to-hip ratio) has also been associated with pancreatic cancer risk [8–10]. The summary RR for a 10-cm greater waist circumference was 1.11 (95 % CI 1.05–1.18) and for a 0.1-unit higher waist-to-hip ratio was 1.19 (95 % CI 1.09–1.31) in the largest meta-analysis [8]. The impact of abdominal obesity on risk appears to be independent of BMI as controlling for BMI does not remove the positive association observed for abdominal obesity [10]. The largest study to examine this question in detail included 20 prospective cohort studies with pancreatic cancer mortality [15], in this study, the positive association for waist-to-hip ratio remained statistically significant after adjusting for BMI (HR 1.07, 95 % CI = 1.02–1.17, per 0.1 unit increment), and a similar magnitude of risk of waist-to-hip ratio was observed for healthy, overweight and obese individuals at baseline.

A number of studies have examined the relationship between obesity at different points in life and pancreatic cancer risk. The association between obesity at early adulthood (ages 18 or 21 years) and pancreatic cancer has been measured in two separate large pooled analyses of prospective cohort studies [10, 15]. In the first pooled study using cancer incidence as the outcome, elevated BMI ($\geq$25 kg/m^2) at ages 18–21 years was associated with a 30 % increase in risk of pancreatic cancer (95 % CI = 1.09–1.56, compared to BMI of 21–22.9 kg/m^2) and was based on 11 studies. In a second pooled analysis examining pancreatic cancer mortality, early adulthood BMI was strongly associated with risk (HR = 1.48, 95 % CI = 1.20–1.84 for BMI 27.5–29.9, and HR = 1.43, 95 % CI = 1.11–1.85 for BMI 30+ compared to BMI 21–22.9) [15]. In this pooled study, BMI during early adulthood was independent of baseline BMI, and substantial weight gain during adulthood was also associated with increased risk (HR 1.29, 95 % CI = 1.12–1.47 for BMI $\geq$ 10 kg/m^2 gain vs. 0–2.4 BMI gain) [15]. However, the association for weight gain was not as large as that observed for early adulthood obesity, suggesting that weight gained during early childhood plays an important role in later risk.

Impact of weight changes at different ages (18, 35, and 50 years) on risk was examined in the NIH-AARP cohort study, a large US prospective cohort study of men and women between 50 and 71 years at baseline (1995–6) [16]. In this study,

BMI at 18 years was strongly associated with risk of pancreatic cancer; men and women with BMI $\geq$ 27.5 kg/m^2 at age 18 years had a 56 % higher risk of pancreatic cancer (95 % CI 1.19–2.03) compared with those with a healthy BMI (18.5–24.9 kg/m^2) [16]. Further adjusting for current BMI had little impact on the association observed with BMI at age 18, and the associations with BMI at 35 and 50 years old were weaker than that of the BMI at age 18, suggesting that early life weight gain could be critical in the risk of pancreatic cancer. While weight gain after the age of 50 was associated with higher risk of pancreatic cancer, no associations were observed for weight gain in earlier time frames (i.e., between 18 and 50 years) in this study [16] and in other studies [17, 18]. As pancreatic cancer patients often lose weight as a result of the cancer, elevated risks were observed among participants losing weight after the age of 50 years [16].

3 Obesity and Pancreatic Cancer Survival

The question has been raised as to whether being overweight may impact survival in pancreatic cancer patients. Several studies have reported elevated risk of dying among patients with higher BMI at diagnosis [7, 19–21]. In one prospective study, the risk of death was 53 % higher in patients with BMI > 35 kg/m^2 prior to diagnosis compared to those with normal BMI (<25 kg/m^2; p trend = 0.002) [7]. The strongest association was observed for patients who were obese 18–20 years prior to diagnosis compared to those who had a healthy BMI (HR = 2.31, 95 % CI, 1.48–3.61; p trend < 0.001) [7], and the associations weakened as BMI measures were obtained closer to diagnosis. The associations between BMI and survival were independent of stage of disease at diagnosis, even though obese patients were more often diagnosed with advanced disease (72.5 % with metastatic disease vs. 59.4 % of healthy weight patients).

Positive associations for obesity and pancreatic cancer survival have also been observed in several retrospective case–control studies where patients were asked to recall their usual adult weight or weight in earlier decades of life [19–21]. The associations reported were consistently in the range of 30–75 % higher risk with BMIs greater than 30 or 35 kg/m^2 (compared to healthy weight) when BMI was calculated prior to diagnosis. Furthermore, these associations do not appear to be modified by stage of disease or other known risk factors [20].

4 Mechanisms for Obesity and Pancreatic Cancer

There are several mechanistic pathways that may explain the associations observed in epidemiological studies and these include (1) hyperglycemia/hyperinsulinemia, (2) inflammatory/immune response and (3) sex steroid hormones. The third pathway is the least compelling for pancreatic cancer given the lack of excess risk in

women (men have higher rates of pancreatic cancer incidence than women), decreased risk associated with increasing parity [22] and a potentially inverse association for exogenous estrogen-only use [23]. All of the associations with estrogen-related risk factors suggest that obesity, through increased estrogen production from adipose tissue, would decrease the risk of pancreatic cancer (rather than increase risk). Therefore, the first two pathways are the most compelling and will be discussed below.

4.1 Hyperglycemia/Hyperinsulinemia

The underlying mechanisms which may explain the association between obesity and pancreatic cancer have been examined using epidemiological study designs and include measuring glucose, insulin, C-peptide and hemoglobin A1c (HbA1c) in cases and controls using prediagnostic, archived blood samples. In addition, the association between long-standing diabetes and pancreatic cancer suggests that glucose intolerance and hyperinsulinemia may be directly involved in the onset of pancreatic cancer. While it is well known that diabetes is commonly diagnosed a few years prior to pancreatic cancer, the etiological aspect of the association was only confirmed with methodologically powerful studies demonstrating a higher risk of pancreatic cancer among individuals with long-standing diabetes. In a large meta-analysis, individuals with long-standing diabetes (10 or more years) had a 50 % higher risk of pancreatic cancer compared to those without diabetes (RR 1.51, 95 % CI 1.16–1.96) [24]. Studies have examined different aspects of diabetes to understand mechanisms.

Elevated glycated hemoglobin (HbA1c), a time-integrated measure of hyperglycemia [25], has been associated with risk of pancreatic cancer in prospective cohort studies with blood samples collected decades prior to diagnosis. Two large prospective cohort analyses conducted analyses using HbA1c and examined how the associations change over time (to diagnosis) [26, 27]. In the EPIC cohort study, elevated HbA1c was associated with a 65 % higher risk of pancreatic cancer among nondiabetics (OR = 1.65, 9 % CI = 1.01–2.70, comparing top to bottom quartiles), and associations did not differ substantially when examined at different time periods prior to diagnosis [26]. Similar associations were reported in a pooled analysis of the five US cohort studies (OR = 1.79, 95 % CI = 1.17–2.72, comparing top to bottom quintile) [27].

Five studies measuring blood glucose levels prior to diagnosis also reported positive associations with pancreatic cancer risk [28–32]. Risk of mortality from pancreatic cancer was higher in nondiabetic individuals who had baseline postload plasma glucose levels above 198 mg/dL, compared to those with levels below 118.8, after excluding the first 5 years of follow-up (RR 1.97, 95 % CI 1.08–3.57) [31]. In a separate study conducted among male smokers, risk of incident pancreatic cancer remained elevated among those who had high fasting serum glucose (>107 mg/dL), compared to <93 mg/dL, 10 or more years prior to diagnosis (RR 2.16, 95 % CI 1.05–4.42) [30].

While these studies support a role for hyperglycemia in pancreatic cancer, the precise role of glucose in carcinogenesis is unclear. Hyperglycemia can occur as a result of insulin resistance, which is tied to hyperinsulinemia, or is due to abnormal pancreatic β cell function. To try and disentangle the underlying mechanisms, epidemiological studies have also measured blood levels of insulin, proinsulin and C-peptide (cleaved from proinsulin to produce insulin).

Elevated fasting serum insulin levels and insulin resistance (measured using homeostatic model assessment—insulin resistance [HOMA-IR]) were associated with a higher risk of pancreatic cancer in a prospective cohort study of male smokers [30], and nonfasting C-peptide levels were positively associated with pancreatic cancer risk in a US study of men and women [33], both supporting the hypothesis that insulin resistance plays a role in the etiology of pancreatic cancer. Consistent with this hypothesis, a large study combining prediagnostic blood samples from five large prospective cohort studies reported consistent and statistically significant positive associations for insulin and proinsulin levels, with no increase for the ratio of insulin to proinsulin levels (marker of normal pancreatic β-cell function) [27]. Furthermore, the association for insulin and proinsulin became more pronounced after restricting the analysis to those with greater time between blood collection and pancreatic cancer diagnosis, and in a mutually adjusted model, only proinsulin levels remained statistically significant (p trend = <0.001) [27]. In contrast, the EPIC cohort study did not observe any associations between fasting or nonfasting C-peptide levels and pancreatic cancer [26], despite reporting positive associations for HbA1c.

Given that peripheral insulin resistance is associated with alterations of numerous metabolic pathways, it is still unclear which ones are involved in pancreatic cancer. It has been proposed that proinsulin itself may play a role in carcinogenesis as it can impact cell proliferation through the insulin receptor itself [34]. Other pathways, however, are likely also at play; insulin resistance is also closely tied with chronic low-grade inflammation [35].

4.2 Inflammation/Immune Response

The role of inflammation in pancreatic cancer has been well described [36], and it is well established that excess adipose tissue in overweight individuals can lead to low-grade inflammation [35]. Chronic inflammation of the pancreas, chronic pancreatitis, is a well-established risk factor for pancreatic cancer [37]. What is less clear, however, is whether systemic low-grade inflammation is directly associated with pancreatic carcinogenesis. Studies that have attempted to answer this question by measuring markers of inflammation in peripheral bloods, including C-reactive protein, interleukin 6 (IL6) and receptors of tumor necrosis factor alpha (TNF-alpha R1, R2) [38–40]. Three prospective studies examining these factors reported no associations for C-reactive protein [38–40] or IL6 levels and risk of pancreatic cancer [39, 40]. In one study, a statistically significant higher risk of pancreatic cancer was observed with elevated levels of TNF-R1 in women, and but not men,

and TNF-R2 levels were associated with risk in subjects who were overweight [39]. However, TNF-R2 was not associated with risk in another study, even when stratified by BMI [40]. As the markers of inflammation used in these studies have been previously associated with obesity [35], there is currently little compelling evidence for a direct role of systemic inflammation in pancreatic cancer.

Obesity, however, is a complex condition that is intricately linked to excessive caloric intake and impacts neuroendocrine factors regulating metabolism and immune function [41]. There is increasing evidence that the impact of obesity on the immune system extends beyond production of proinflammatory markers from adipocytes and involves other components of the immune response, including the adaptive immune response [41, 42]. There is growing evidence that obese individuals have higher risk of infection and experience reduced immunocompetence [43]. The implications of changes in adaptive immune response associated with obesity on cancer risk have not been addressed directly, but more research is currently being directed toward understanding the role of the immune response in cancer risk [44].

5 Summary

Obesity has only recently been confirmed as a risk factor for pancreatic cancer. The highest risk associated with obesity is observed among subjects with elevated BMI in early adulthood, compared to those who have a healthy BMI. In addition, abdominal obesity is associated with an increased risk of pancreatic cancer independently of BMI. The positive association with being overweight is dose-dependent, and individuals who are morbidly obese (BMI > 35 kg/m^2) experience a 55 % higher risk of pancreatic cancer. The association between BMI and pancreatic cancer is consistent by sex and race, although overweight Asians may not be at higher risk. Obese individuals also experience lower survival rates from pancreatic cancer. The mechanisms underlying the association with obesity are likely to be linked to insulin resistance and associated pathways and develop over several decades. Research on immune response and its role on the etiology of pancreatic cancer may reveal new mechanisms linked to obesity.

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Obesity and Endometrial Cancer

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Abstract

Endometrial cancer is the sixth most common cancer in women worldwide and the most common gynecologic malignancy in the developed world. This chapter explores the current epidemiologic evidence on the association between obesity and endometrial cancer risk and mortality. Using body mass index (BMI) as a measure of obesity, we found that obesity (defined as BMI > 30 and < 35 kg/m^2) was associated with a 2.6-fold increase in endometrial cancer risk, while severe obesity (BMI > 35 kg/m^2) was associated with a 4.7-fold increase compared to normal-weight women (BMI < 25 kg/m^2). Increased central adiposity also increased endometrial cancer risk by 1.5- to twofold. Among both healthy and endometrial cancer patient populations, obesity was associated with a roughly twofold increase in endometrial cancer-specific mortality. This risk reduction was also observed for obesity and all-cause mortality among endometrial cancer patients. In the few studies that assessed risk associated with weight change, an increased endometrial cancer risk with weight gain and weight cycling was observed, whereas some evidence for a protective effect of weight loss was found. Furthermore, early-life obesity was associated with a moderately increased risk of endometrial cancer later in life. There are several mechanisms whereby obesity is

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hypothesized to increase endometrial cancer risk, including increased endogenous sex steroid hormones, insulin resistance, chronic inflammation and adipokines. Further research should focus on histological subtypes or molecular phenotypes of endometrial tumors and population subgroups that could be at an increased risk of obesity-associated endometrial cancer. Additionally, studies on weight gain, loss or cycling and weight loss interventions can provide mechanistic insight into the obesity–endometrial cancer association. Sufficient evidence exists to recommend avoiding obesity to reduce endometrial cancer risk.

Keywords
Endometrial cancer · Obesity · Incidence · Survival · Biomechanisms

1 Basic Epidemiology of Endometrial Cancer

1.1 Incidence Rates

Endometrial cancer is the sixth most common cancer in women worldwide, with an estimated 320,000 incident cases in 2012 [1]. In the United States (U.S.), it is the fourth most common cancer in women and the most common gynecologic malignancy diagnosed, with an estimated 49,154 incident cases of uterine cancer in 2012 [2].

Endometrial cancers can be divided into two histological subtypes [3]. Type I endometrial cancers are estrogen-driven and have endometrioid differentiation, while Type II endometrial cancers are not estrogen-dependent and are classified as non-endometrioid (serous, clear cell, mucinous) [4]. Type I endometrial cancers represent approximately 70–80 % of all endometrial cancers [5] and tend to have a more favorable prognosis than Type II cancers, which are usually more aggressive and consequently associated with poorer prognosis [6].

Worldwide incidence rates of endometrial cancer have been increasing, particularly in the twenty-first century, where age-standardized incidence rates have increased from 6.5 per 100,000 in 2002 [7] to 8.2 per 100,000 in 2012 [1]. Furthermore, Type I endometrial cancers have been increasing in the U.S. and in Europe [8–10]. This increased incidence of endometrial cancer can likely be attributed to changes in lifestyle risk factors (e.g., diet, sedentary behavior and use of hormone replacement therapy), which are all strongly associated with endometrial cancer risk [8, 11].

1.2 Mortality Rates

An estimated 76,000 endometrial cancer deaths occurred worldwide in 2012 [1]. The five-year survival rates for endometrial cancer are relatively high and estimated to be 82 % in the U.S. [12]. Given the better cancer screening and treatment programs, mortality rates for endometrial cancer are lower in developed countries compared to developing countries [7]. Survival rates for endometrial cancer increase with earlier diagnosis [13].

1.3 Major Risk Factors

Risk of endometrial cancer increases with age, and most cases are diagnosed postmenopause [5]. Endometrial cancers diagnosed in older women tend to be of higher grade and stage compared to younger women [14]. In the U.S., incidence rates are higher in white women compared to other ethnic groups, while mortality is significantly worse in black women compared to white women [15, 16]. Other risk factors for endometrial cancer risk include long-term exposure to unopposed estrogens, high postmenopausal concentrations of estrogens, nulliparity, history of breast cancer and first-degree family history of endometrial cancer [5, 17]. Among endometrial cancer patients, risk factors for endometrial cancer mortality (all-cause or endometrial cancer-specific) include prediagnosis obesity, type 2 diabetes mellitus and heart disease [18–21]. The World Cancer Research Fund Continuous Update Project panel has deemed there to be *convincing* evidence for the association between body fatness and increased risk of endometrial cancer [22]. Obesity ranks among the strongest risk factors for endometrial cancer development [11], and it is strongly hypothesized that the increasing global prevalence of obesity, particularly in developed countries, is contributing to the overall increase in endometrial cancer incidence [11, 23]. The purpose of this chapter is to provide an updated review of the extant literature on obesity and endometrial cancer and to highlight the current gaps in the epidemiologic evidence.

2 Literature Review Methods

A search for studies of endometrial cancer incidence and mortality related to obesity was performed using PubMed to search the MEDLINE database. Search terms used to identify obesity were “body mass index,” “BMI,” “waist circumference,” “hip circumference,” “waist-to-hip ratio,” “body weight,” “obesity,” “adiposity” and “anthropometry,” along with “endometrial cancer” and “endometrial neoplasms” as search terms to indicate endometrial cancer. The search was not restricted by date, but only included studies in English up to March 2016. Overall, 38 cohort studies and 42 case–control studies investigating obesity and endometrial cancer risk were identified, with three pooled studies from the Epidemiology of Endometrial Cancer

Consortium (E2C2) [24], an NCI-supported consortium consisting of over 45 studies worldwide. Twelve studies investigating obesity and endometrial cancer mortality in both healthy and endometrial cancer patient populations were identified using the above search terms along with "survival," "mortality" and "death."

Studies were excluded if no point estimates and 95 % confidence intervals (CIs) were provided for risk and mortality estimates (n = 6 excluded). For studies with multiple publications, the most recent update or largest sample size publications were selected for this review (n = 9 excluded). To provide more uniform assessments of endometrial cancer risk and mortality, only studies presenting estimates for categorical adiposity measurements were included (n = 10 excluded). An additional three studies were identified that investigated obesity and mortality, but were not included because of limited event observations (<20 deaths) [25–27]. This additional exclusion resulted in 28 cohort studies, 29 case–control studies and one pooled study for inclusion in this review for endometrial cancer incidence. There were three studies [28–30] that investigated obesity and endometrial cancer-specific mortality in healthy populations and three studies [18, 31, 32] for endometrial cancer-specific or all-cause mortality in endometrial cancer patient populations.

In addition, studies that presented risk estimates stratified by other variables were pooled in order to obtain one representative estimate for each study. Since BMI categorization varied across studies, risk estimates were separated into obesity (class I—generally BMI $\geq$ 30 or 30 $\leq$ BMI < 35) and severe obesity (class II or III—generally BMI $\geq$ 35). Random-effect models were used to calculate pooled estimates with 95 % CIs for each set of studies [33].

3 Obesity and Endometrial Cancer Risk

3.1 BMI and Risk

There were 25 cohort studies, 28 case–control studies and one pooled study from the E2C2 investigating the relation between BMI and endometrial cancer risk identified, with almost all studies showing a statistically significant positive association. Using data from 26 case–control studies [34–59], the effect estimates of obesity (30 < BMI < 35) and endometrial cancer risk ranged from 1.00 (95 % CI 0.60–1.50) [40] to 9.18 (95 % CI 4.30–19.62) [34] (Fig. 1). The overall pooled risk estimate for endometrial cancer risk associated with obesity for case–control studies was 2.32 (95 % CI 2.08–2.58), compared to normal-weight individuals (generally BMI < 25). Similarly, 25 cohort studies [17, 28, 29, 60–81] ranged in effect estimates from 1.50 (95 % CI 1.10–2.10) [63] to 4.50 (95 % CI 2.62–7.72) [17], resulting in an overall pooled estimate of 2.49 (95 % CI 2.28–2.73), compared to normal-weight individuals (generally BMI < 25). The pooled study from the E2C2 reported an effect estimate of 2.11 (95 % CI 1.46–3.05) [24], and the overall pooled estimate for obesity and endometrial cancer risk was 2.65 (95 % CI 2.43–2.90).

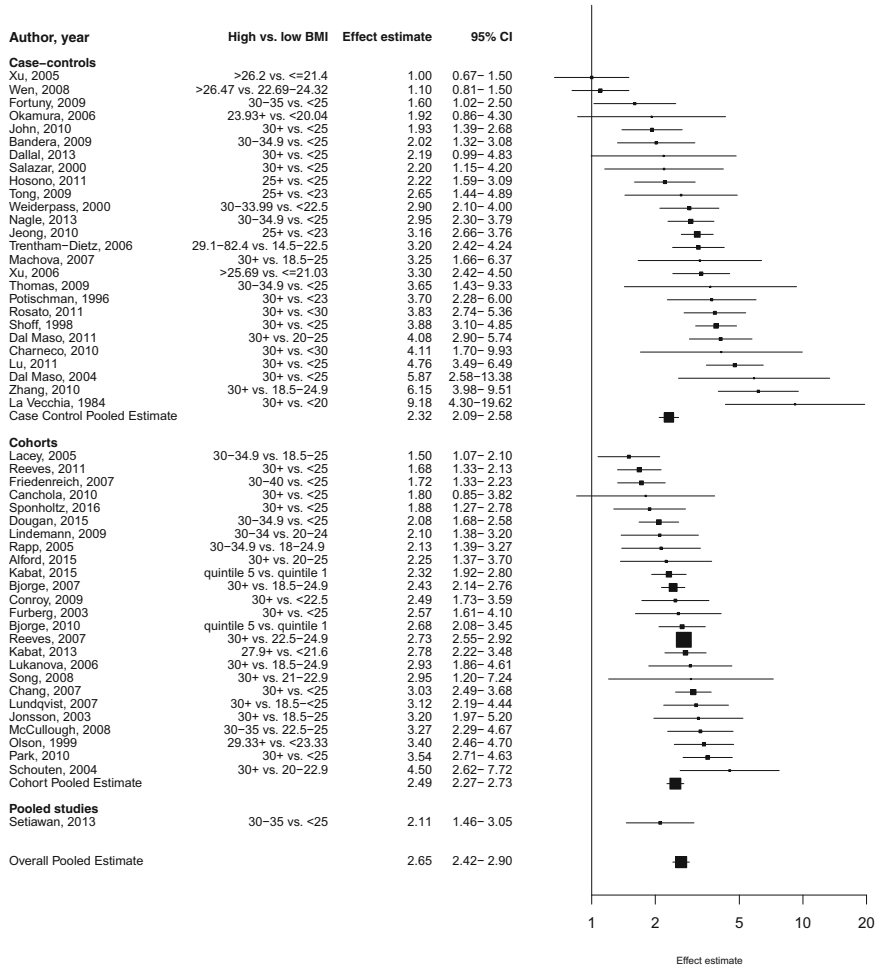

Fig. 1 Case–control and cohort studies of obese BMI and endometrial cancer risk

Effect estimates for endometrial cancer risk in relation to severe obesity were notably higher than associations with obesity (Fig. 2). Seven case–control studies [38, 46–48, 59, 82, 83] and seven cohort studies [63, 64, 68, 70, 73, 79, 81] investigated this relation, resulting in pooled estimates of 6.45 (95 % CI 4.98–8.35) and 3.61 (95 % CI 2.85–4.58), respectively. Additionally, the pooled study from the E2C2 reported an estimate of 4.80 (95 % CI 2.13–10.82) [24]. The overall pooled estimate for severe obesity and endometrial cancer risk was 4.66 (95 % CI 3.78–5.75).

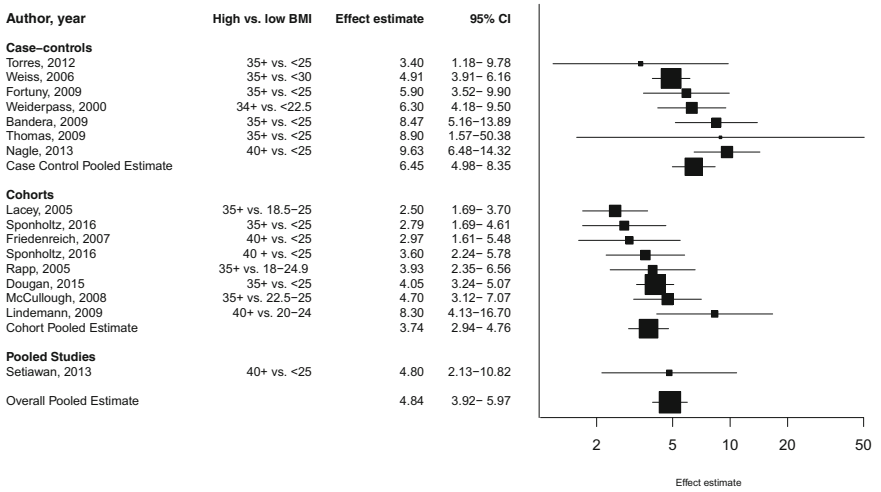

Fig. 2 Case–control and cohort studies of severely obese BMI and endometrial cancer risk

3.2 Central Adiposity and Risk

Recently, central adiposity measures, defined either as waist circumference or as waist-to-hip ratio, have also been considered in etiologic studies of anthropometry and endometrial cancer risk. To date, five case–control [40, 45, 54, 57, 84] and five cohort studies [68, 72, 74, 80, 81] examining waist circumference showed statistically significant pooled estimates of 2.30 (95 % CI 1.71–3.09) and 1.58 (95 % CI 1.18–2.12), respectively, for higher waist circumference (generally >90 cm) and endometrial cancer risk (Fig. 3). The overall pooled estimate for all studies combined was 1.92 (95 % CI 1.57–2.35). Although the strength of association was weaker, higher waist-to-hip ratio (generally >0.85) was also associated with an increased risk of endometrial cancer risk. Three of the five case–control studies that examined waist circumference and endometrial cancer risk also considered waist-to-hip ratio, and their pooled estimate was 1.78 (95 % CI 1.24–2.55) [40, 45, 54]. All five cohort studies that measured the effect of waist circumference on endometrial cancer risk also measured waist-to-hip ratio, along with one additional study [68, 72, 74, 76, 80, 81]. The pooled estimate for waist-to-hip ratio on endometrial cancer risk was 1.29 (95 % CI 1.13–1.47). The overall pooled estimate for higher waist-to-hip ratio and risk of endometrial cancer was 1.43 (95 % CI 1.33–1.54) from these nine studies.

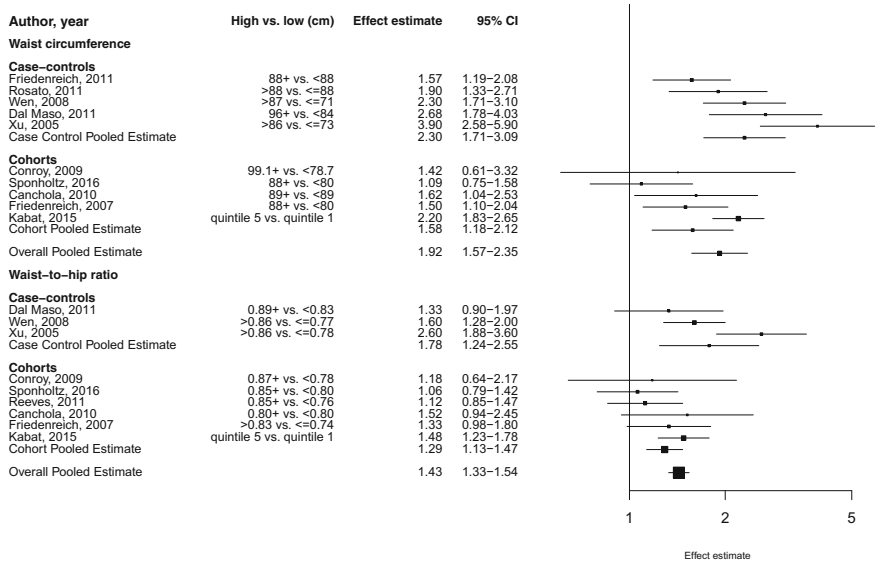

Fig. 3 Central adiposity and endometrial cancer risk

3.3 Weight Change (Gain/Loss), Weight Cycling and Risk

To date, 17 studies have investigated the effect of weight change (gain or loss) on the risk of endometrial cancer (Fig. 4). In general, weight gain was significantly associated with an increased risk of endometrial cancer in both case–control [38, 42, 43, 48, 55, 56, 59] and cohort [17, 27, 62, 67, 68, 74, 75, 79, 81, 85] studies. There was considerable heterogeneity between studies with respect to weight gain measurement, and thus, pooled estimates are not presented. Most studies examined weight gain from early adulthood (age 18–25 years) and found that weight gain of roughly 20 kg was associated with an approximately twofold increase in endometrial cancer risk.

Studies in weight loss [42, 74, 79, 85] trended toward a protective effect on endometrial cancer risk, although this effect was statistically significant in only one study [79]. Similar to studies of weight gain, studies on weight loss were heterogeneous in measurements of weight loss, which precluded comparing the estimates or pooling them. Lastly, only three studies [42, 59, 86] investigated the role of weight cycling (purposeful loss of weight, followed by weight gain). All studies indicated an increased risk of endometrial cancer with weight cycling; two of these studies were statistically significant [42, 59]. In these studies, odds ratios for ever versus never experiencing weight cycling over lifetime ranged from 1.27 (95 % CI 1.00–1.61) [42] to 2.30 (95 % CI 1.54–3.43). Additionally, an increased number of weight cycles appeared to attenuate the risk as these estimates were statistically nonsignificant [42, 86].

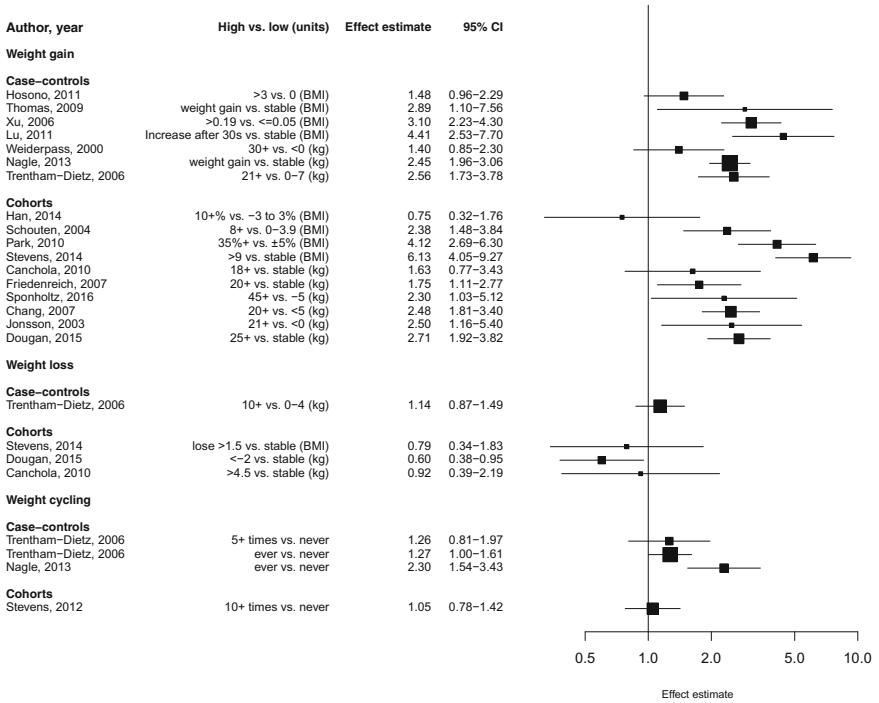

Fig. 4 Weight change (gain and loss), weight cycling and endometrial cancer risk

3.4 Childhood/Adolescence and Early Adult Weight and Risk

The role of childhood/adolescence or early adulthood obesity on endometrial cancer risk later in life was examined in 14 studies [17, 38, 43, 48, 54, 55, 59, 67, 74, 75, 79, 81, 85, 87] (Fig. 5). Early adulthood obesity increased endometrial cancer risk by 33 % (95 % CI 0.94–1.88) for case–control studies [38, 43, 48, 55, 59] and by 57 % (95 % CI 1.38–1.79) for cohort studies [17, 67, 74, 75, 79, 81, 85] compared with normal weight in early adulthood. The overall pooled estimate for early adulthood obesity and endometrial cancer risk was 1.44 (95 % CI 1.22–1.70). Similarly, increased endometrial cancer risk associated with childhood/adolescent obesity was smaller in magnitude for case–control studies [43, 54] and very close to the null for cohort studies [79, 88]. These risk estimates must be interpreted with caution since accurate exposure measurements for early adulthood or childhood/adolescent obesity were often not available for these studies. BMI reporting tended to rely on the participants' ability to recall their early-life anthropometry, and thus, measurement error likely affected these results.

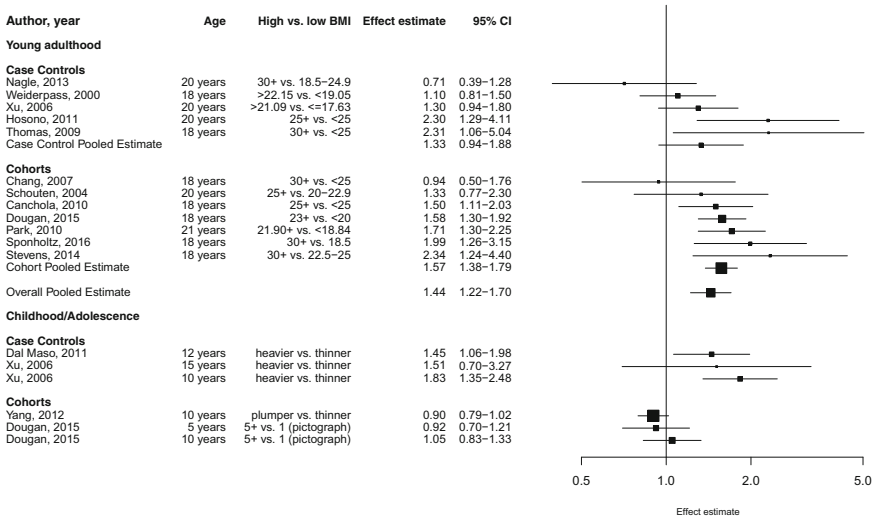

Fig. 5 Childhood/adolescence and early adult weight and endometrial cancer risk

4 Obesity and Endometrial Cancer Survival

4.1 Weight/BMI and Survival

Only six studies have investigated the association between BMI and mortality (all-cause or endometrial cancer-specific) among healthy or endometrial cancer patient populations (Fig. 6). With respect to endometrial cancer-specific mortality, there were six studies with effect estimates for the association with obesity [18, 29–32, 66], three of which were in healthy populations [28–30]. All point estimates were above the null value, resulting in a pooled estimate of 2.39 (95 % CI 2.04–2.80) in healthy populations and 1.91 (95 % CI 1.29–2.82) in endometrial cancer patient populations. Severe obesity was also significantly associated with endometrial cancer-specific mortality among healthy populations [28, 30], with a pooled estimate of 4.69 (95 % CI 2.68–8.22), as well as among endometrial cancer patients [31, 32], with a pooled estimate of 1.96 (95 % CI 1.25–3.07). Of the three studies that examined the association between obesity and all-cause mortality in endometrial cancer patient populations [18, 31, 32], all observed a positive association, with a pooled estimate of 1.64 (95 % CI 1.29–2.09). Two of these studies also analyzed the association between severe obesity and all-cause mortality [31, 32], and both reported statistically significant positive associations, with a pooled estimate of 2.06 (95 % CI 1.55–2.74).

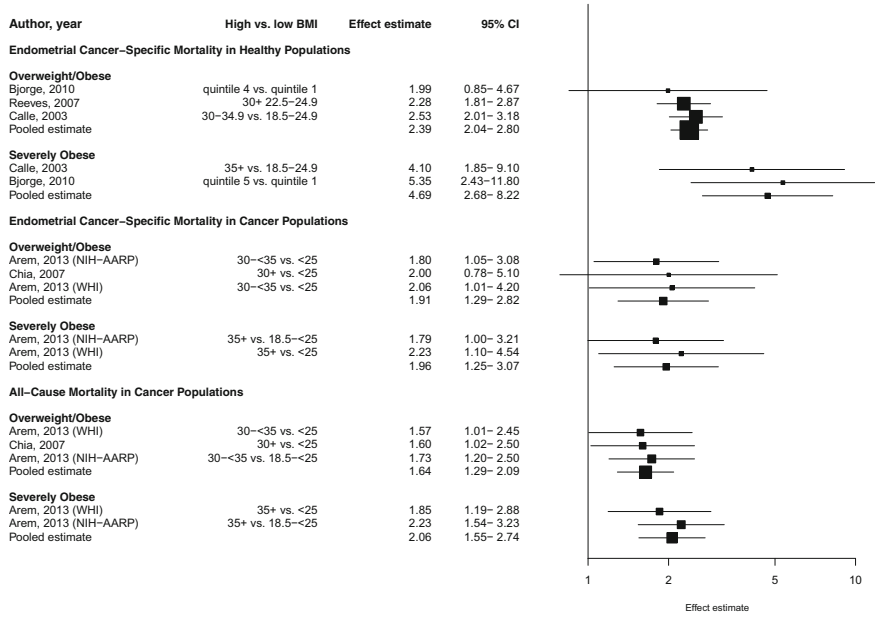

Fig. 6 Obesity (BMI) and all-cause or endometrial cancer-specific mortality

5 Biologic Mechanisms Involved in the Association of Obesity and Endometrial Cancer Risk and Survival

Given the strong associations between obesity and increased endometrial cancer risk and mortality, elucidating the mechanisms whereby this association occurs can improve our understanding of the etiology of this disease and aid in developing more efficient strategies for cancer prevention. There are several proposed mechanisms whereby obesity can lead to endometrial carcinogenesis (Fig. 7) [88, 89]. These include pathways involving endogenous sex steroid hormones, insulin resistance and inflammation.

5.1 Endogenous Sex Steroid Hormones

The "unopposed estrogen" theory suggests that endometrial cancer risk is increased in women with high plasma levels of bioavailable estrogen, or low plasma levels of progesterone [90]. These altered sex steroid hormone levels have been associated with Type I endometrial carcinomas [91]. Exposure of the endometrium to estrogen when unopposed by progesterone stimulates endometrial cell growth and proliferation, thus increasing the likelihood of malignant cell development [92]. Bioavailable estrogen increases IGF-1 receptor levels and reduces insulin growth

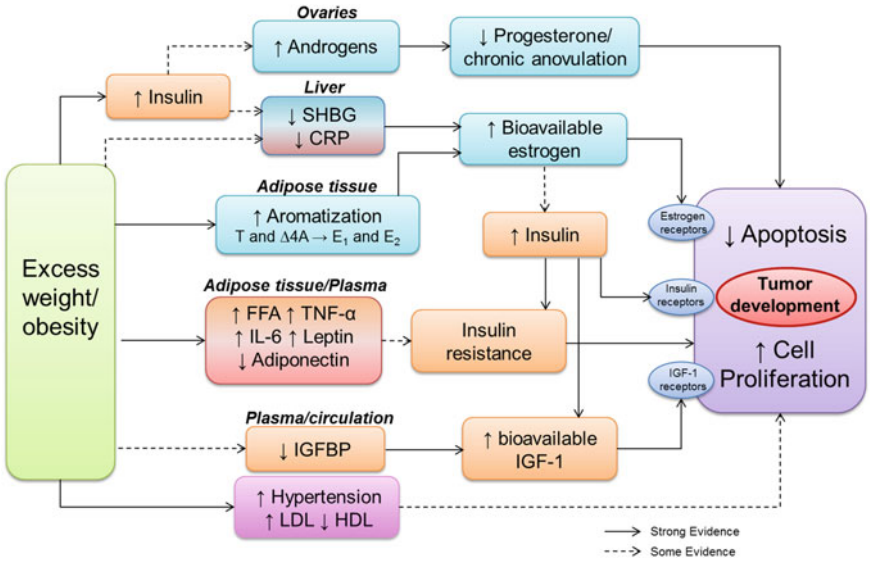

Fig. 7 Hypothesized biologic pathways relating excess obesity to endometrial cancer risk. *Note* *Δ4A* androstenedione; *CRP* C-reactive protein; *E1* estrone; *E2* estradiol; *FFA* free fatty acids; *HDL* high-density lipoprotein; *IGFBP* insulin growth factor binding protein; *IGF-1* insulin-like growth factor-1; *IL-6* interleukin-6; *LDL* low-density lipoprotein; *SHBG* sex-hormone-binding protein; *T* testosterone; *TNF-α* tumor necrosis factor-α

factor binding protein (IGFBP) levels, thus increasing the affinity of IGF-1 with its receptor within endometrial tissues [93]. Conversely, progesterone down-regulates estrogen receptors, stimulates the synthesis of IGFBP-1, reduces inflammation and promotes cell differentiation and apoptosis within the endometrium [88, 92, 94].

Several case–control studies have reported increased total [35, 95–98] and bioavailable [35, 97] estrogen levels and decreased plasma SHBG levels [35, 98] in postmenopausal women with endometrial cancer compared to controls. One prospective cohort study [99] also reported an increased risk of endometrial cancer risk among postmenopausal women in the top tertile for levels of free estradiol compared to the lowest tertile. Therefore, increases in the synthesis of endogenous estrogen by adipose tissue, coupled with decreased SHBG production by the liver, leads to increased plasma levels of bioavailable estrogen, thereby increasing endometrial cancer risk in obese postmenopausal women [90, 100]. On the other hand, excess weight does not appear to be related to increased bioavailable estrogen levels in premenopausal women with normal androgen levels [101]. Instead, excess weight has been suggested to cause chronic anovulation and reduce progesterone synthesis in premenopausal women, which may then increase bioavailable estrogen levels and the risk of endometrial cancer [90, 99].

Similar to estrogen levels, free testosterone levels were 79 % greater in postmenopausal women with excess weight (BMI $\geq$ 30 kg/m^2) compared to women

with a BMI of ≤ 22 kg/m^2 [102]. Increased levels of circulating androgens have also been associated with an increased Type I endometrial cancer risk in both pre- and postmenopausal women [95, 103, 104]. While androgens do not have a direct effect on endometrial cell proliferation, increased levels of androgens are converted into bioavailable estrogen through aromatization within endometrial and adipose tissues [89]. In premenopausal women, chronic anovulation and decreased progesterone levels may occur because of greater androgen production/conversion of androgens to estrogens [90].

Studies in women with polycystic ovarian syndrome (PCOS), a metabolic condition characterized by increased androgen levels, chronic anovulation and insulin resistance [105], have provided some causal evidence between obesity, endogenous sex steroid hormones and endometrial cancer. Two cohort studies have demonstrated an increased risk of endometrial cancer in women with PCOS [105, 106]. Furthermore, weight loss in obese women with PCOS has resulted in normalization of androgen levels and ovulatory cycles [107, 108]. Thus, suggesting a reduction in adipose tissue may decrease the risk of endometrial cancer through reductions in adipose-derived sex steroid hormones.

Taken together, endometrial cancer risk may be increased in women with excess weight directly as a result of greater levels of bioavailable estrogen and lower plasma SHBG levels, as well as indirectly through increased androgen levels. More specifically to premenopausal women, greater estrogen and androgen levels may lead to increased endometrial cancer cell proliferation as a result of reduced progesterone levels and/or chronic anovulation.

5.2 Insulin Resistance

Obesity is associated with chronically increased insulin levels and IGF-1 activity, mechanisms that directly promote cell proliferation and inhibit apoptosis within the endometrium in pre- and postmenopausal women [88, 89]. More specifically, insulin promotes tumor growth by binding to IGF-1 and insulin receptors within the endometrium [109] and has been previously associated with faster endometrial cancer progression [110]. Glucose may also contribute to tumor growth by providing an energy source to cancer cells [111]. Insulin down-regulates IGFBP-1 activity, leading to an increase in bioavailable IGF-1 levels [112]. However, progesterone can counteract these effects by stimulating the production of IGFBP-1, the most abundant IGFBP located in endometrial tissue, thus reducing the quantity of bioavailable IGF-1 [89]. Excess adiposity can ultimately lead to the development of insulin resistance and type 2 diabetes, as a result of chronically increased release of free fatty acids (FFA) into the plasma by adipose tissue [113]. These increased levels of circulating FFA will promote their uptake and oxidation by hepatic and muscle tissues, therefore limiting the use of glucose as a source of energy [113].

Case–control studies reported that significantly more endometrial cancer cases had elevated homeostatic model assessment of insulin resistance (HOMA-IR) scores, which are indicative of insulin resistance, risk of type 2 diabetes, greater

IGF-1, insulin and glucose levels compared to controls [114, 115]. Similarly, women within the highest quartile of fasting insulin [116] and HOMA-IR scores [115] had a greater than twofold increase in risk of endometrial cancer compared to women in the lowest quartile, independent of anthropometry measures (e.g., BMI and waist-to-hip ratio). Type 2 diabetes and insulin resistance have been consistently associated with an increased risk of endometrial cancer in meta-analyses [38, 117–124]. Some studies reported attenuations in the strength of the associations between type 2 diabetes and/or insulin resistance with endometrial cancer risk after controlling for BMI [119, 120], while others did not [38, 117, 118, 122]. These results suggest that the associations between type 2 diabetes/insulin resistance and endometrial cancer risk may be partially explained by BMI [120]. It is also possible that the combination of excess weight and diabetes/insulin resistance may lead to even greater risks of endometrial carcinogenesis [118] as a result of interactions between increased insulin levels with other adiposity-related biologic mechanisms, such as chronic inflammation or increased estrogen production in postmenopausal women [116]. Finally, it is well known that modest weight loss of 5–10 % can reduce serum glucose levels, improve insulin sensitivity/reverse insulin resistance and decrease IGF-1 levels [125, 126]. Therefore, weight loss may be an efficient strategy for endometrial cancer prevention, as it would contribute to reducing adiposity levels and IGF-1 levels, as well as potentially reversing insulin resistance.

Insulin also indirectly stimulates endometrial carcinogenesis by increasing androgen production within the ovaries, which can lead to chronic anovulation and progesterone deficiencies, as well as decrease the synthesis of SHBG by the liver. Consequently, increased levels of bioavailable estrogens can be diffused into the endometrium [89, 127]. Indeed, Goodman-Gruen and Barrett-Connor [128] reported that postmenopausal women with impaired glucose tolerance or type 2 diabetes had greater levels of total and bioavailable estradiol compared to postmenopausal women with normal glucose tolerance, independent of age and BMI. Decreases in SHBG production by the liver in response to greater insulin levels are proposed to cause this increase in estrogen levels in women with type 2 diabetes [122].

In summary, greater endometrial cancer risk has been consistently associated with increased insulin levels, the presence of insulin resistance and type 2 diabetes. There is also sufficient evidence to suggest direct and indirect associations of endometrial cancer with increased insulin and IGF-1 levels, with amplification of these associations in the presence of obesity.

5.3 Adipokines and Inflammation

A variety of pro- (e.g., tumor necrosis factor (TNF)-α, leptin, interleukin (IL)-6, C-reactive protein (CRP)) and anti- (e.g., adiponectin) inflammatory cytokines, known as adipokines, are secreted by adipose tissue [88, 129, 130]. Obesity is known to increase the release of pro-inflammatory markers, such as TNF-α and IL-6 [131], while decreasing the release of anti-inflammatory markers and

promoting a chronic low-grade inflammatory state [132]. IL-6, in turn, stimulates the production and release of CRP by the liver [133].

Chronic, low-grade inflammation has been hypothesized to increase the risk of endometrial cancer by promoting cell proliferation and the production of free radicals that cause DNA damage [134]. Inflammatory markers can also indirectly influence endometrial cancer risk by promoting insulin resistance, hyperglycemia or aromatization activity within adipose tissue and the endometrium [112, 132, 135, 136]. Leptin, a prominent adipokine, stimulates the production and release of IL-6, TNF-α and FFA and also reduces tissue sensitivity to insulin and promotes aromatase activity [137, 138]. Conversely, adiponectin reduces circulating blood glucose and insulin levels, counteracts the pro-inflammatory effects of other cytokines (e.g., TNF-α, IL-6 and CRP), increases tissue sensitivity to insulin and promotes FFA oxidation [139–142]. Leptin will also directly promote cell growth, whereas adiponectin suppresses cell proliferation within the endometrium [143, 144]. Therefore, a greater leptin/adiponectin ratio is associated with increased endometrial cancer risk [145] and has been shown to be a surrogate marker of insulin resistance in diabetic and non-diabetic individuals [146].

Dossus et al. [132] noted positive and significant associations between CRP and IL-6 with endometrial cancer risk; however, these associations became non-statistically significant after controlling for BMI. Friedenreich et al. [131] added to these findings by reporting statistically significant positive associations between levels of TNF-α, IL-6 and CRP with endometrial cancer risk in the age-adjusted model, but only CRP remained significantly associated with endometrial cancer risk in the multivariable model (i.e., following adjustments for BMI, age and menopausal status among other risk factors). Similar results were found in a case–control study in which a significant positive association between CRP, but not IL-6 and TNF-α, and endometrial cancer risk after adjusting for BMI was observed [147]. Several case–control studies also reported greater levels of serum leptin, lower levels of serum adiponectin and/or greater leptin/adiponectin ratio in cases versus controls [39, 58, 129, 131, 145, 148–152]. These differences in leptin and adiponectin levels, or the leptin/adiponectin ratio, remained after controlling for BMI [39, 129, 149] and/or other covariates (e.g., age, diabetes and hypertension) [58, 131, 145, 148, 151, 152].

Some studies have reported possible effect modification by BMI when assessing the association between adipokine and endometrial cancer risk [129, 131]. More specifically, Cust et al. [129] reported a stronger inverse association between adiponectin levels and endometrial cancer risk in obese women. In addition, Friedenreich et al. [131] reported significant positive associations between endometrial cancer risk and CRP in women with a BMI of ≥ 30 kg/m^2, whereas IL-6 was significantly associated with endometrial cancer risk in women with a BMI of ≤ 25 kg/m^2. Finally, significant decreases in a number of pro-inflammatory adipokines (e.g., IL-6 and TNF-α) coupled with increases in adiponectin levels following an approximate 10 % weight loss [130, 153] suggest that moderate weight loss may reduce the risk of endometrial cancer development through reductions in adipokine levels.

In summary, greater endometrial cancer risk has been associated with an increased low-grade, pro-inflammatory state induced by excess adiposity. There is also evidence to suggest that the overall adipokine–endometrial cancer risk association is independent of BMI and other risk factors (e.g., diabetes, hypertension and estradiol levels), but that the link between specific adipokines with endometrial cancer may also be modified by BMI.

5.4 Metabolic Syndrome

Metabolic syndrome encompasses a number of risk factors/conditions that can increase the risk of metabolic complications, such as type 2 diabetes, cardiovascular disease and cancer [154]. These risk factors include: (1) obesity/excess central adiposity/high waist circumference, (2) hypertension, (3) elevated blood glucose levels/insulin resistance, (4) elevated triglyceride levels and (5) low high-density lipoprotein (HDL) cholesterol levels [154].

A few case–control studies reported significantly greater risk of endometrial cancer in study participants diagnosed with the metabolic syndrome [28, 57, 84], in addition to those presenting individual components of the metabolic syndrome [50, 84, 155]. More specifically, an increased risk of endometrial cancer was noted in individuals with hypertension [28, 50, 58, 84, 151, 155, 156], impaired fasting glucose/insulin resistance [28, 58, 84, 129, 151, 155], obesity/high waist circumference [28, 84, 155] and high triglyceride levels [28, 129, 155, 157]. The risk of endometrial cancer was also inversely associated with HDL cholesterol levels [129]. Conversely, both no association [129, 157] and an inverse association [158] were reported between total serum cholesterol and/or low-density lipoprotein (LDL) levels with endometrial cancer risk. It has been hypothesized that this lack of, or reverse, association between cholesterol, LDL and endometrial cancer risk may be explained by an increase in bioavailable estrogens [157, 158]. Indeed, Wallace et al. [159] observed lower total cholesterol and LDL levels in menopausal estrogen users, compared to nonusers. Lastly, some studies reported an increased endometrial cancer risk with each additional metabolic syndrome component [28, 57, 129].

Many [28, 129, 151, 155, 156], but not all [157] studies reported that the associations between each metabolic syndrome component and endometrial cancer risk were independent of BMI. Furthermore, the associations between metabolic syndrome components and endometrial cancer risk were strongest for overweight versus normal-weight women [61, 84, 129]. Thus, it is hypothesized that some of the effects of the metabolic syndrome on endometrial cancer risk may be mediated by the presence of obesity/excess weight. In fact, weight loss of approximately 10 % led to reductions in a number of metabolic syndrome components (fasting blood glucose, total cholesterol, triglycerides and LDL levels) [130].

Taken together, the presence of the metabolic syndrome increases the risk of developing endometrial cancer. The presence of excess adiposity and diabetes that often accompany metabolic syndrome provides evidence for the increased risk of

endometrial carcinogenesis as a result of greater bioavailable estrogens and circulating insulin/insulin resistance.

5.5 Mechanisms Related to Survival

There is limited evidence regarding the biomechanisms involved in the association between obesity and endometrial cancer survival [31, 160]. The leading cause of mortality in women with endometrial cancer is cardiovascular disease [161]. Therefore, it is hypothesized that obese women with endometrial cancer may have a higher mortality rate because of metabolic complications (e.g., insulin resistance and chronic inflammation) [89]. Indeed, a meta-analysis of all-cause mortality in cancer patients reported a hazard ratio of 1.76 (95 % CI 1.34–2.31) for diabetic versus non-diabetic women with endometrial cancer [162]. Bjorge et al. [28] reported an increased risk of mortality due to endometrial cancer in individuals with metabolic syndrome, greater BMI, hypertension and triglyceride levels. Despite evidence suggesting increased endometrial cancer risk as a result of obesity-related metabolic complications, the mechanism by which these complications may affect endometrial cancer recurrence and mortality requires further investigation [100].

6 Conclusion and Future Research Directions

There is abundant epidemiologic evidence demonstrating a strong and consistent association between obesity, as measured by BMI, and endometrial cancer risk. However, there is considerably less evidence on the effect of obesity on mortality (all-case and endometrial cancer-specific) among both healthy and endometrial cancer patient populations. Associations were even stronger when severe obesity was considered as observed effect estimates increased with both endometrial cancer risk and mortality. Increased waist circumference and waist-to-hip ratio were also strongly associated with increased endometrial cancer risk in pooled analyses of studies from the literature. Additionally, studies tended to show that obesity during childhood/adolescence or early adulthood also increased risk of endometrial cancer. Weight gain in adult life and weight cycling were associated with an increased risk of endometrial cancer, while weight loss was a protective factor.

Since observational epidemiologic studies are prone to effects of confounding, reverse causation and measurement error, the true effect of obesity on cancer risk cannot always be assessed without bias. Mendelian randomization could provide a method by which the obesity to cancer association could be more accurately measured because of the strong genetic component of obesity [163, 164]. By controlling for genetic variants of obesity, it is possible to determine an unbiased estimate of the causal effect of obesity on cancer risk, if additional defined assumptions are maintained, including that the genetic variant only affects cancer through its effects on obesity. However, measurement of genetic variants requires

genotyping and identification of gene loci associated with obesity; thus, there have been very few studies on Mendelian randomization with respect to obesity and cancer risk [165–167]. These studies have provided mixed results, and there are very limited studies with respect to endometrial cancer. One study by Nead et al. [122] has since demonstrated a causal effect of increased insulin levels with endometrial cancer risk using Mendelian randomization. Further studies using Mendelian randomization can more accurately determine the true casual effect of obesity on endometrial cancer risk.

As the epidemic of childhood obesity continues globally [168, 169], it is of increasing importance to understand the effects of early-life obesity on future disease risk. In this literature review, there were very few studies on the effect of childhood obesity on endometrial cancer risk and no studies on endometrial cancer mortality. The few studies to date suggest an increased risk of endometrial cancer with early-life obesity [43, 54, 79]; however, these studies were limited by self-reported approximations of childhood obesity. Additional studies on the effect of childhood obesity on endometrial cancer risk and survival using more accurate measures of obesity are necessary to better quantify this relation. Furthermore, the effects of weight gain or loss and weight cycling can aid in providing mechanistic insight into the risk of cancer associated with obesity [170].

There has been some evidence demonstrating the differential effect of obesity on Type I versus Type II endometrial cancers, since obesity is a stronger risk factor for Type I endometrial cancers and does indeed show a stronger association with Type I endometrial cancers in most studies [24, 66, 70, 85, 171, 172]. When considering other histological tumor subtypes, stronger associations of obesity–endometrial cancer risk have been found in endometrioid adenocarcinomas compared to other carcinomas or uterine sarcomas [55, 59, 66, 73, 173]. Several endometrial tumor molecular phenotypes have also been examined for potential effect modification in the obesity–endometrial cancer association. Amankwah et al. [171] demonstrated a stronger association between obesity and microsatellite-instable (MSI) tumors compared to microsatellite-stable (MSS) tumors. MSI endometrial cancers are indicative of impairment in DNA mismatch repair (MMR), and one study by Win et al. [174] has examined the effect of MMR gene mutations on early adulthood obesity and risk of endometrial cancer and found that there is an increased association in non-carriers compared to carriers. Evidence on histological or molecular subtypes of endometrial tumors remains limited, and further studies will contribute to the understanding of the obesity–endometrial cancer association.

Some studies have examined differential effects of obesity on endometrial cancer risk within population subgroups [29, 34, 40, 43, 52, 55, 67, 68, 70, 72, 74, 75, 79, 80, 87, 175, 176]. There have been mixed findings in terms of menopausal status with some studies demonstrating a stronger obesity–endometrial cancer association in postmenopausal women [29, 68], in premenopausal women [34, 43] or no difference between groups [40, 55, 79]. Two studies have also examined the association, stratified by race and largely found no difference between groups [75, 175]. There appears to be a consensus among studies that the obesity–endometrial cancer association is stronger in never users of hormone therapy [67, 68, 70, 74, 79, 80]

and oral contraceptives [40, 68, 87]. Lastly, there have also been inconsistent findings on potential effect modification by increased physical activity, with some studies showing a stronger obesity–endometrial cancer association in inactive women [52, 176] and other studies observing no difference based on physical activity levels [55, 72, 87]. A limited number of studies have examined modifying effects of other risk factors, and further research is needed to provide additional mechanistic insights into the obesity–endometrial cancer association. Furthermore, certain population subgroups may have stronger obesity–endometrial cancer risk associations and would consequently have an increased benefit with a reduction in body weight.

Although a number of hypothesized biologic pathways linking obesity and endometrial cancer development have been previously discussed [89, 177], experimental studies are needed to establish the causal associations between these biologic risk factors and endometrial cancer development. Furthermore, assessments of biologic risk factors independently of obesity are needed, since many of the proposed risk factors may be present, or their effects amplified, as a result of excess adiposity. Well-powered intervention studies aimed at reducing excess adiposity may provide strong evidence on the biologic markers that indirectly affect endometrial cancer risk through excess adiposity. Finally, further studies are necessary to investigate the effects of biologic risk factors on endometrial cancer progression and survival. These additional studies will improve our understanding of the proposed biologic pathways and aid in developing more efficient strategies for endometrial cancer prevention.

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Obesity and Prostate Cancer

Yin Cao and Edward Giovannucci

Abstract

Prostate cancer is a complex, heterogeneous disease. Factors related to detection, particularly PSA screening, further increase heterogeneity in the manifestation of the disease. It is thus not possible to provide a simple summary of the relationship between obesity and prostate cancer. Findings on obesity, often defined using body mass index (BMI), and total prostate cancer risk have been mixed; however, obesity is relatively consistently associated with a higher risk of aggressive prostate cancer, with aggressiveness defined in various ways (e.g., advanced stage, fatal, poorer prognosis in men with prostate cancer). Many methodologic issues (e.g., influence of PSA screening, detection bias and treatment) need to be thoroughly considered in both existing and future etiologic and prognostic research. Biological mechanisms supporting the link are under investigation, but may involve insulin and IGF axis, sex steroid hormones and alterations in metabolism. Some promising data suggest that molecular sub-types of prostate cancer may offer insights into etiology, but further study is required.

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A full evaluation of body fatness and weight change over the life course would not only provide insights to the underlying mechanisms but also allow more effective interventions.

Keywords
Obesity · Prostate cancer · Prostate-specific antigen screening · Heterogenity

1 Burden of Prostate Cancer

An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15 % of the cancers diagnosed in men, with almost 70 % of the cases occurring in more developed regions. Age-standardized prostate cancer incidence rates vary more than 25-fold worldwide [1]. In the USA, prostate cancer is the most frequently diagnosed cancer in men, with 60 % higher incidence rates in blacks than in non-Hispanic whites [2]. Although differences in prostate-specific antigen (PSA) screening may account largely for the global variation in incidence, geographic differences were apparent already in the era prior to PSA screening, highlighting a potential role of lifestyle factors, including obesity, to account for the variation in rates.

Prostate cancer is the fifth leading cause of death from cancer globally in men with an estimated 307,000 deaths in 2012 [1]. There is less variation in mortality rates worldwide ($\sim$10-fold) than is observed for incidence. Rates of mortality are highest in countries in the Caribbean and among African-American men in the USA. During the past decades, prostate cancer mortality rates have shown declines in some countries, most notably in the USA since 1990s, which may be attributable in part to earlier detection through PSA screening and subsequent earlier treatment [3]. Notwithstanding the considerable mortality associated with this disease, most men with prostate cancer die with and not from their cancer. Accumulating evidence suggests that overweight and obese men may have poor outcome compared to men with normal weight, and it is crucial to review evidence on obesity and mortality and recurrence of prostate cancer, as proper management of this modifiable lifestyle factor may help improve prostate cancer outcomes.

In considering the epidemiology of prostate cancer, it is critical to take into account certain features of the natural history and heterogeneity of the disease. In a recent synthesis of 19 available autopsy studies, among men aged 70–79, prostate cancer was found in 36 % of Caucasians and 51 % of African-Americans [4]. PSA screening detects many indolent cancers that otherwise would not have been diagnosed. Thus, it is important to consider, in addition to total prostate cancer, those cancers with lethal potential for several reasons. First, some evidence suggests that risk factor patterns may differ for potentially lethal and indolent disease. This suggests either that there may be separate etiologies for indolent and aggressive

prostate cancer, or that some risk factors may affect progression rather than incidence [5]. Secondly, some forms of detection biases may, for example, lead to an underdetection of prostate cancer in obese men, yet despite the apparent lower incidence, these men could still be at greater risk of fatal cancer. Potential useful indicators are advanced stage disease at diagnosis, high-grade cancer and fatal or metastatic cancer.

2 Epidemiological Evidence

2.1 Adulthood Obesity

2.1.1 Overall Obesity

Findings on obesity, often defined using body mass index (BMI), and total prostate cancer risk have yielded inconsistent findings. Nonetheless, cumulative data support a positive association between obesity and advanced/fatal prostate cancer, while the association with total or non-advanced prostate cancer has been mostly null or even inverse [6–9]. A recent meta-analysis suggests that for localized prostate cancer, there was an inverse linear relationship with BMI (relative risk (RR) 0.94; 95 % confidence interval (CI) 0.91–0.97 for every 5 kg m^2 higher BMI). In contrast, obesity was positively associated with advanced stage prostate cancer (RR 1.09; 95 % CI 1.02–1.16 for every 5 kg m^2 higher BMI) [7]. A meta-analysis that included studies up to 2010 suggests that among healthy population, a 5 kg m^2 increase in BMI was associated with a 15 % (RR 1.15; 95 % CI 1.06–1.25) higher risk of dying of prostate cancer. Obese men also have higher rates of cancer-specific mortality after diagnosis. A 5 kg m^2 higher BMI was associated with a 20 % (RR 1.20; 95 % CI 0.99–1.46) increased risk of prostate cancer-specific mortality [6]. However, in contrast, a recent analysis of 18 prospective cohort studies across 6 countries in southern and eastern Asia found that obesity was not associated with prostate cancer mortality [10]. The fact that Asian populations may be more susceptible to abdominal and visceral fat accumulation rather than overall adiposity as measured by BMI, as well as differences in detection and potentially distinct nature of disease among Asians [11] compared to Western populations may contribute to the null association. More research in other race/ethnicities is warranted.

Evidence on obesity and prostate cancer recurrence was limited. Meta-analysis for studies up to 2010 suggests that a 5 kg m^2 higher BMI was significantly associated with a 21 % increased risk of biochemical recurrence (RR 1.21; 95 % CI 1.11–1.31), with a slightly stronger association for patients who had radical prostatectomy (RR 1.25; 95 % CI 1.12–1.40) compared to patients treated with radiation therapy (RR 1.15; 95 % CI 1.03–1.28) [6]. Some [12, 13] but not all the subsequent studies [14] supported the positive association. Thus, the evidence for a role of obesity on recurrence appears suggestive but not definitive at this point.

2.1.2 Abdominal Obesity

The association between abdominal obesity and risk of total prostate cancer has been inconsistent. A recent updated analysis from the Health Professionals Follow-up Study (HPFS) suggests that waist circumference was not associated with total prostate cancer risk [15], consistent with previous report with shorter follow-up [14], and two partly overlapping meta-analyses [8, 16]. However, more recent meta-analysis showed a 56 % ($P = 0.007$) increased risk of total prostate cancer for waist circumference >102 cm (40.2 in) [17]. Some evidence suggests that abdominal obesity is associated with more advanced disease. In the European Prospective Investigation into Cancer and Nutrition (EPIC), waist circumference (RR per 5 cm 1.06; 95 % CI 1.01–1.10) and waist-to-hip ratio (RR per 0.1 unit 1.21; 95 % CI 1.04–1.39) were positively associated with diagnosis of more advanced prostate cancer [18]. Waist circumference was significantly associated with more aggressive disease in the Melbourne Collaborative Cohort Study [19], but it was not associated with advanced stage or high-grade disease in the HPFS [15].

The role of abdominal obesity in prostate cancer recurrence and survival has been less investigated. A recent study measured visceral adipose tissue using computed tomography among prostate cancer patients who underwent radical prostatectomy and found that BMI, waist circumference or VAT was not associated with biochemical recurrence [20].

2.1.3 Weight Change

Research on weight change and prostate cancer risk, recurrence and survival is limited. In a recent meta-analysis of four studies, adult weight gain was not associated with risk of total prostate cancer (RR per 5 kg increase 0.98; 95 % CI 0.94–1.02), and the summary RR per 5 kg adult weight gain was 0.96 (95 % CI 0.92–1.00) for localized prostate cancer and 1.04 (95 % CI 0.99–1.09) for advanced prostate cancer [21]. In a retrospective cohort study of 1337 men with clinically localized prostate cancer who underwent prostatectomy, compared with men who had stable weight (from 5 years before surgery to 1 year after surgery), those whose weight increased by more than 2.2 kg had almost twice the recurrence risk (RR 1.94; 95 % CI 1.14–3.32) [12]. Analysis among 4376 men diagnosed with clinically localized prostate cancer suggests that a weight gain > 5 % after diagnosis was associated with an almost doubled increased rate of prostate cancer-specific mortality (RR 1.93; 95 % CI 1.18–3.16) [22]. These findings merit further research.

2.2 Early-Life Obesity

Overweight and obesity in childhood and adolescence may influence or reflect sex hormone levels during periods of growth and development and thus may be important for later prostate cancer risk [23]. For body size in early adulthood (≤30 years), the findings were inconsistent [24–28]. Obesity in childhood has been inversely associated with risk of total, advanced or aggressive prostate cancer

[27, 29, 30], whereas other studies have shown no association [31, 32]. In a recent updated analysis of the HPFS, high BMI at age 21 was inversely associated with total prostate cancer (RR 0.89; 95 % CI 0.80–0.98 for BMI ≥ 26 versus 20–21.9 kg m^2, P_{trend} = 0.01) and with fatal and advanced disease [15]. In addition, higher cumulative average BMI was associated with reduced risk of total, non-advanced and less aggressive disease in men ≤65 years at diagnosis. However, no clear association was observed between childhood body size and prostate cancer. The authors observed greater attenuation overall when adjusting for BMI at age 21 in analyses of cumulative average BMI or waist circumference than the reverse, supporting the possibility that body size in early adulthood is more strongly related to prostate cancer development than body size later in life.

3 Methodology Issues

3.1 PSA Screening

Before PSA screening was introduced, potentially lethal cases could be identified as those with advanced stage (T3b or higher) at diagnosis; thus, pre-PSA cases were enriched with those of lethal potential, as compared to the distribution in screened populations, among which over 90 % of cases are well-differentiated tumors with low metastatic potential [33]. Therefore, epidemiologic studies of overall prostate cancer in the pre-PSA era tended to observe relative risk estimates closer to those found for lethal disease in contemporary studies.

Additionally, PSA screening may also be a potential confounder in epidemiological studies. Men who take part in regular screening practice, including PSA screening, tend also to take part in other health-related behaviors [34]. Thus, studies in the PSA era should account for PSA screening practices in their study design or data analysis.

3.2 Detection Bias

It has also been suggested that obesity makes the early detection of prostate cancer more difficult due to less PSA screening, lower accuracy of digital rectal examination in obese men and high missing rates due to large prostate [35]. In addition, obese men have lower PSA values due to increased blood volume and PSA hemodilution [36]. Among men with prostate cancer, PSA values are 7 % lower in overweight patients (BMI 25–30 kg/m^2), 14 % lower in obese patients (BMI 30–35 kg/m^2) and 18 % lower in severely obese patients (BMI > 35 kg/m^2), compared to men with normal weight patients (BMI < 25 kg/m^2) [36], with similar reductions in PSA levels reported for overweight and obese cancer-free men [37]. As such, obese men have lower PSA-driven biopsy rates. In the USA, where prostate biopsies are largely driven by PSA screening, obese men have a reduced chance of undergoing biopsy

compared to normal weight men, leading to the detection of fewer cancers in obese individuals and biasing the association between obesity and prostate cancer toward the null. In countries with lower PSA screening rates, such as Europe and Australia, this detection bias is reduced and meta-analysis of studies from these regions demonstrates a positive association between obesity and prostate cancer risk [9].

Although the existence of detection bias could not be fully ruled out, studies suggest that elevated BMI was significantly associated with a higher risk of prostate cancer-specific mortality in those without PSA screening [38] and in both pre- and PSA screening eras [39], suggesting that biological mechanisms play a role.

3.3 Treatment

Alternatively, difficulties in treatment, such as increased risk of positive surgical margins [40–42], and the greater day-to-day variation in prostate location that leads to lower dose and less effective radiation [43] could also contribute to the poorer outcome observed in diagnosed patients. However, the association with recurrence was still significant after adjusting for margin status in many studies [6]. A study among only patients with organ-confined disease and negative surgical margins also suggests that obesity remains associated with biochemical recurrence following radical prostatectomy [44].

4 Biological Mechanisms

A recent large case–control analysis of 22 studies in the PRACTICAL consortium found that genetic variants previously associated with higher BMI were minimally inversely associated with prostate cancer risk (RR per standard deviation higher BMI genetic score 0.98; 95 % CI 0.96–1.00; $P = 0.07$) [45], supporting that other factors play major roles in the link between obesity and prostate cancer. However, higher BMI genetic score appeared to be associated suggestively with higher risk of prostate cancer-specific mortality, especially among men with low-grade disease. These findings require confirmation. The following mechanisms haven been proposed so far.

4.1 Insulin and IGF Axis

Obesity induces insulin resistance [46], a condition whereby some organs become resistant to insulin's ability to shuttle glucose into cells, especially after eating a meal high in carbohydrates. To compensate for this resistance to insulin, the pancreas produces more insulin, which leads to an increase in blood insulin levels. Insulin could directly signal growth, or it could do this by increasing the levels of other growth factors (insulin-like growth factors [IGF]), or it could make cells more

sensitive to other growth factors and therefore may exert a cancer-promoting influence.

Direct epidemiologic evidence linking circulating insulin and prostate cancer risk is limited and mixed: A case–control [47] and a recent case–cohort study [48] observed positive associations, whereas three other prospective studies observed no association [49–51]. In addition, findings are inconclusive between C-peptide, a marker for insulin secretion, and risk of prostate cancer [52–54], including a recent analysis in HPFS (highest vs lowest quartile RR 1.05; 95 % CI 0.82–1.34, P_{trend} = 0.95) [52].

Circulating IGF-1 concentrations are regulated by growth hormone, present in systemic circulation and expressed in body tissues. Approximately 0.5–1 % of IGF-1 is free, with the majority being bound in the serum by acid-labile subunit and IGFBPs, including IGFBP-3, the most ubiquitous of the binding proteins. Whether obesity is associated with increased IGF levels is controversial, with most studies showing no association between total IGF-1 and obesity [55–57]. Some studies suggest that free IGF-1 levels may be more relevant. However, free IGF-1 measured by immunoassays has not been consistently associated with obesity. Because immunoassays are not able to take into account the modifying effects of IGFBPs on interactions between IGF-1 and its receptor, other measures, such as kinase receptor activation assay, have been proposed. A recent study using such method found that 24-h mean bioactive IGF-1 levels were not reduced in obese women and did not correlate with BMI [58].

Higher circulating IGF-1 levels are consistently associated with an increased risk of prostate cancer in epidemiologic studies [59]. A stronger association with low-grade prostate cancer was suggested in a pooled analysis of 12 prospective studies [60] and recent reports from EPIC [61] and the HPFS [62]. The growth of poorly differentiated cancers may be more autonomous because the PI3k-Akt pathway is constitutively active due to molecular defects (e.g., loss of PTEN, which is associated with higher-grade tumors). Thus, high-grade prostate cancers may be less sensitive to the action of IGF-1 than low-grade cancers [63]. Findings between IGFBP-3 and risk of prostate cancer have been inconsistent [60].

It is unclear whether the insulin and IGF axes interact to affect prostate cancer carcinogenesis. Recently, the role of IGFBP-1, a marker for insulin activity, which also binds IGF-1 and inhibits its action, has emerged [51, 62, 64]. High insulin levels inhibit production/release of IGFBP-1 and are associated with lower IGFBP-1 concentrations. In HPFS, higher pre-diagnostic fasting IGFBP-1 levels were associated with a lower risk of prostate cancer (highest vs. lowest quartile RR 0.67; 95 % CI 0.52–0.86, P_{trend} = 0.003), which remained similar after adjusting for IGF-1, and was primarily driven by lower-grade and non-advanced prostate cancer. Men in the bottom IGFBP-1 and top IGF-1 tertiles had a 78 % increased risk of prostate cancer compared with men in the top IGFBP-1 and bottom IGF-1 tertiles [62].

4.2 Sex Steroid Hormones

Androgens are required for the normal growth and development of the prostate gland. Most prostate tumors respond to androgen deprivation therapy until they establish an androgen-independent growth mechanism. Inhibition of the conversion of testosterone to the more potent dihydrotestosterone (DHT) by finasteride, a 5α-reductase inhibitor, reduced the occurrence of prostate cancer by approximately 25 % (95 % CI 19–31 %) during a 7-year follow-up [65]. The decrease was entirely observed in low-grade cancers, so the ultimate impact on fatal prostate cancer may be minimal [66]. Some evidence suggests that lower levels of testosterone in obese men might be linked to poorly differentiated and hormone-insensitive tumors [67, 68]. However, the Endogenous Hormones and Prostate Cancer Collaborative Group pooled 18 prospective studies that included 3886 men with incident prostate cancer and 6438 control subjects and observed no associations between the risk of prostate cancer and serum concentrations of testosterone, calculated free testosterone, DHT, dehydroepiandrosterone sulfate, androstenedione, androstanediol glucuronide, estradiol or calculated free estradiol, with similar findings for both localized and advanced diseases, suggesting that endogenous estrogen concentrations are not related to prostate cancer risk [69].

Interestingly, in the same pooled analysis by the Endogenous Hormones and Prostate Cancer Collaborative Group, serum concentration of sex hormone-binding globulin (SHBG) was modestly inversely associated with prostate cancer risk (highest vs. lowest quintile RR 0.86, 95 % CI 0.75–0.98; $P_{\text{trend}} = 0.01$) [69]. SHBG is a glycoprotein with high binding affinity for testosterone and DHT and lower affinity for estradiol. SHBG is negatively associated with obesity [69, 70] and IGF-1 [69]. Although the possibility that the inverse association observed was due to the negative relationship between concentrations of SHBG and IGF-1 could not be ruled out, the role of SHBG in prostate cancer carcinogenesis requires further research.

Early studies among prostate cancer patients showed that low pretreatment testosterone levels were associated with higher Gleason score [71], advanced stage [72, 73], positive surgical margins [73] and worse overall survival for men with metastatic prostate cancer [74, 75]. However, reverse causality is likely as low pretreatment testosterone levels could be a consequence of prostate cancer itself rather than that aggressive prostate is a result of the hormonal milieu in which it develops. To address these concerns, a recent analysis of 963 prostate cancer cases from the Physicians' Health Study (PHS) and the HPFS suggests that pre-diagnostic circulating sex hormones, including total testosterone, SHBG, SHBG-adjusted testosterone, free testosterone, DHT, androstanediol glucuronide or estradiol, were not associated with lethal prostate cancer or total mortality [76].

4.3 Metabolic Syndrome and Diabetes Mellitus

The role of obesity in cardiovascular disease and other diseases including some cancers is mediated in part or largely through alterations in metabolism. Although the basis for clustering of these factors is controversial, empirical definitions such as the metabolic syndrome may yield some etiologic insights. A recent meta-analysis summarized the result of 14 studies that evaluated the association between metabolic syndrome, its components and risk of prostate cancer [17]. A nonsignificant increased risk was observed, though no clear association was observed in cohort studies. Interestingly, a significant association was observed in the 8 European studies (RR = 1.30, $P = 0.03$), but not in the 4 US or 2 Asiatic studies. Also of note, the associations were driven by waist circumference and high blood pressure, rather than BMI, dysglycemia or dyslipidemia (including high triglycerides or low HDL cholesterol).

A diagnosis of type 2 diabetes mellitus has been associated with a decreased risk of total prostate cancer [77]. This association has been stronger for studies conducted in the PSA era, suggesting that the inverse association is stronger for more indolent cancers. Detection bias does not appear to entirely account for the association [77]. In contrast to incidence, diabetes may be associated with worse prognosis in prostate cancer. A recent meta-analysis included 11 cohort studies that examined mortality in men with prostate cancer [78]. In the meta-analysis, diabetes mellitus was associated with an increased incidence of all-cause mortality among men with prostate cancer (RR 1.50; 95 % CI 1.25–1.79), prostate cancer-specific mortality (RR 1.26; 95 % CI 1.20–1.33) and non-prostate cancer mortality (RR 1.83; 95 % CI 1.33–2.52).

4.4 Tissue-Based Factors

Molecular factors in prostate cancer tissue linking obesity and poor prostate cancer outcome is an emerging area of research. Such studies, by incorporating molecular features that underlie tumor heterogeneity, may yield insights. Such studies in the future may help unravel some of the inconsistent findings regarding obesity and prostate cancer, but research to date has been limited to a few examples.

TMPRSS2:ERG, a hormonally regulated gene fusion, presents in about half of prostate tumors [79]. In a recent analysis in the PHS and HPFS, the detrimental effects of obesity on prostate cancer outcomes are limited primarily to men with tumors harboring the *TMPRSS2:ERG* gene fusion. Among men with ERG-positive tumors, the RR for lethal prostate cancer was 1.48 (95 % CI 0.98–2.23) per 5-unit higher BMI before diagnosis, 2.51 (95 % CI 1.26–4.99) per 8-inch higher waist circumference before diagnosis and 2.22 (95 % CI 1.35–3.63) per 5-unit higher BMI at baseline. In contrast, the corresponding RR among men with ERG-negative tumors was 1.10 (95 % CI 0.76–1.59; $P_{interaction} = 0.24$), 1.14 (95 % CI 0.62–2.10; $P_{interaction} = 0.09$) and 0.78 (95 % CI 0.52–1.19; $P_{interaction} = 0.001$) [80]. If

confirmed, this finding could potentially inform prostate cancer therapy development and secondary prevention strategies.

Fatty acid synthase (FASN) is an enzyme critical in the synthesis of endogenous fatty acids, which can be modified and packaged into structural lipids required for cell division. Elevated FASN enzyme, mRNA and enzymatic activity have been seen in human breast cancer cell lines [81], ovarian tumors [82] and prostate tumors [83], and polymorphisms in *FASN* were associated with BMI [84]. In HPFS, SNP rs1127678 was significantly related to higher BMI and interacted with BMI for both prostate cancer risk ($P_{interaction} = 0.004$) and prostate cancer mortality ($P_{interaction} = 0.056$). Among overweight men (BMI ≥ 25 kg/m^2), but not leaner men, the homozygous variant allele carried a relative risk of advanced prostate cancer of 2.49 (95 % CI 1.00–6.23) compared with lean men with the wild type. Overweight patients carrying the variant allele had a 2.04 (95 % CI 1.31–3.17) times higher risk of prostate cancer mortality. Similarly, overweight patients with elevated tumor FASN expression had a 2.73 (95 % CI 1.05–7.08) times higher risk of lethal prostate cancer. In contrast, among men who had normal body weight, FASN expression level was not significantly associated with lethal prostate cancer ($P_{interaction} = 0.02$). Significant interactions of BMI with *FASN* polymorphisms and FASN tumor expression suggest that FASN may be a potential link between obesity and poor prostate outcome and raise the possibility that FASN inhibition could reduce prostate cancer-specific mortality, particularly in overweight men [83].

5 Conclusions

Prostate cancer is a complex, heterogeneous disease. Factors related to detection, particularly PSA screening, further increase heterogeneity in the manifestation of the disease. It is thus not possible to provide a simple summary of the relationship between obesity and prostate cancer. At a first level, it is useful to separate manifestations of relatively indolent disease (e.g., organ-confined, low-grade, non-lethal, total cancer in the PSA era) and aggressive disease (advanced stage, lethal, poor prognosis). Overall, although there are some exceptions, obesity does not appear to increase risk of indolent prostate cancer. Some evidence even suggests a potential protective association, though it is unclear whether this is biologically related (e.g., low testosterone levels) or related to lower detection (e.g., obesity may lower PSA levels).

In contrast, obesity is relatively consistently, though with exceptions, associated with a higher risk of aggressive prostate cancer, with aggressiveness defined in various ways (e.g., advanced stage, fatal, poorer prognosis in men with prostate cancer). A number of mechanisms, not mutually exclusive, may account for this association: (1) later detection in obese men, (2) poorer response to treatment and (3) direct biological mechanisms (e.g., hyperinsulinemia). In part, if less aggressive cancers are detected in obese men, for any reason (see above), obese men will be selected to have more aggressive cancer if diagnosed by the exclusion of diagnosed

indolent cancers. Whatever the explanation(s), under most circumstances it is reasonable to assume from a clinical perspective that obese men diagnosed with prostate cancer are likely to have a worse prognosis independent of other known clinical predictors. Some promising data suggest that molecular sub-types of prostate cancer may offer insights into etiology, but further study is required.

Together, these data provide encouraging evidence for using weight management to prevent aggressive prostate cancer, prostate cancer disease progression and reduce prostate cancer-specific mortality. However, many methodologic issues (e.g., influence of PSA screening, detection bias and treatment) need to be addressed in etiologic and prognostic research. More data are needed to understand the timing of body fatness/weight gain relative to the diagnosis/treatment of prostate cancer. A full evaluation of body fatness and weight gain over the life course would not only provide insights into the underlying mechanisms but also allow more effective interventions. Such interventions may include increasing self-awareness and more early detection efforts among overweight or obese healthy individuals, and more counseling on healthy lifestyle (e.g., physical activity) after diagnosis, and appropriate personalized treatment for overweight and obese patients.

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Obesity and Ovarian Cancer

Shelley S. Tworoger and Tianyi Huang

Abstract

Ovarian cancer is the most fatal gynecologic cancer and is an important source of cancer-related mortality, particularly in developed countries. Despite substantial research examining adiposity (primarily adult body mass index [BMI]), the overall evidence suggests only a weak positive association between adiposity and risk of ovarian cancer, with stronger associations observed for population-based case–control studies compared to prospective studies. Ovarian cancer is not one disease and emerging data suggest that higher BMI may only be associated with risk of certain histologic subtypes, including low-grade serous and invasive mucinous tumors. Interestingly, some larger studies and meta-analyses have reported a stronger relationship with premenopausal ovarian cancers, which are more likely to be of these subtypes. Relatively few studies have conducted detailed examinations of other adiposity-related factors such as measures of abdominal adiposity, early-life body size and weight change. While the underlying mechanisms that may relate adiposity to risk are unclear, increased inflammatory biomarkers have been associated with risk and hormonal factors, including androgen levels, may be important for the development of

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mucinous tumors. Future research should leverage the large sample sizes of consortia to evaluate associations by key tumor characteristics as well as consider patterns of weight change over the life course with both ovarian cancer risk and survival.

Keywords
Ovarian cancer · Body mass index · Inflammation · Histologic subtypes

1 Introduction

In 2014, body fatness was listed as a probable risk factor for ovarian cancer by World Cancer Research Fund/American Institute for Cancer Research, although the link of overweight and obesity with other cancer sites, such as postmenopausal breast, colorectal and endometrial cancer, has been well established for many years [1, 2]. Conversely, according to the US National Cancer Institute, ovarian cancer is not considered an obesity-related cancer; however, a potential relationship between obesity and ovarian cancer cannot be ruled out: 'Some studies have shown a weak association between increasing body mass index (BMI) and risk of ovarian cancer, especially in premenopausal women, although other studies have not found an association' [3]. Similarly, the American Cancer Society lists ovarian cancer as only possibly being linked to overweight or obesity [4]. As such, current cancer prevention recommendations specifically for ovarian cancer do not include reducing adiposity, which reflects the weaker and less consistent epidemiologic evidence regarding the association between obesity and ovarian cancer.

Worldwide, ovarian cancer is the seventh most common female cancer and second most fatal gynecologic malignancy, with an estimated 238,700 new cases and 151,900 deaths in 2012 [5]. Incidence and mortality are higher in more developed (9.1 and 5.0 per 100,000, respectively) than less developed areas (5.0 and 3.1 per 100,000, respectively) [5]. Between 1998 and 2008, a modest decrease in ovarian cancer incidence was observed in the USA, perhaps in part due to the reduction in use of postmenopausal hormone therapy [6]; the prevalence of obesity, however, increased slightly over the same period [7], again supporting an overall weak association of obesity with ovarian cancer. Of note, ovarian cancer is a heterogeneous disease, with several histologic subtypes that reflect different developmental pathways [8]. Such etiologic heterogeneity may mask the role of obesity in ovarian tumor development and progression.

In this chapter, we first review important biological hypotheses, proposed mechanisms and experimental evidence that link obesity with ovarian cancer. Then, we review epidemiological and clinical data addressing this relationship, including studies that examine the risk of ovarian cancer using different measures of obesity (e.g., BMI, fat distribution, weight gain) or by histologic subtype, as well as studies

that examine the impact of obesity on prognosis. Limitations and caveats in interpreting these findings are discussed. We also briefly review current evidence for other obesity-related factors, such as physical activity, diet, inflammation and stress, in relation to ovarian cancer. We conclude with future prospects of research directions on obesity and ovarian cancer.

2 Potential Mechanisms

It is now recognized that adipose tissue not only serves as a depot for calorie storage but also acts as an endocrine organ that integrates various physiological processes involving glucose homeostasis, immunity and reproductive function [9, 10]. Based on this, several widely accepted biological pathways have been proposed as general mechanisms to link obesity and cancer risk, including dysregulation of endogenous sex steroid hormones, insulin resistance and hyperinsulinemia, bioavailability of insulin-like growth factor 1 (IGF-1) and adipokine-mediated inflammation [1, 2]. These mechanisms have been explored in the context of ovarian cancer development.

Obesity has been shown to increase circulating estrogen and androgen levels, particularly among postmenopausal women [11, 12], and these endogenous sex hormones have been implicated in the pathogenesis of ovarian cancer [13, 14]. Estrogens may be positively associated with ovarian cancer risk by promoting the proliferation of ovarian epithelial cells [15], although epidemiologic evidence on pre-diagnostic estrogen concentrations and ovarian cancer risk is limited and not supportive [16–18]. A recently published study suggested that estradiol was not associated with risk overall, but there was a positive association for the endometrioid subtype [17]. This subtype is more likely to be estrogen and progesterone receptor positive than other histologies [19]. Despite lack of epidemiologic evidence, possibly due to the difficulty in estrogen measurement in women and limited sample sizes to address histologic-specific associations, the estrogen hypothesis is consistent with observations that ovarian cancer risk is increased with longer use of estrogen-only postmenopausal hormones [20–22], which substantially elevates circulating estrogen concentrations, and decreased with longer use of oral contraceptives [23, 24], which reduces ovarian estrogen synthesis. Evidence from some observational studies provides some support for the hypothesis that higher circulating androgen levels may increase ovarian cancer risk [16–18]. Polycystic ovarian syndrome (PCOS), a common benign gynecologic disorder characterized by hyperandrogenism, is associated with higher risk of ovarian cancer [25]. Smaller studies of circulating androgens, however, do not support an association [26–28]. Two recent, larger studies suggested that androgens were only associated with low-grade serous and mucinous tumors [17, 29]. Overall, sex hormones may play a role for specific subtypes of ovarian cancer, supporting examination of adiposity with ovarian cancer by histologic subtype.

Adiposity is also associated with alterations in insulin-related pathways, including increases in IGF-1. Experimental data suggest that IGF-1 and its receptors promote the growth of ovarian carcinoma cells, while blocking IGF signaling system shows anti-tumor properties [30, 31]. Some [32, 33], but not all [34–37], epidemiologic studies support a positive association between pre-diagnostic circulating levels of IGF-1 and risk of ovarian cancer. Four studies published before May 1, 2015, were meta-analyzed [38], showing no significant associations between ovarian cancer and IGF-1 or IGF binding protein 3. Several studies also suggest elevated levels of IGF-1 and its binding protein 2 in ovarian cancer patients [39–42].

Increased inflammation is a hallmark of adiposity [43]. Notably, ovarian tumors are characterized by dysregulation of interleukin (IL)-6 and tumor necrosis factor (TNF) α[44–48], and patients with high circulating IL-6 and TNFα have worse survival [49, 50]. However, prospective studies evaluating circulating levels of these markers have been mixed, although most were small [51–54]. Conversely, pre-diagnosis C-reactive protein (CRP) levels have been consistently positively associated with ovarian cancer risk, particularly for overweight women [52–57], suggesting a role for this pathway.

In addition, adipose tissues release fatty acids into circulation, which is central for lipid synthesis and metabolism. Substantial data indicate that lipid synthesis and metabolism are dysregulated in ovarian tumors [58, 59]. Three prospective studies have examined circulating total cholesterol, HDL or LDL with ovarian cancer risk. An early study that did not adjust for covariates observed no association for total cholesterol [60], but another study reported an adjusted threefold higher risk comparing the top versus bottom tertile [61]. A registry study observed a significant 52 % lower risk comparing HDL ≥ 1.0 versus <1.0 mmol/L, but no association for total cholesterol or LDL [62]. However, pre-diagnostic LDL was positively associated with ovarian cancer death [63]. Further, in patients undergoing gynecologic surgery who were injected with a radio-labeled LDL lipid emulsion, ovarian tumors had 8 times higher uptake of LDL than benign or normal tissue [64], and LDL can increase proliferation in ovarian cancer cell lines [65]. Recent work suggests that statin use, which lowers cholesterol levels, may be associated with a lower ovarian cancer risk [66, 67].

Overall, biological evidence supports that adiposity-related factors can influence carcinogenesis; however, epidemiologic data are less supportive that these pathways are associated with ovarian cancer risk. Further studies of these pathways controlling for adiposity are critical to understand the biological underpinnings of a potentially association.

3 Body Mass Index and Overall Ovarian Cancer Risk

More than 50 studies have been conducted to investigate the association between BMI and ovarian cancer considering all subtypes together, with several systematic reviews, meta-analyses and pooled analyses [68–73]. Overall, the results suggest a

weak-to-moderate positive association between BMI and ovarian cancer risk. An early meta-analysis [68], which included 28 prospective and case–control studies, reported a 30 % increased risk of ovarian cancer for obesity (BMI $\geq$ 30; 95 % CI 1.12, 1.50) and a 16 % increased risk of overweight (BMI 25–29.9; 95 % CI 1.01, 1.32), compared to normal weight (BMI 18.5–24.9). Significant heterogeneity in the risk estimates was noted across studies, which was attenuated after excluding one prospective cohort study with 1.1 million Norwegian women that found no overall association [74]. Of the remaining 27 studies, 24 found evidence for a potential positive association and 10 reached statistical significance. This meta-analysis also suggested a stronger effect estimate for obesity among case–control studies (odds ratio 1.49; 95 % CI 1.29, 1.72) than prospective studies (relative risk 1.12; 95 % CI 0.95, 1.32).

A pooled meta-analysis of 47 studies was conducted by Collaborative Group on Epidemiological Studies of Ovarian Cancer and reported a positive association between BMI and ovarian cancer risk [70]. The overall relative risk was 1.13 (99 % group-specific CI 1.06–1.20) per 5 kg/m^2 higher BMI, although this result was primarily driven by associations in case–control studies with population-based controls (relative risk 1.10; 99 % CI 1.05–1.16). Notably, the risk estimate was not statistically significant among 17 prospective studies (relative risk 1.03; 99 % CI 0.99–1.07), and no association was observed for 13 case–control studies using hospital controls. Further, there was a significant difference in the association by postmenopausal hormone use, with increased ovarian cancer risk with higher BMI observed for never users, but not ever users.

A disadvantage of meta-analyses is that they ignore the different analytical strategies employed across studies. Therefore, the Pooling Project of Prospective Studies of Diet and Cancer, with primary data from 12 prospective cohort studies, pooled all data giving a total of 2036 epithelial ovarian cancer cases among 531,583 women [72]. The data were analyzed with standardized exposure definitions, adjustment for confounding, and handling of missing data. No association was observed for adult BMI; the summary relative risk was 1.03 (95 % CI 0.86, 1.22) comparing BMI $\geq$ 30 versus 18.5–23 kg/m^2. This study also showed similar results for age- and multivariable-adjusted models, suggesting that residual confounding may have little influence on the risk estimates.

The Ovarian Cancer Association Consortium meta-analyzed original data from 15 population-based case–control studies (13,548 cases, 17,913 controls) to investigate the association between BMI and ovarian cancer risk using common analytic strategies [75]. For recent BMI, which was defined as the self-reported BMI within 1–5 years prior to diagnosis (for cases) or reference date (for controls), the pooled odds ratios (95 % CIs) per 5 kg/m^2 higher BMI were 1.04 (1.00, 1.08) for invasive tumors and 1.18 (1.14, 1.23) for borderline tumors. For maximum BMI, which was calculated from recalled maximum lifetime weight, the pooled odds ratios (95 % CIs) per 5 kg/m^2 higher BMI were 1.06 (1.01, 1.11) for invasive tumors and 1.17 (1.08, 1.26) for borderline tumors. Interestingly, the significant positive associations with recent BMI held after adjusting for maximum BMI, but the associations for maximum BMI were no longer significant.

A recent meta-analysis of 28 prospective studies (24 studies for BMI) representing the most updated summary (19,825 cases from 6,681,795 participants) sheds light on the potential dose–response relationship between BMI and ovarian cancer risk [69]. Each 5-unit higher BMI was associated with 7 % (95 % CI 1.03, 1.11) increased risk of ovarian cancer. There was moderate heterogeneity across studies, which appeared to be driven by the same Norwegian study [74] as in the prior meta-analysis [68]. In contrast to prior analyses that found no association [70, 72] or statistically nonsignificant positive associations among prospective studies [68], this is the first meta-analysis providing prospective evidence for a significant positive association with adulthood BMI. Another interesting finding was the nonlinear pattern linking BMI with ovarian cancer risk—the positive association was apparent for the range of BMI above 27.6 kg/m^2 and the strength of the association increased with higher BMI.

In addition to studies that focused on ovarian cancer, a number of studies have evaluated obesity with total cancer risk and reported the associations with cancers of particular sites, including ovary [76–79]. These studies highlighted that the association between obesity and ovarian cancer was weaker in magnitude compared to other cancer sites. For example, in a recent cohort study of 5.24 million UK women, the relative risk of each 5 kg/m^2 higher BMI was 1.09 (99 % CI 1.04, 1.44) for ovarian cancer and 1.62 (99 % CI 1.56, 1.69) for uterine cancer [77].

Several methodological considerations should be considered when interpreting these results. First, information on BMI was obtained through self-reported weight and height in most studies. Despite reasonable correlations between self-reported and measured weight and height, women tend to underreport their weight, particularly among overweight or obese women [80–82]. Second, many large cohort studies only collected information at baseline and were unable to investigate the potential impact of changes in BMI on ovarian cancer. The results based on a single measure of BMI may be biased toward the null due to misclassification over time. One meta-analysis suggested that the heterogeneity across studies may be due to large cohort studies with long follow-up but only a single, baseline BMI assessment, which generally reported no or even suggestively inverse associations [68]. Third, BMI measures general adiposity and does not indicate the location of adiposity. This may lead to additional measurement error if biological pathways related to fat distribution are more relevant for the carcinogenesis of ovarian cancer. Finally, it is important to consider timing of BMI assessment relative to diagnosis, as preclinical or clinical symptoms of ovarian cancer, such as cachexia, peritoneal fluid retention and tumor growth, may lead to remarkable changes in body weight. In prospective studies, this issue is usually addressed by lagged analysis. For example, a sensitivity analysis in one pooled study excluded the first 4 years of follow-up after BMI assessment at baseline in the cohort studies, although the results were similar [70]. In case–control studies, women recall their body weight months to years before diagnosis, when it is possible that preclinical disease had already begun to influence weight. Further, recall bias may play a role, and such differential misclassification may explain the stronger positive associations reported in case–control studies.

4 Obesity and Ovarian Cancer Risk by Histologic Subtypes

Ovarian cancer is a highly heterogeneous malignancy. The histologic subtypes of ovarian cancer, including serous, endometrioid, mucinous and clear cell tumors, may originate through different etiologic pathways [8, 14, 83, 84], displaying a high level of heterogeneity in genetic origin, clinical behavior and disease progression, as well as in their relations with reproductive, hormonal and lifestyle factors [73, 85–87]. In particular, obesity may be etiologically more relevant to endometrioid tumors, as this subtype has similar histology with endometrial cancer, which has strong positive associations with obesity [88]. Further, mucinous tumors, which have molecular similarity with the intestinal mucosa, have similar risk factor profiles to colon cancer, an established obesity-related cancer. Emerging evidence also suggests that low- versus high-grade serous invasive tumors are pathophysiologically and genetically distinct [89, 90]. Advances in tumor classification and subtyping provide the foundation to elucidate the potential difference by histologic subtypes. However, individual studies are generally underpowered to examine different ovarian cancer subtypes separately.

In the Ovarian Cancer Association Consortium of 15 case–control studies, higher BMI was not associated with invasive serous tumors, the most common subtype, but significantly increased risks were noted for borderline serous tumors, invasive endometrioid tumors and invasive mucinous tumors [75]. When further examining invasive serous tumors by menopausal status and grade, there was an increased risk among premenopausal women and for low-grade invasive serous tumors; high-grade invasive serous tumors, the most fatal subtype, were not associated with BMI. Another population-based case–control study found no overall association for invasive serous, endometrioid or mucinous tumors, but an increased risk of clear cell subtype [91]. When further examining invasive serous tumors by location, an increased risk was observed for serous peritoneal tumors but not for serous tumors of ovary or fallopian tube.

Individual prospective studies generally reported null results for specific histologies due to insufficient power. However, the pooled analysis of 12 cohorts also reported that BMI was not associated with any histologic subtype, including serous, endometrioid and mucinous tumors [72, 74]. A meta-analysis of 47 studies suggested significantly increased risks of serous, endometrioid and mucinous tumors, and the risks were higher for borderline serous tumors and invasive mucinous tumors [70]. Another study observed a positive association with waist–hip ratio for mucinous tumors only [92].

Understanding the subtype-specific associations has important implications; however, the evidence is relatively limited due to unavailability of histology in many studies. For example, histologic subtype was only available for 68 % of cases in a pooled analysis [70]. Despite the improvement over time in the standards and reproducibility for classifying ovarian tumor histology, subtype misclassification is a concern, particularly when including older and more recent studies. Therefore,

large consortia with consistent histology evaluation are needed to estimate the subtype-specific associations with obesity.

5 Other Anthropometric Measures and Overall Ovarian Cancer Risk

As BMI is relatively easy to obtain, previous studies have predominantly used this as a measure of obesity. This facilitates synthesis of findings across studies. However, BMI does not provide data on fat distribution and is potentially problematic for older individuals, as increased BMI may be due to loss in fat-free, lean body mass rather than accumulation of body fat. As a result, a limited number of studies have evaluated waist circumference, hip circumference and waist-to-hip ratio with ovarian cancer risk.

To date, three large prospective studies have examined central adiposity measures in relation to ovarian cancer risk [92–94]. None observed statistically significant associations for waist circumference, hip circumference or waist-to-hip ratio, although the risk estimates from these studies were generally suggestive of weak positive associations. Also, these studies suggested that the associations for measures of fat distribution were weaker compared to that of BMI. A meta-analysis summarizing all published prospective studies reported a marginally positive association for waist circumference (relative risk 1.06; 95 % CI 1.00, 1.12 per 10 cm higher waist circumference). No associations were observed for hip circumference or waist-to-hip ratio [69]. Interestingly, height consistently displays a strong positive association with ovarian cancer risk. Fifteen of sixteen cohort studies reported a positive association; 10 reached statistical significance [69]. Methodological considerations for BMI also apply to studies of other anthropometric measures. Potential measurement error in waist circumference and hip circumference is of particular concern, as these anthropometric measures are less likely to be self-reported accurately than weight and height [95]. Given the paucity and inconsistency of evidence on abdominal and hip adiposity, additional studies are required to elucidate their associations with ovarian cancer risk overall and by histology.

6 Adiposity During Different Periods of Life and Overall Ovarian Cancer Risk

Despite the modest association between obesity and ovarian cancer risk, it is possible that adiposity across the life course may influence cancer risk differently. For example, postmenopausal obesity is positively associated with breast cancer risk, but early-life adiposity is inversely associated with risk [96, 97], while endometrial cancer is most strongly related to current adiposity [98]. This may be

attributed to the interplay with hormonal milieu and reproductive behaviors that substantially differ before and after menopause. Given the important role of hormonal and reproductive factors in ovarian cancer etiology, it is possible that the interaction between obesity and these factors may also vary by periods of life, resulting in a differential impact on ovarian cancer risk.

In general, the association between obesity and ovarian cancer has been stronger among premenopausal than postmenopausal women. A pooled analysis of 12 cohort studies reported an increased risk in premenopausal women (RR BMI $\geq$ 30 vs. 18.5–23 kg/m^2: 1.72; 95 % CI 1.02, 2.89), but not postmenopausal women (comparable RR 1.07; 95 % CI 0.87, 1.33) [72]. Further, there was an inverse association of ovarian cancer with hip circumference in the Nurses' Health Study (mostly postmenopausal) and a positive association in the Nurses' Health Study II (mostly premenopausal) [93]. However, in the European Prospective Investigation into Cancer and Nutrition, baseline BMI had a stronger association with postmenopausal than premenopausal risk [92]. Similarly, most [71, 91, 99], but not all [100], case–control studies reported higher risk estimates for adiposity during premenopausal years than postmenopausal years.

Research also has examined adiposity in childhood and early adulthood. A meta-analysis of six cohorts found significantly increased risk of ovarian cancer for every 5 units in BMI during early adulthood (relative risk 1.12; 95 % CI 1.05, 1.20) [69]. Evidence of nonlinearity was also noted for the association, with the risk increasing more sharply for BMI above 30 kg/m^2. A consortium of case–control studies reported 8 % (95 % CI 1.03, 1.14) increased risk of invasive ovarian cancer and 15 % (95 % CI 1.08, 1.24) increased risk of borderline ovarian cancer per 5 kg/m^2 higher recalled BMI at age 18 or 20 [75]. One prospective study examined associations of average body fatness at ages 5 and 10 with risk [101]. There was a weak inverse association in older women (RR for heaviest versus most lean = 0.81; 95 % CI 0.53–1.24, P for trend = 0.04) and a nonsignificant positive association in younger women (RR = 2.09; 95 % CI 0.98–4.48; *P* for trend = 0.10). Birth weight generally has not been associated with risk [101–103].

7 Weight Change and Ovarian Cancer Risk

The influence of weight change on ovarian cancer risk has not been considered in most studies, as adiposity was often evaluated based on a single assessment. Weight change reflects the trajectory of adiposity during certain periods of life and is more likely to capture the long-term effect of obesity accumulated over time. Further, if the results for weight gain were consistent with those observed for other measures of adiposity, it would lend support to the causal role of obesity in ovarian cancer development.

A recently published dose–response meta-analysis of prospective observational studies evaluated the association between adult weight gain and cancer risk, including ovarian cancer [104]. Adult weight gain was defined as the difference in

weight between early adulthood (i.e., age 18–25 years) and study baseline. In two studies that included only postmenopausal women and had data on postmenopausal hormone use [105, 106], there was 13 % increased risk (95 % CI 1.03, 1.23) of postmenopausal ovarian cancer among women with no/low hormone use for each 5 kg weight gain from early adulthood to study enrollment. Further, in the European Prospective Investigation into Cancer and Nutrition, an increased risk (relative risk 2.41; 95 % CI 1.19, 4.87) was observed among premenopausal women when comparing the mid-category of weight gain (i.e., 10–15 kg) with stable weight (i.e., ±5 kg) [92]. However, there were no associations for higher weight gain categories. Results from the Nurses' Health Study comparing biennially updated body weight versus recalled weight at age 18 also suggested no association for adult weight gain [107]. A Swedish cohort study observed no association of ovarian cancer with weight change between age 25 and study baseline, but did report an increased risk of breast and endometrial cancer [108]. A more recent meta-analysis of six cohort studies also found no association between weight gain since early adulthood and risk [69]. In addition, three of the four case–control studies that examined adult weight gain with ovarian cancer risk found no association [91, 100, 109]; only one study found a significant positive association among nulliparous women [110]. Overall, these studies are not strongly supportive of an association of weight gain with ovarian cancer risk.

Since almost all studies evaluated adult weight gain using a combination of self-reported current weight and recalled past weight, measurement error may attenuate the risk estimates. Also, the assessment of weight change was based on differences between two discrete time points in most studies, which does not capture the trajectory of body weight. Further, most studies only counted weight gain since early adulthood until study enrollment and did not accounted for weight change after baseline. This may mask the true association if weight change during specific life period is etiologically relevant to ovarian cancer development. These challenges need to be addressed in future studies.

8 Obesity-Related Factors and Ovarian Cancer

A number of lifestyle and dietary factors that influence on body weight have been investigated with ovarian cancer risk. Associations have generally been inconsistent for dietary factors (e.g., lactose, animal fat, vegetables, fruits, red meat) that influence obesity [111]. Healthy dietary patterns or dietary quality indices are associated with lower risk of obesity [112–114] also have not been associated with risk [115–117]. Similarly, results have been very mixed for the association between physical activity and ovarian cancer [118]. Several large prospective studies reported an increased risk with higher levels of activity [119–122], which in one study was largely due to premenopausal activity, although premenopausal inactivity was also associated with an increased risk of endometrioid tumors [122]. Further, based on limited evidence, there was no association for hypertension [123, 124],

and conflicting results for diabetes [125–128] and hypercholesterolemia [124, 129]. Taken together, these obesity-related factors are only proxies for adiposity, but their equivocal associations with ovarian cancer add additional evidence to the very modest association between obesity and ovarian cancer risk.

9 Obesity and Ovarian Cancer Prognosis

For most cancer sites, obesity also is an important factor for prognosis [76]. Since ovarian cancer has very high fatality, identifying and confirming additional prognostic factors beyond what has been known (e.g., age, tumor stage, invasiveness, surgical debulking) is important. However, as noted previously, ovarian cancer itself can alter adiposity to increase weight (e.g., ascites) or reduce weight (e.g., cachexia) [130]. Considering adiposity well before diagnosis may address this challenge. Further, women who are obese may have less optimal surgical debulking (a strong predictor of survival) and be underdosed for chemotherapy due to dose capping by weight [131–134]. As such, the study of obesity and ovarian cancer survival is particularly complex. That said, omental adipose depots provide a permissive tumor micro-environment for metastatic implants [135] and that dysregulation of adipokines may contribute to upregulation of pro-angiogenic pathways [136, 137], supporting that adiposity may influence survival.

Studies evaluating obesity and mortality among ovarian cancer patients are limited, with small sample size. A meta-analysis of 10 studies showed poor survival associated with obesity at a young age [138]. Neither BMI at the time of diagnosis nor 1–5 years prior to diagnosis was associated with overall ovarian cancer survival, although when restricting to patients with advanced-stage ovarian cancer, obesity before diagnosis was associated with 45 % increased mortality. In contrast, obesity was associated with higher mortality among ovarian cancer patients in a meta-analysis of 14 studies (RR 1.17; 95 % CI 1.03, 1.34), and the estimates were similar regardless of the timing (i.e., before diagnosis, at diagnosis or after initiating chemotherapy) [139]. Similar results were observed in a meta-analysis of 17 cohort studies for obesity 5 years before diagnosis and during early adulthood, but whether obesity at diagnosis was associated with ovarian cancer survival remained unclear [140]. More recent evidence comes from the Ovarian Cancer Association Consortium, which included 12,390 invasive ovarian cancer cases from 21 studies [141]. BMI was reported from up to 5 years before diagnosis to time of diagnosis. Compared to a BMI of 18.5–24.9, overall mortality was 10 % higher (95 % CI 0.99, 1.23) for a BMI of 30–34.9 and 12 % higher (95 % CI 1.01–1.25) for a BMI $\geq$ 35. The association was strongest for low-grade serous and endometrioid tumors. Studies also suggest that BMI was inversely associated with quality of life in ovarian cancer patients [142, 143].

10 Future Directions and Conclusion

Overall, existing evidence supports a weak positive association between adiposity and risk of ovarian cancer. However, emerging evidences suggests that higher BMI may only be associated with risk of specific subtypes of ovarian cancer, notably low-grade or borderline serous tumors and invasive mucinous tumors, but not with high-grade serous carcinomas. Further, recent work suggests a potentially stronger association of adiposity with premenopausal ovarian cancers, which are less likely to be of high-grade serous histology. Notably, the strength and pattern of associations appear to differ for prospective cohort versus case–control study designs, with each having key limitations.

Future research is critical to better clarify the role of adiposity in ovarian cancer risk and survival. Importantly, consortia that obtain primary data from studies to conduct pooled analyses using harmonized variables will be crucial to increase sample sizes. This is necessary to consider associations by tumor subtypes, especially rare histologies, as well as interactions by menopausal status, postmenopausal hormone use and other factors. Further, prospective studies with repeated weight assessments over the life course will be particularly important in examining adiposity at different times of life and trajectories of weight change over time. Such studies can also be used to examine how adiposity at different times may influence survival in ovarian cancer patients. Methodological rigor and detailed case treatment information will further enhance our understanding of this relationship. In summary, adiposity is not a strong risk factor for ovarian cancer, particularly compared to reproductive and hormonal factors; however, continued research is critical to identify specific populations and ovarian cancer subtypes for which weight reduction may be most beneficial.

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Obesity and Liver Cancer

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Abstract

Obesity and related metabolic disorders have become globally prevalent posing a challenge for the chronically damaged liver and predisposing the development and progression of cancer. The rising phenomenon of "obesity epidemic" may provide means for understanding why liver cancer is one of the few malignancies with rising incidence in developed countries over the last decades. Non-alcoholic fatty liver disease associated with obesity, insulin resistance, and type 2 diabetes is an increasingly recognized trigger for liver cancer in Western populations characterized by low prevalence of established risk factors for liver cancer such as viral hepatitis and hepatotoxin exposure. Accumulating evidence has established an association between higher body mass index as an indicator of general obesity and higher risk of primary liver cancer. The associations are stronger in men, in patients with underlying liver disease and in white ethnic

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groups. Abdominal obesity, weight gain in adult life and metabolic factors related to visceral fat accumulation were also suggested as important risk factors for liver cancer; however, more studies are needed to evaluate these associations. The association of obesity and metabolic parameters with liver cancer survival remains controversial. It is unclear which exact mechanisms could provide links between obesity and liver cancer risk. Recent evidence has implicated several molecular pathways in obesity-associated liver cancer. These include insulin resistance leading to increased levels of insulin and insulin-like growth factors, chronic inflammation, adipose tissue remodeling, pro-inflammatory cytokine and adipokine secretion, and altered gut microbiota. These mechanisms coincide with inflammatory and metabolic processes occurring in non-alcoholic fatty liver disease predisposing cancer development and progression. In the context of the current evidence, better understanding of the role of obesity and related metabolic factors may help in improving current strategies for liver cancer prevention.

Keywords

Obesity · Metabolic factors · Inflammation · Non-alcoholic fatty liver disease · Liver cancer · Prevention

Abbreviations

HCC	Hepatocellular carcinoma
IBDC	Intrahepatic bile duct cancer
ICC	Intrahepatic cholangiocarcinoma
HCV	Hepatitis C virus
HBV	Hepatitis B virus
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
WCRF	World Cancer Research Fund
BMI	Body mass index
EPIC	The European Prospective Investigation into Cancer and Nutrition
WHO	World Health Organization
WC	Waist circumference
JNK-c	Jun N-terminal kinase
NF-kβ	Nuclear factor-kappaB
TLR	Toll-like receptors
IGF-I	The insulin-like growth factors I
IGF-II	The insulin-like growth factors II
IGFBP4	The insulin-like growth factors binding protein-4
HOMA	Homeostasis model assessment
ROS	Reactive oxygen species
TNF	Tumor necrosis factor

IL-6	Interleukin 6
CRP	C reactive protein
DCA	Deoxycholic acid
HSCs	Hepatic stellate cells

1 Introduction

Worldwide, primary liver cancer is the fifth most common cancer in men and the ninth most common cancer in women [1, 2]. In 2012, worldwide 782,000 new cancer cases were diagnosed and nearly 746,000 deaths occurred [3]. The prognosis is very poor, with a 5-year survival rate between 5 and 9 %, and thus, primary liver cancer is the second leading cause of cancer-related death worldwide [4]. The predominant form of primary liver cancer is hepatocellular carcinoma (HCC), which accounts for approximately 85–95 % of all primary liver cancer cases, followed by intrahepatic bile duct cancer (IBDC), a cancer that develops in the bile ducts inside the liver [1, 5]. There is a large variation in incidence rates of HCC across geographic regions. More than 80 % of cases with HCC are detected in less developed countries [6]. In general, incidence rates are higher in men than in women [1]. In men, highest incidence rates are detected in Eastern and South-Eastern Asia (age-adjusted incidence rate >20 per 100,000), and lowest rates in Northern Europe and South-Central Asia (age-adjusted incidence rate <5 per 100,000). In women, the highest incidence rates occur in Eastern Asia and Western Africa [age-adjusted incidence rate >8 per 100,000] and the lowest in Northern Europe [age-adjusted incidence rate <2 per 100,000] [1]. However, over the last decades, the incidences of both types of primary liver cancer, HCC and intrahepatic cholangiocarcinoma (ICC) have also increased in the "lower-risk" Western countries such as the USA [7]. Major known risk factors for HCC include chronic infection with hepatitis C virus (HCV) and hepatitis B virus (HBV), exposure to toxins, such as aflatoxin, and excessive alcohol consumption [6]. This could partly explain the geographic variation of HCC occurrence because prevalence of liver cirrhosis in consequence of infection with hepatitis B or C virus, and exposure to toxins is more common in low-income countries compared with high-income countries [5, 8]. The documented increase in HCV- and HBV-related HCC, however, does not fully explain the recent increase in HCC incidence in Western populations, as 20–50 % of HCC remain idiopathic. Different lines of evidence identify non-alcoholic fatty liver disease (NAFLD) as a possible relevant risk factor for occurrence of HCC [9]. NAFLD is the most common form of liver disease in Western countries characterized by accumulation of excessive fat in the liver in the absence of alcohol abuse (12). NAFLD includes a spectrum of liver disorders, ranging from simple steatosis (infiltration of fat in the liver) to the more severe form

non-alcoholic steatohepatitis (NASH) [10, 11]. Obesity can alter hepatic pathology, metabolism and promote inflammation, NAFLD and induce pathologic progression and development of NASH. NASH is characterized by prominent steatosis and inflammation and can lead to cirrhosis and ultimately HCC [12]. NAFLD is strongly associated with obesity and its metabolic complications, such as metabolic syndrome and type 2 diabetes [13]. In this context, the increased prevalence of obesity and associated NAFLD could possibly explain rising incidence of primary liver cancer in Western countries over the last decades.

Here, we review the existing evidence on the links between obesity and its metabolic complications—NAFLD, metabolic syndrome and diabetes type 2—and liver cancer incidence and survival. Furthermore, we evaluate current knowledge on potential mechanisms that may possibly explain obesity-associated liver cancer risk and could thereby provide new targets for liver cancer prevention in societies affected by the obesity epidemic.

2 General and Abdominal Obesity, Weight Gain and Risk of Liver Cancer

Recently, an expert review report of the World Cancer Research Fund (WCRF) concluded that there is a sufficient body of evidence to establish higher body fatness as a risk factor for HCC [14]. This evidence comes from studies investigating body fatness based on body mass index measurements (BMI: weight/height^2 [kg/m^2]), that is considered as an indicator of general obesity. In a dose–response meta-analysis of 12 prospective studies, the risk of HCC was increased by 30 % per each 5 kg/m^2 higher BMI [14] (Fig. 1). Parallel lines of evidence have been provided by a number of independently conducted systematic reviews and meta-analyses [15–19]. In those studies, a higher risk of liver cancer was observed in the highest category of BMI compared to the lowest. Using established cut-off values for the BMI, including normal weight (BMI: 18.5 $\leq$ 25.0 kg/m^2), overweight (BMI: 25 $\leq$ 30 kg/m^2) and obesity (BMI: 30 kg/m^2) [20], a meta-analysis of 26 prospective studies (including 25,337 participants) observed 18 % higher risk of HCC for individuals with overweight [relative risk and 95 % confidence intervals: 1.18 (1.06–1.31)], and 83 % higher risk in individuals with obesity [relative risk and 95 % confidence intervals: 1.83 (1.59–2.11)] compared to individuals with normal weight [19]. Another meta-analysis of 8 studies including 1,779,471 cohort individuals revealed that the nature of the observed association between BMI and risk of liver cancer was nonlinear (P for nonlinearity <0.001). The relative risks were 1.02 (95 % CI = 1.02–1.03), 1.35 (95 % CI = 1.24–1.47) and 2.22 (95 % CI = 1.74–2.83) for BMI category above 25, 30 and 35 kg/m^2 compared with the reference (the median value of the lowest category), respectively [16]. Similar nonlinear association, with the most pronounced increase in risk among persons with a BMI > 32 kg/m^2, was reported in another meta-analysis of 21 prospective studies (including 17,624 cases) [17]. In that study, patients with HCV or cirrhosis (but not patients with HBV) with excess weight had a

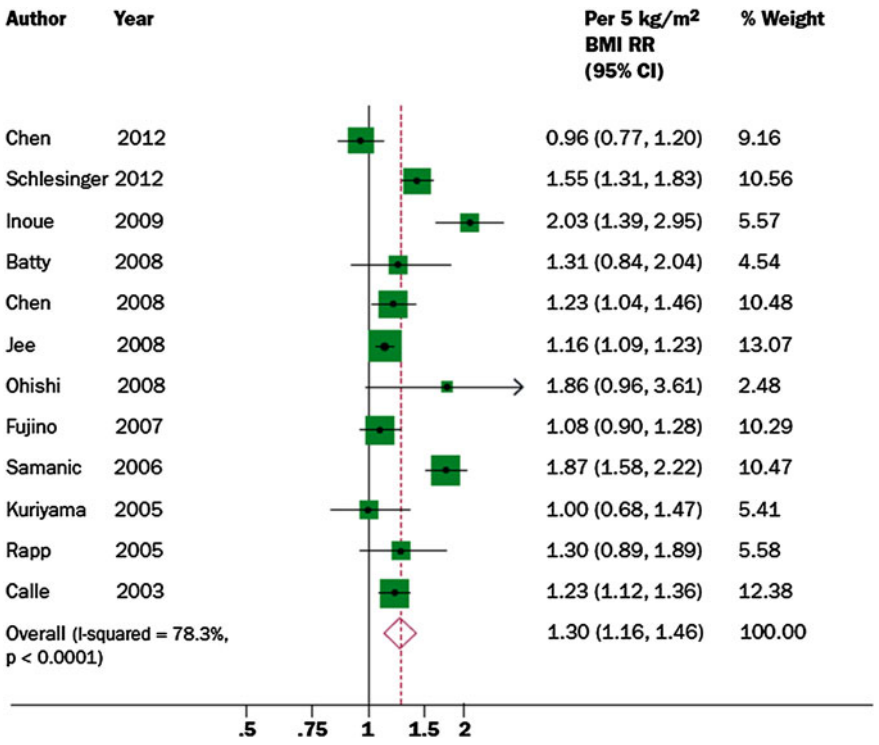

Fig. 1 Dose–response meta-analysis of BMI and liver cancer, per 5 kg/m^2. Adapted from WCRF/AICR continuous update report for liver cancer [14]

higher risk of liver cancer development than general populations with excess weight. Overall, the conducted meta-analyses reported high heterogeneity of results for the association of obesity with liver cancer that could be mostly accounted for by sex, ethnicity and underlying liver diseases: Stronger associations were seen in men than in women, and in individuals with underlying liver disease or with HCV infection or cirrhosis compared to individuals from the general population. Interestingly, BMI seemed to be more strongly associated with risk in white populations compared with other ethnic groups. A more detailed analysis that evaluated associations according to ethnic groups were recently published within a large sample of the multiethnic cohort study, a population-based prospective cohort study among 482 incident HCC cases identified among 168,476 participants after a median follow-up of 16.6 years [21]. In that study, BMI was strongly associated with liver cancer in Japanese, white, and Latino men, whereas there was no association in black men. Moreover, the study also revealed that BMI strongly correlated with total fat mass, measured by dual-energy X-ray absorptiometry, both in men and women and in all ethnic groups. In contrast, there was a lower correlation value for BMI and visceral or liver fat measured by abdominal magnetic resonance imaging in black men and women [21]. Overall, BMI

is strongly correlated with body fat, and thus, it is considered as a good marker for evaluation of total body fatness [22]. However, an important limitation of BMI is that it does not allow accounting for body fat distribution. Therefore, anthropometric measures of abdominal obesity might be more appropriate to reflect differences in body shape and fat distribution, as compared to BMI. However, evidence on the association between measures for abdominal obesity such as waist circumference (WC), waist-to-hip and waist-to height ratio and risk of primary liver cancer remain insufficient [23, 24]. First lines of evidence on the association between abdominal obesity and risk of HCC have been provided by the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort—a large European multi-center cohort study conducted among 359,525 men and women among which during a mean follow-up of 8.6 years 177 cases of HCC have been diagnosed [25]. In that study, abdominal obesity was defined based on established cut-off values provided by the World Health Organization (WHO) (waist circumference ≥ 102 cm for men and ≥ 88 cm for women, and waist-to-hip ratio ≥ 95 can for men and ≥ 0.80 for women) [20]. The data revealed a twofold higher risk of HCC for individuals above the cut-off values for abdominal obesity compared with individuals below these cut-points after controlling for established liver cancer risk factors, such as age, sex, alcohol intake, smoking, education, infection of hepatitis b and c virus and even after accounting for general obesity (as assessed by BMI). These findings point out that abdominal obesity might be a risk factor for HCC independently from general obesity [25]. Rather than studying markers of total adiposity, studies of obesity and HCC should move beyond BMI and use a better measure for fat-specific depots [26]. When evaluating the role of obesity in liver cancer risk, it is also important to account for the age of onset of obesity —i.e. early life versus later life. So far, only one study reported on the association between early adulthood obesity and risk of developing HCC, suggesting that obesity is associated with an increased risk at a young age in the absence of major HCC risk factors [27]. Furthermore, anthropometric measures such as BMI and WC represent an assessment of a static exposure status and it remains unclear whether dynamic measures of obesity such as weight gain are also associated with a higher risk. Data from the previously mentioned study within the EPIC cohort suggested that weight gain during adulthood (since age 20) was an independent risk factor for HCC reporting a 2.5-fold higher risk of HCC (95 % CI = 1.49–4.13) for the highest versus the lowest tertile of weight gain after taking into account baseline BMI and WC measurements [25]. These results have been further extended with regard to the association between adult weight gain with HCC mortality in a Japanese cohort of 31, 018 men and 41, 455 women aged 40–79 years. In that study, during a median 19-year follow-up, 527 deaths from HCC (338 men, 189 women) were documented. Weight gain since age 20 years was positively associated with liver cancer mortality among women with an underlying liver disease. Thus, women with history of liver disease had an about twofold higher HCC risk for weight gain of 5.0–9.9 kg compared with women with a stable weight (change of −4.9 to 4.9 kg) after controlling for important risk factors [28].

3 Metabolic Complications of Obesity in Relation to Liver Cancer

3.1 Non-alcoholic Fatty Liver Disease

Recent studies have suggested that NAFLD and particularly its aggressive form—NASH—are associated with an increased risk of primary liver cancer, mainly HCC [29]. In Western countries, up to 22 % of HCC cases could be attributed to NAFLD [30]. The estimated prevalence of NAFLD is around 20–35 % in developed countries mirroring the observed rates for obesity and the metabolic syndrome. It appears to be more common in men, and it increases with age and after menopause. Some data suggest that Mexican Americans are more likely to have NAFLD and blacks are less likely compared with non-Hispanic whites. More advanced stages of NAFLD are associated with older age, higher BMI, diabetes, hypertension, high triglycerides, and/or insulin resistance. Most NAFLD-related HCCs are believed to develop in the background of a cirrhotic liver [31]. The risk factors for HCC in the setting of NAFLD have not been established [32]. A study from the US indicated one of the most common etiologies of liver disease and cryptogenic cirrhosis (29 %), where half of the patients had histologic or clinical features associated with NAFLD [33]. It has been estimated that in morbidly obese patients that underwent bariatric surgeries, the prevalence of NAFLD can be as high as 98 % [34]. Moreover, this study carried out in a population of young adult, clinically asymptomatic obese patients confirmed the high prevalence of echographically detectable liver steatosis in massive obesity even in young adult patients [34]. Lipid accumulation in NAFLD triggers cancer-related pathways including c-Jun N-terminal kinase (JNK), nuclear factor-kappaB (NF-kβ) and toll-like receptors (TLR) signaling pathway, and overexpression of oncogenic genes [35]. The results from an obesity surgery cohort demonstrated that NAFLD is indeed frequent with over two thirds demonstrating histological presence of NAFLD and 18 % with definitive NASH by liver biopsy [36]. In an experimental study, it has been observed that both genetic and dietary factors related to obesity could promote NASH, liver dysplasia and HCC tumorigenesis in animal models [37]. In livers of obese mice, the occurrence of dysplastic and cancerous lesions showed morphological features of NASH without fully developed cirrhosis [35]. This indicates that liver hyperplasia is evident at the earliest stage of NAFLD and the transformation of malignant liver cells was resultant from the development of NASH instead of cirrhosis [35]. A study by Gutzman et al. [38] suggested also that NAFLD may predispose patients to HCC in the absence of cirrhosis. Finally, NAFLD was suggested to progress to HCC based on the metabolic syndrome development with obesity [39].

3.2 Metabolic Syndrome

Metabolic syndrome is defined as a cluster of metabolic alterations including abdominal obesity, dyslipidemia, hypertension, diabetes and insulin resistance [40].

It has been consistently associated with increased risk of cardiovascular diseases, and it has been also linked to risk of cancer at several sites [41]. NAFLD has been recognized as a hepatic manifestation of metabolic syndrome and its associated complications [42]. NAFLD appears to be most strongly associated with obesity and insulin resistance states including diabetes and with other features of the metabolic syndrome, such as high triglycerides and low high-density lipoprotein cholesterol levels [32]. Individuals with NAFLD/NASH-associated HCC were shown to exhibit a higher prevalence of metabolic features (type 2 diabetes, hypertension, dyslipidemia, coronary artery disease) compared to individuals with non-NAFLD/NASH-HCC. Nevertheless, even in the absence of cirrhosis, the NAFLD/NASH as the hepatic entity of the metabolic syndrome may itself pose an independent risk factor for HCC [43]. Indeed, liver tumors arising in patients with features of metabolic syndrome are with a larger size, well differentiated and mainly occur in the absence of significant fibrosis [44]. In a large pooled European cohort study comprising 578,700 individuals and 266 primary liver cancer cases, a metabolic syndrome score, based on BMI, blood pressure and circulating concentrations of glucose, total cholesterol and triglycerides, was significantly associated with increased risk of primary liver cancer [45]. Further analysis of single metabolic risk factors revealed that particularly BMI and glucose were significantly associated with higher primary liver cancer risk [45]. These findings were confirmed by another large population-based study in the USA that reported a twofold increased risk of HCC in individuals with metabolic syndrome compared to healthy ones [9]. In this context, data from Japanese population also confirmed these findings and reported that most of the patients with NASH who develop HCC were men having high rates of obesity, type 2 diabetes, and hypertension [46]. Additionally, males developed HCC at a less advanced stage of liver fibrosis than females [46]. A meta-analysis of 25 studies indicated the presence of multiple metabolic disorders, including obesity, type 2 diabetes, dyslipidemia and hypertension, as a clinical characteristic of NAFLD-associated HCC [47]. Indeed, almost all NAFLD-associated HCCs (99 %) had at least one type of metabolic disease and 76 % had two or more [47]. Another study showed that the presence of NASH and metabolic syndrome are common metabolic factors in patients with HCC (without infection by HBV and HCV) [48]. In a case–control study, the presence of dyslipidemia (defined by elevated triglycerides and/or lowered high-density lipoprotein) was associated with an increased odds for HCC (Odds ratio: 1.35 (95 % CI = 1.26–2.45) [9, 39]. Moreover, an analysis including cohorts from Austria, Norway and Sweden indicated a twofold increased risk for hypertension regarding the development of HCC [45].

3.3 Type 2 Diabetes

Recent evidence has also pointed to the involvement of more advanced metabolic complications, such as type 2 diabetes in the risk of primary liver cancer. Summary findings of a meta-analysis including 25 prospective studies indicated that diabetes

mellitus is associated with twofold higher risk of HCC compared to individuals without diabetes [49]. These data have been supported by a systematic review on the association between anti-diabetic medication use and risk of liver cancer summarizing data from 10 studies including 22,650 cases of HCC in 334,307 patients with type 2 diabetes. The meta-analysis of 8 observational studies showed a 50 % lower HCC incidence with metformin use, 62 and 161 % higher HCC incidence with sulfonylurea or insulin use, respectively. A recent study has confirmed these results [50]. Possible synergistic effects of metabolic factors have been suggested by the results revealing the highest risk of HCC for individuals with both obesity (BMI $\geq$ 30 kg/m^2) and type 2 diabetes [51–53].

In summary, a number of studies have underscored the importance of obesity, NAFLD and related metabolic complications in the development of primary liver cancer. Nevertheless, still broadened researches are needed to better understand the molecular link between the obesity-associated metabolic risk factors and HCC risk.

4 Pathophysiological Mechanisms Linking Obesity and Liver Cancer

The exact pathophysiological mechanisms behind the observed association between obesity, type 2 diabetes and risk of HCC are not completely understood [54]. As described above, one possible explanation for these relations includes the strong association with NAFLD [10, 55]. On the other hand, clinical and epidemiological data have failed to demonstrate hepatic tumor expression in fatty liver tissue [29] leading to the hypothesis that there may not be a single direct link between liver fat accumulation and hepatic carcinogenesis. Parallel lines of evidence have brought the notion on a number of obesity-related pathways during the progression of NASH that could be implicated as potential intermediary risk factors linking obesity and hepatocellular carcinogenesis (Fig. 2) [56]. It has been suspected that an excess fat storage, particularly within the abdomen and around the organs (the visceral fat), is associated with accumulation of fat in the liver, which might be associated with abnormalities in the hepatic metabolism, such as hyperinsulinemia and chronic low-grade inflammation [57–59]. In addition, the adipose tissue itself is defined as an endocrine organ secreting a number of hormones and proteins (growth factors and adipocytokines) known to be involved in altered metabolism and associated disease risk, including some types of cancer [60–62]. Below we review current evidence implicating insulin resistance, chronic inflammation, adipokine secretion, and altered gut microbiota as main intermediate pathways in obesity-liver cancer association.

4.1 Hyperinsulinemia

Hyperinsulinemia exerts coinciding effects with hyperglycemia, type 2 diabetes, and central obesity, thereby suggesting that it may be one of the central mechanisms

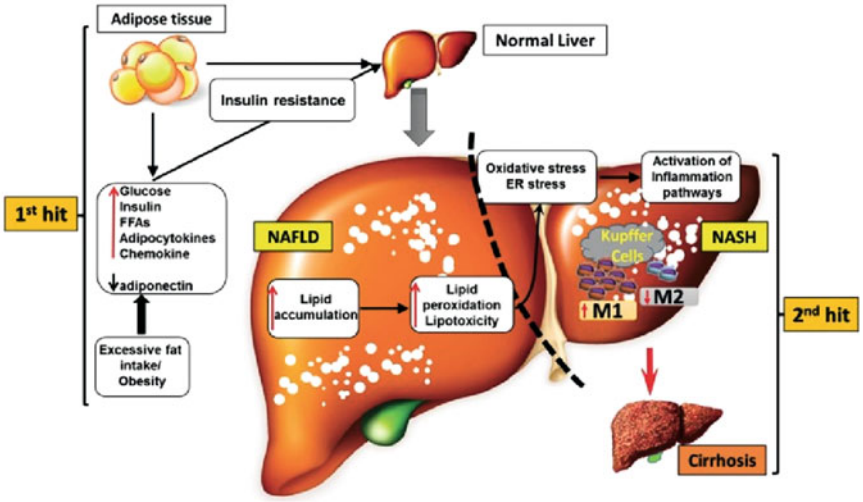

Fig. 2 Pathophysiological mechanisms during the progression to NASH. The development of NASH is initiated by several different risk factors including a high-fat diet, physical inactivity, and genetic predispositions that often lead to obesity and insulin resistance. Exaggerated fat intake and obesity lead to hyperglycemia, hyperlipidemia, and the over expressions of adipocytokines and chemokines and further contribute to insulin resistance in adipose tissue and the liver. Insulin resistance results in hepatic triglyceride (TG) synthesis and the increased delivery of free fatty acids (FFAs) to the liver. Additionally, hepatic steatosis acts as a "first hit" that is followed by a "second hit" in which inflammatory mediators can cause NASH and even cirrhosis. An enhanced storage of TG provokes a series of harmful consequences related to hepatocytes, such as uncontrolled lipid peroxidation, oxidative stress, and endoplasmic reticulum (ER) stress, which can activate hepatic inflammatory pathways. In particular, the recruitment of macrophage/Kupffer cells and an M1-dominant phenotypic shift in macrophages in the liver play a key role in the pathological progression of NASH. Adapted from Hu et al. [56]

to explain the obesity-liver cancer link [54]. First lines of evidence in support of this hypothesis came from the Paris Prospective Study cohort, a cohort study of 6237 non-diabetic French working men aged 44–55 years at baseline [63]. In that study, after 23.8 years of follow-up, peripheral hyperinsulinemia—indicative of very high portal insulin concentrations—was associated with a higher risk of fatal liver cancer [63]. Data from the EPIC cohort suggested that elevated concentrations of C-peptide were associated with twofold higher risk of HCC (relative risk: 2.25, 95 % CI = 1.43–3.54; $P < 0.0005$). These findings could be explained by the fact that the liver, in comparison with other organs, is exposed to high insulin concentrations. Furthermore, hyperinsulinemia is often present in patients with chronic HCV infection and is associated with more advanced hepatic fibrosis. Mechanistic studies demonstrated enhanced hepatic tumor growth in the presence of high insulin concentrations. High insulin levels may directly promote cell proliferation and survival through the phosphoinositide 3-kinase/protein kinase B and Ras/mitogen-activated protein kinase pathways [64]. Furthermore, the insulin-like growth factors

I and II (IGF-I and IGF-II), their receptors and their binding proteins play an increasingly role in tumor formation, growth, and metastasis in vivo [65]. Within circulation and tissue compartments, IGF is bound with high affinity to a family of structurally related binding proteins (IGFBP) characterized by different properties [66]. In the rat model of hepatocarcinogenesis, the expression of IGF axis components including IGF-I, IGF-II, IGF-IR, IGFII/M6PR, and individual IGFBP were examined in the sequence of preneoplastic hepatic foci and HCC. Finally, increased expressions of IGF-I and IGF binding protein-4 (IGFBP-4) in altered parenchymal cells, and a decreased expression of IGFBP-1 has been demonstrated. IGF-II was not detected in these pre-neoplastic foci and HCC arising in this model had decreased expressions of IGF-I and IGFBP-4, but IGFBP-1 expression was not significantly altered. Moreover, some HCC showed a more than 100-fold overexpression of IGF-II, whereas other tumors were completely negative for IGF-II expression [67]. In another study, it has been also observed that IGF-1 levels decrease when liver steatosis is worsened showing statistically significant difference between mild-moderate and severe steatosis with no correlation between IGF-1 levels and either homeostasis model assessment (HOMA) or insulin levels [68]. The results from a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey, 1988–1994 showed that there may still be an important underlying etiological connection between the IGF-1 axis and hepatic steatosis. However, after controlling for important HCC risk factors, this association and trend were extenuated, highlighting the importance of metabolic factors (related to glucose homeostasis and adiposity) in this relation [69].

4.2 Chronic Low-Grade Inflammation

Obesity induces production of pro-inflammatory molecules—chemokines and cytokines—required for the initiation and progression of HCC [70, 71]. Although acute liver inflammation can play a vital and beneficial role in response to liver damage or acute infection, the effects of chronic liver inflammation, including liver fibrosis and cirrhosis, are sufficient in a fraction of individuals to initiate the process of transformation and the development of HCC [72]. Chemokines and their receptors can also contribute to the pathogenesis of HCC, promoting proliferation of cancer cells, the inflammatory microenvironment of the tumor, evasion of the immune response, and angiogenesis [71]. In obese patients, accumulation of lipids in the liver promoted activation of an inflammatory response. At the same time, lipid accumulation increases demand on the endoplasmic reticulum leading to uncontrolled production of reactive oxygen species (ROS). ROS stimulate inflammatory signaling and induce oxidative damage including strand breaks and nucleotide modifications, and DNA damage leading to genomic instability. Thus, sustained hepatic inflammation results in damage to parenchyma, oxidative stress, and compensatory regeneration/proliferation. These inflammation-associated processes could be associated with increased incidence of hepatocellular carcinogenesis; however, evidence remains scarce. In animal models, it was shown that obesity may promote HCC development

through elevated production of tumor necrosis factor (TNF) and interleukin 6 (IL-6). In clinical studies, higher levels of IL-6 and C reactive protein (CRP) have been found among patients with HCC, when compared to controls. Recently, data from the EPIC cohort provided first lines of evidence for an independent association between several inflammatory and metabolic biomarkers and HCC risk suggesting their role as intermediate factors in the obesity-liver cancer association [73]. Moreover, a combination of these biomarkers was able to improve risk assessment of HCC beyond established risk factors such as infection with HBV/HBC, smoking, alcohol consumption, etc. (Fig. 3). Notably, these associations were independent of established HCC risk factors and adiposity measures, suggesting that these inflammatory biomarkers may play role as candidate intermediate factors of the association with HCC risk [73]. These data have been confirmed by a case–control study nested in a Japanese cohort with 188 HCC cases and 605 controls which reported that higher concentrations of CRP and Il-6 have been associated with an around twofold and fivefold higher risk of liver cancer, respectively [74]. These associations were independent of hepatitis virus infection, lifestyle-related factors and radiation exposure. Despite these arising data, exact roles of various inflammatory biomarkers as mediators of the association between obesity and HCC have not been evaluated.

4.3 Abnormal Adipokine Production

Recently, adipose tissue has been established as an endocrine organ that secretes a variety of biologically active adipokines, such as leptin, adiponectin and resistin. Adipokines play an important role in the physiology of adipose tissue, including food intake and nutrient metabolism, insulin sensitivity, stress, inflammation and bone growth. Several studies reported that adipokine dysregulation contribute to liver fibrosis and influence the pathological state of chronic liver diseases [75–80]. The dysregulated expression of adipokines may therefore provide explanatory mechanisms in the association of obesity with HCC [81]. Among various adipokines, two molecules—leptin and adiponectin—gained much attention in the recent research.

4.3.1 Leptin

Leptin is a well-established adipokine closely linked with the higher BMI and thereby considered as a good proxy measure of general adiposity [82]. Leptin increases with increasing fatty mass as a compensatory mechanism to preserve insulin sensitivity, but persistent hyperleptinemia could be implicated in liver fibrogenesis and carcinogenesis [83, 84]. A recent meta-analysis of 33 studies among 2612 individuals concluded that circulating leptin levels were higher in patients with NAFLD than in controls. Higher levels of circulating leptin were associated with increased severity of NAFLD, and the association remained significant after exclusion of studies involving adolescent populations and morbidly obese individuals [85]. Leptin could play a role in the development of NAFLD through insulin resistance, steatosis, worsening hepatic inflammation and ultimately fibrosis. Leptin has angiogenic properties, promotes cell proliferation and

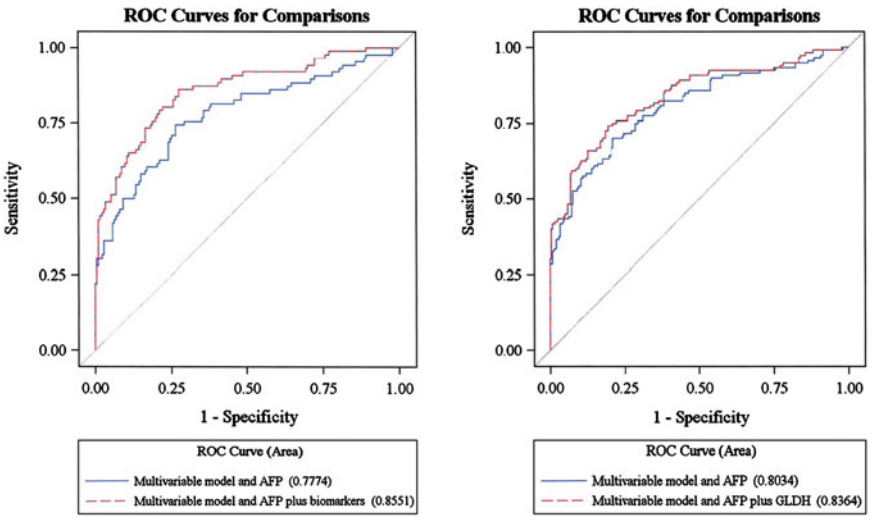

Fig. 3 Predictive ability of inflammatory and metabolic biomarkers and GLDH beyond the multivariable adjusted model and AFP levels. The biomarkers included in the model have been associated with HCC risk. These include CRP, Il-6, C-peptide, and non-HMW adiponectin. Multivariable model is taking into account matching factors: study center; gender; age (±12 months); date (±2 months); fasting status (<3, 3–6, or >6 h); and time of the day (±3 h) at blood collection. Women were additionally matched according to menopausal status (pre-, peri- [unknown], or postmenopausal) and exogenous hormone use (yes, no, or missing) at blood donation. Further adjusted for education (no school degree or primary school, secondary school, high school, or missing), smoking (never, former, current, or missing), alcohol at baseline, drinking status at baseline (non-drinker or drinker), diabetes (no, yes, or missing), coffee (g/day), HBsAg/anti-HCV (negative, positive, or missing), BMI, and WHtR adjusted for BMI. Adapted from Aleksandrova et al. [72]

migration, and interacts with growth factors, all of which could promote tumor growth [84]. However, the role of leptin in the development of liver cancer remains controversial with some studies suggesting an important role of leptin in liver fibrosis and carcinogenesis [86], while others demonstrating an inhibitory role of exogenous leptin on tumor size in murine model of HCC [87]. So far, the association of leptin and liver cancer was explored in only one prospective epidemiological study, which suggested a null association [73].

4.3.2 Adiponectin

Adiponectin is one of the most abundantly secreted adipokines in blood circulation, which actions are mainly exerted by the activation of AMP-activated kinase and peroxisome proliferator-activated receptor alpha [88]. Whereas the liver probably is not a source of circulating adiponectin, it is a major target organ of adiponectin metabolism [88]. Adiponectin is implicated in the regulation of steatosis, insulin resistance, inflammation and fibrosis; therefore, it could be expected that that

hyperadiponectinemia might suppress liver tumorigenesis and elevated levels of adiponectin would be associated with a reduced risk of HCC [89]. In contrast, experimental studies indicated that adiponectin treatment increased apoptosis of HCC and inhibited its proliferation [89, 90]. Some studies have shown that circulating adiponectin levels are higher in subjects with liver cirrhosis and that they increase in line with fibrosis stage [91]. Paradoxically, several human studies suggested that elevated adiponectin concentrations are associated with higher HCC risk. A hospital-based cohort study in Japan showed that high serum levels of adiponectin were positively associated with the development of HCC in patients with chronic HCV [92]. A nested case–control study conducted in middle-aged Japanese adults with hepatitis virus infection showed that both total and high-molecular weight adiponectin are associated with a higher risk of HCC [93]. A more recent large European cohort study added to this line of evidence suggesting adiponectin and its non-high-molecular weight isoform to contributed substantially to HCC risk [73]. However, null findings have been reported by another cohort study from France, in which serum levels of adiponectin measured in 248 patients with compensated HCV cirrhosis were found to be unassociated with HCC occurrence [91]. Positive associations between adiponectin and HCC risks could be explained by the fact that impaired liver function due to liver disease (including cirrhosis) may lead to hyperadiponectinemia.

4.3.3 Novel Adipokines

Apart from established adipokines, such as leptin and adiponectin, a recent systematic review evaluated the potential link between newly described adipokines and liver histology in biopsy-proven NAFLD patients [76]. Thirty-one cross-sectional studies were included, resulting in a total of seven different investigated adipokines, most of which suggested to be involved in the inflammatory response that develops within the context of NAFLD, either at hepatic or systemic level, and/or hepatic insulin resistance. Based on this literature review clinical studies suggest that chemerin, resistin and adipocyte-fatty-acid-binding protein potentially are involved in NAFLD pathogenesis and/or progression [76]. However, major inconsistency still exists, and there is a high need for larger studies using standardized assays to determine adipokine levels. So far there have not been studies to evaluate potential involvement of inflammation-associated adipokines as potential mediators of the association between obesity and liver cancer risk.

Gut microbiota and bile acid metabolism

Based on animal studies, it was hypothesized that genetic obesity provokes alterations of gut microbiota profile, thereby increasing the levels of deoxycholic acid (DCA), a secondary bile acid produced solely by the 7 alpha-dehydroxylation of primary bile acids carried out by gut bacteria. The enterohepatic circulation of DCA

provokes DNA damage and consequent cellular senescence in hepatic stellate cells (HSCs) which, in turn, secrete various inflammatory and tumor-promoting factors in the liver, thus facilitating HCC development in mice [94].

5 Obesity and Liver Cancer Survival

The emerging link between obesity and increased risk of HCC raises the question whether such association could be also observed for prognosis and postoperative complications of HCC. A number of studies have investigated these associations. On the one hand, some studies demonstrated that HCC patients with higher BMI exhibited significantly better prognosis than HCC patients with lower BMI after hepatic resection surgery [95–97]. However, on the other hand, no significant differences in the prognosis were detected between individuals with different levels of BMI in other studies [98–100]. In addition, studies reported that obesity does not influence surgical outcomes in hepatocellular carcinoma patients undergoing curative hepatectomy [101]. A recent systematic review including a total of 14 studies suggested that BMI was not associated with survival (including overall and disease-free survival) in HCC patients. In addition, in these patients, higher BMI was not related to postoperative complications (ascites, bile leaks, and 30-day mortality) [102]. However, HCC patients with higher BMI had increased risk of wound infections. The reason for lack of association between BMI and liver cancer prognosis is not clear. More studies are, therefore, warranted covering large spectrum of anthropometric characteristics of obesity in order to evaluate association between obesity and liver cancer survival.

6 Summary

Accumulating evidence has established an association between higher BMI as an indicator of general obesity and increased risk of primary liver cancer. The associations proved to be stronger in men, in patients with underlying liver disease and in white ethnic groups. Abdominal obesity, weight gain in adult life and metabolic factors related to visceral fat accumulation were also suggested as important risk factors for liver cancer; however, more studies are needed to evaluate these associations. Potential mechanisms that may link obesity and liver cancer include insulin resistance leading to increased levels of insulin and insulin-like growth factors, chronic inflammation due to adipose tissue remodeling, pro-inflammatory cytokine and adipokine secretion, and altered gut microbiota. The association between obesity and metabolic parameters and liver cancer survival remains controversial. More research is warranted in order to evaluate the role of inflammatory

and metabolic biomarkers as intermediate risk factors for risk of obesity-associated liver cancer. Better understanding of these associations may help in improving current strategies of liver cancer prevention, particularly in societies with high obesity prevalence.

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Obesity Biomarkers, Metabolism and Risk of Cancer: An Epidemiological Perspective

Katharina Nimptsch and Tobias Pischon

Abstract

Obesity is associated with metabolic alterations that may pose a biological link between body fatness and risk of cancer. Elucidating the role of obesity-related biomarkers in cancer development is essential for developing targeted strategies aiming at obesity-associated cancer prevention. Molecular epidemiological studies of the past decades have provided evidence that major hormonal pathways linking obesity and cancer risk include the insulin and insulin-like growth factor-1 (IGF-1) axis, sex-steroid hormones, adipokines and chronic low-grade inflammation. These pathways are interrelated with each other, and their importance varies by obesity-related cancer type. The insulin/IGF-1 axis has been implicated to play an important mediating role in the association between obesity and risk of pancreatic, colorectal and prostate cancer. Endogenous sex-steroid hormone concentrations, in particular obesity-associated pre-diagnostic elevations of estrogens and androgens, play an important role in postmenopausal breast cancer and endometrial cancer development. The adipokines adiponectin and leptin and adipocyte-mediated chronic low-grade inflammation represented by the acute-phase C-reactive protein may explain a substantial part of the association between obesity and risk of colorectal cancer. There is less evidence on whether these hormonal pathways play a mediating role in other obesity-associated types of cancer. In this chapter, the molecular epidemiologic evidence from prospective studies relating circulating obesity-related biomarkers to cancer risk is summarized, taking into account available evidence from Mendelian Randomization investigations aiming at improving causal inference.

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1 Introduction

Obesity is associated with metabolic alterations that may impact disease risk. The adipose tissue is not a mere energy storage but an active endocrine organ. Adipose tissue, in particular visceral fat, facilitates adverse metabolic effects such as insulin resistance and adipokine-mediated chronic low-grade inflammation that pose the link to chronic diseases [1, 2]. Major hormonal pathways that have been implicated to pose a biological link between body fatness and risk of obesity-associated types of cancer include the insulin and insulin-like growth factor axis, sex-steroid hormones, adipokines and chronic low-grade inflammation [3, 4]. It is unlikely that one of these suggested pathways accounts alone for the association between obesity and cancer. In contrast, these pathways are interrelated with each other in a complex manner and the importance of specific metabolic pathways varies by obesity-related cancer types (Fig. 1).

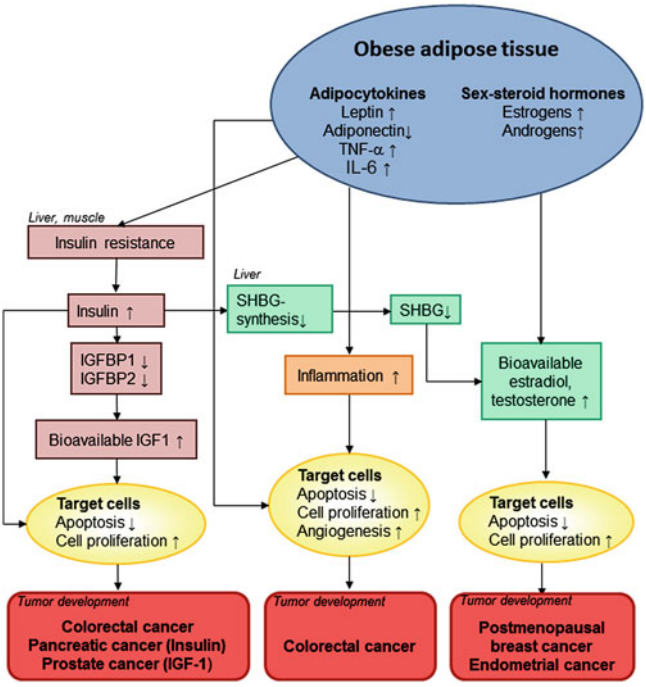

Fig. 1 Major hormonal pathways linking obesity with risk of cancer

During the past decades, a growing number of molecular epidemiological studies investigated the association between blood concentrations of obesity-related biomarkers and risk of cancer in order to examine whether the hypothesized pathways may explain the observed associations with obesity. The difficulty in conducting such studies is that the existence of a tumor may affect the biomarkers and metabolic pathways that are being investigated; therefore, traditional case–control studies that compare biomarker levels in diseased and non-diseased persons are of limited value in these instances. To avoid such possibility of reverse causation as much as possible, pre-diagnostic biomarker measurement is necessary, which requires a prospective cohort study design. In these studies, biomarker measurements are conducted among individuals free of cancer; study participants are then followed up over time for the incidence of cancer of interest; and biomarker levels at baseline are then related to cancer risk. It is evident that—depending on the incidence of the type of cancer of interest—such cohorts require large sample size. To be more cost efficient, often special study designs are applied, such as nested case–control or case–cohort designs embedded in large cohorts. In these studies, biomarker levels at baseline are measured among all incident cases but then compared to the levels of only a subgroup of the original cohort (case–cohort study) or to a number of matched controls that are selected using risk set sampling from the original cohort (nested case–control study). Such designs allow valid inferences about exposure–disease relationships that are almost identical to cohort analyses with only negligible loss of statistical efficiency. However, even in prospective study designs it cannot be excluded that occult cancer may have influenced findings or that other factors may explain the observed association between biomarkers and cancer risk. This possibility may be minimized by excluding cancer cases that were diagnosed shortly after blood collection from analysis and by careful adjustment for potential confounders. More recently, Mendelian Randomization studies have been found to be useful as a tool to investigate the association between biomarkers and cancer risk since these types of studies may circumvent reverse causation bias and confounding [5]. Thus, an advantage of the Mendelian Randomization approach is that genetic variants associated with lifelong differences in biomarker concentrations can be used as unbiased proxy variables, because on a population level, such variants are generally unrelated to lifestyle factors such as physical activity and diet that typically act as confounders in analyses relating obesity-related biomarkers to cancer risk. In this chapter, the molecular epidemiologic evidence from prospective studies relating circulating obesity-related biomarkers such as biomarkers of the insulin/IGF-1 axis, sex-steroid hormones, adipokines and inflammatory biomarkers to cancer risk is summarized. In addition, available evidence from Mendelian Randomization investigations aiming at improving causal inference in the association of obesity-related biomarkers with cancer risk is reviewed.

2 Insulin/IGF-Axis

There is abundant evidence that obesity is associated with insulin resistance and that weight loss improves insulin sensitivity [6]. The term insulin resistance refers to a condition in which skeletal muscles, liver and adipose tissue show a reduced response to insulin, i.e., a reduced insulin-mediated uptake of blood glucose as well as reduced fatty acid utilization by muscle cells and adipocytes, as well as reduced synthesis and storage of glycogen and decreased suppression of gluconeogenesis in the liver [7, 8]. Chronically elevated blood concentrations of insulin are typically a consequence of long-term insulin resistance, because more insulin is produced by the pancreatic beta cells in order to compensate for elevated blood glucose concentrations. This hyperinsulinemia, which also occurs in fasting states, has been hypothesized as one pathway explaining the positive association between obesity, especially abdominal obesity and elevated cancer risk. Chronically elevated insulin levels may affect cancer risk either through direct mitogenic effects or indirectly through the IGF-1 pathway [9]. Direct growth-promoting effects of insulin include suppression of apoptosis and promotion of cell proliferation [10]. The IGF-1 system is tightly linked to insulin metabolism. Both insulin and IGF-1 act as tissue growth factors and hormonal modulators of energy metabolism, with the difference that insulin mainly exerts short-term (post-prandial) effects whereas IGF-1 stimulates longer-term growth effects [9]. IGF-1 exerts mitogenic effects through anti-apoptotic properties [11]. The growth-promoting processes of insulin and IGF-1 are mediated by specific receptors (insulin receptor, IR; IGF-1 receptor, IGF1R) that are expressed on normal tissues but can also be expressed by neoplastic cells [9]. Interaction of insulin and IGF1R stimulate potentially carcinogenic pathways such as MAPK [12]. Hyperinsulinemia enhances the availability of free, bioactive IGF-1 by upregulating hepatic IGF-1 synthesis on the one hand and downregulating the hepatic production of two binding proteins (IGFBP-1 and IGFBP-2) on the other hand. However, evidence linking obesity to circulating IGF-1 concentrations is mixed and the relationship seems to be nonlinear with highest concentrations of IGF-1 observed in moderately overweight individuals [13, 14].

The relatively frequently observed concurrent occurrence of type 2 diabetes and cancer gave a first plausible hint that hyperinsulinemia, which is commonly observed in diabetics, may play a role in carcinogenesis. Comparing diabetics with non-diabetics, a higher risk of cancer of the pancreas, liver, breast, colorectum, urinary tract and female reproductive organs was observed, with strongest associations (about twofold higher risk) for cancers of the liver, pancreas and endometrium [15].

Serologic evidence for a role of hyperinsulinemia in carcinogenesis comes from prospective studies in which pre-diagnostic biomarkers of insulin metabolism were related to later cancer risk. Because insulin is produced by pancreatic beta cells, the pancreas is immediately exposed to chronically high insulin synthesis. In addition, high expression of IGF-1 as well as of both insulin and IGF-1 receptors has been observed in pancreatic cancer cell lines [16, 17]. Pre-diagnostic insulin

concentrations were associated with higher risk of pancreatic cancer in a large prospective cohort of male smokers [18] as well as in an analysis pooling data from five prospective US cohort studies [19]. In both these analyses, associations with insulin became stronger after exclusion of patients diagnosed with pancreatic cancer within 10 years of their blood collection, suggesting that observed associations are not due to reverse causation bias. In contrast, evidence for an association between pre-diagnostic concentrations of IGF-1 or the ratio of IGF-1 to IGFBP-3, a marker of free IGF-1, and risk of pancreatic cancer is weak. While weak positive associations with free IGF-1 have been observed in a large US cohort [20] and a prospective study from Japan [21], no associations were observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) [22] and a pooled analysis of four US cohorts [23].

The insulin and IGF-1 pathway may also explain at least part of the association between obesity and higher risk of colorectal cancer. In the EPIC study, circulating C-peptide at baseline as indicator for long-term insulin secretion was associated with higher risk of colorectal cancer [24]. Also a meta-analysis of prospective cohort studies suggests a positive association of biomarkers of insulin metabolism (C-peptide or fasting insulin) and colorectal cancer risk [25]. In terms of circulating IGF-1, no association was observed in EPIC, but a meta-analysis including the findings in EPIC and ten other prospective cohorts found that high pre-diagnostic IGF-1 concentrations were associated with a moderately higher risk of colorectal cancer [26].

Studies investigating biomarkers of insulin metabolism in relation to risk of postmenopausal breast cancer have not observed consistent positive associations [25, 27–30], but there is evidence that IGF-1 is modestly associated with higher risk of breast cancer independent of menopausal status from a pooled analysis of data from 17 prospective studies [13]. With respect to endometrial cancer, as to date a limited number of prospective studies have investigated pre-diagnostic biomarkers of the insulin/IGF-1 pathway in relation to disease risk. In a nested case–control study of the Women's Health Initiative (WHI), however, a strong positive association between fasting insulin and risk of endometrial adenocarcinoma (making up 82 % of all endometrial cancer cases) was observed among women not using hormone therapy, and the association was slightly attenuated after adjustment for BMI [31]. Counterintuitively, however, in the same study pre-diagnostic IGF-1 concentrations were inversely associated with risk of endometrial cancer. A meta-analysis including four prospective studies on IGF-1 and risk of ovarian cancer did not provide evidence for this pathway [32]. While epidemiologic evidence relating circulating insulin or C-peptide [33–39] to risk of prostate cancer is inconclusive, pre-diagnostic circulating IGF-1 concentrations have been consistently related to higher risk of prostate cancer, especially low-grade tumors [40]. Prospective investigations on insulin/IGF-1 and risk of liver cancer are scarce, although higher pre-diagnostic concentrations of C-peptide have been related to higher risk of liver cancer in EPIC [41]. Prospective studies on the association of circulating insulin, C-peptide or IGF-1 and other obesity-associated cancers such as renal cell cancer and esophageal adenocarcinoma are as to date scarce.

In summary, hyperinsulinemia may potentially explain at least part of the positive association between obesity and risk of pancreatic cancer and colorectal cancer, whereas a role of IGF-1 is implicated for colorectal cancer and prostate cancer. Evidence is less clear for other obesity-associated types of cancer. Future research should consider Mendelian Randomization studies investigating genetically determined higher insulin or IGF-1 in relation to risk of colorectal or pancreatic cancer, which could improve causal inference by circumventing reverse causation and residual confounding. We are aware of only one previous Mendelian Randomization study in this context, which observed that genetically determined higher insulin was associated with higher risk of endometrial cancer, supporting a causal association of insulin in endometrial cancer etiology [42].

3 Sex-Steroid Hormones

Adiposity is associated with higher formation of endogenous sex-steroid hormones including estrogens, progesterone and androgens, especially in postmenopausal women [43]. In addition, obesity-related hyperinsulinemia and the consequential high bioactivity of IGF-1 reduce the hepatic secretion of sex hormone-binding globulin (SHBG), which results in higher bioavailability of sex-steroid hormones. Alterations in sex-steroid hormones have been suggested to explain a large proportion of the association of obesity with postmenopausal breast cancer and endometrial cancer [3]. Thus, clinical and experimental evidence suggests that sex-steroid hormones, in particular estrogen and progesterone, play an important role in the regulation of cell proliferation and apoptosis in breast cancer and endometrial cancer [3]. Many established risk factors of both breast and endometrial cancers such as early menarche, late menopause, estrogen replacement therapy but also obesity are related to the lifetime exposure to estrogen. Epidemiologic investigations have provided evidence that endogenous sex-steroid hormone concentrations are related to later risk of both postmenopausal breast cancer and endometrial cancer. In the EPIC study, it was shown that total and bioavailable androgens and estrogens were associated with approximately twofold higher risk of postmenopausal breast cancer [44]. The study also showed that both BMI and waist circumference were positively associated with free testosterone, estrone and estradiol and the positive association between BMI and risk of postmenopausal breast cancer was attenuated substantially after adjustment for total or free estrogens. Similarly, in a pooled analysis of nine earlier prospective studies, sex-steroid hormones including testosterone, estrone and estradiol were associated with higher postmenopausal breast cancer risk and the positive association with BMI was largely accounted for by adjustment for estradiol [45]. These observations provide convincing evidence that a substantial proportion of the association between obesity and risk of postmenopausal breast cancer can be explained by the obesity-related alterations in sex-steroid hormone concentrations.

With respect to endometrial cancer, there is evidence that high estradiol may not only lead to higher cell proliferation and less apoptosis, but also exert cancer-promoting effects through upregulation of IGF-1 synthesis in endometrial tissue [46]. The relationship between sex-steroids hormones and endometrial cancer has been described within the framework of the "unopposed estrogen hypothesis", which implicates that women with high endogenous concentrations of the mitogenic estrogen may be at increased endometrial cancer risk especially when these are not or insufficiently counterbalanced by progesterone, which stimulates the metabolism of estradiol and inhibits IGF-1 actions [3, 47]. Epidemiological studies have observed higher endometrial cancer risk associated with high blood concentrations of estrogens in postmenopausal women. Furthermore, higher levels of endogenous androgens, i.e., androstenedione and testosterone, have been related to higher endometrial cancer risk in pre- and postmenopausal women [47]. In line with these observations, women with polycystic ovary syndrome, a condition related to higher androgen concentrations and hyperinsulinemia, are at increased risk of endometrial cancer [48]. In a nested case–control study combining data from three prospective cohort studies, a strong association of pre-diagnostic blood concentrations of estrogens and androgens with endometrial cancer risk was observed in postmenopausal women [43].

Although androgens play an important role in the physiological growth of the prostate and despite the fact that androgen deprivation therapy is a standard therapy for prostate cancer, pre-diagnostic blood concentrations of sex-steroid hormones (androgens and estrogens) are unlikely to play a role in the development of prostate cancer as results from a pooled analysis of 18 prospective studies have shown [49]. Similarly, the limited number of studies relating pre-diagnostic sex-steroid hormones to ovarian cancer risk is not supportive of blood estrogen levels playing an important role and provides limited evidence for a role of circulating androgens in this gynecological obesity-associated type of cancer [50, 51].

In summary, while there is good evidence for sex-steroid hormones explaining a large proportion of the positive association between obesity and risk of postmenopausal breast cancer and endometrial cancer, this pathway is less likely to be of importance in other obesity-associated types of cancer.

4 Adipokines

Soluble substances produced by adipose tissue have been collectively named adipocytokines or adipokines [8]. These adipocyte-derived hormones have been suggested to play a role in the pathogenesis of obesity-associated cancers. Adiponectin and leptin are the most abundantly produced adipokines compared with other adipokines such as resistin, plasminogen activator inhibitor (PAI)-1 or hepatocyte growth factor (HGF). Other substances produced by adipose tissue include a number of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and others.

4.1 Adiponectin

In contrast to many other adipokines, adiponectin expression is downregulated in obese adipose tissue. Thus, lower adiponectin concentrations are observed in obese individuals compared with normal-weight individuals [52]. Adiponectin plays an important role in energy metabolism and has insulin-sensitizing and anti-inflammatory properties [8, 53]. In addition, anti-neoplastic properties such as inhibition of proliferation and promotion of apoptosis have been observed to be upregulated by adiponectin in cancer cells [54]. High adiponectin concentrations have been suggested to play a protective role in the development of cancer either directly through inhibition of cell growth and induction of apoptosis or indirectly through improved insulin sensitivity and reduced inflammation [54]. Epidemiological evidence for an association between pre-diagnostic adiponectin concentrations and obesity-associated cancer has emerged from several investigations. In EPIC, higher circulating adiponectin concentrations were associated with a lower risk of colorectal cancer [55]. Furthermore, non-high-molecular-weight (HMW) adiponectin, which has a higher anti-inflammatory potential than HMW-adiponectin, was particularly associated with lower risk of colorectal cancer. In nested case–control studies of two large US-based prospective cohort studies, pre-diagnostic adiponectin concentrations were associated with lower risk of colorectal cancer only in men but not in women [56]. Similar sex differences were observed in a meta-analysis that included 13 epidemiological studies—both case–control and prospective studies—in which a weak inverse association between adiponectin and colorectal neoplasia was observed in men but not in women [57]. However, in this meta-analysis, stronger associations were observed in smaller studies and studies of lower quality, suggesting that the true association between adiponectin and colorectal cancer might have been overestimated. Studies on the association between genetic variants in the *ADIPOQ* gene and risk of colorectal cancer have produced diverse findings. In a meta-analysis including six case–control studies, three polymorphisms in the *ADIPOQ* gene were associated with colorectal cancer, but associations were restricted to Asian populations while not seen in Caucasian populations [58]. In a pooled analysis of epidemiological studies on colorectal cancer where genetic markers were also available, polymorphisms in the *ADIPOQ* gene that have been identified in genome-wide association studies on adiponectin concentrations were not related to colorectal cancer risk [59], arguing against a causal contribution of adiponectin in the association between obesity and colorectal cancer. Whether adiponectin may play a mediating role in the association of obesity and other types of cancers has been less often investigated. In a case–cohort investigation of the WHI, higher adiponectin concentrations tended to be associated with lower risk of postmenopausal breast cancer [60]. This inverse association did not persist after adjustment for insulin, suggesting that part of the association observed with adiponectin is explained by insulin, which is also mechanistically plausible. In a nested case–control study of male smokers, an inverse association between pre-diagnostic adiponectin and risk of renal cell carcinoma was observed, which accounted for a large proportion in the positive

association between BMI and renal cell carcinoma [61]. On the other hand, no association between circulating adiponectin and risk of endometrial cancer, the cancer type that shows the strongest association with obesity, was observed in the Nurses Health Study, but the number of included cases was limited [62]. Interestingly, adiponectin, in particular HMW-adiponectin, has been associated with higher risk of hepatocellular carcinoma in two nested case–control studies of prospective cohorts including EPIC [63, 64], but not in another nested case–control study [65]. Overall, these mixed observations support the need of future prospective studies to clarify the potentially mediating role of adiponectin in obesity-associated cancer.

4.2 Leptin

Leptin is a classical adipokine that is primarily expressed by adipose tissue [66]. Thus, circulating leptin reflects adipose tissue mass and, typically, leptin is found in higher concentrations in obese compared with lean individuals [67]. The physiological function of leptin is long-term modulation and regulation of dietary intake and energy balance [68]. Besides, there is mechanistic evidence that leptin may explain the positive association between obesity and risk of cancer. Experimental studies have demonstrated cancer-promoting activities of leptin, such as promotion of cell proliferation, migration and angiogenesis and inhibition of apoptosis [69]. In addition, it has been demonstrated that leptin receptor is expressed in human colon and breast cancer cell lines, which points to a role of leptin in the growth of these cancers [69, 70]. There is some evidence from epidemiological studies investigating circulating leptin concentrations and risk of obesity-related cancer, but most evidence exists for colorectal cancer [69]. In a prospective study from Sweden, higher circulating leptin was associated with higher risk of colon cancer in men but not in women [71]. Similarly, in EPIC pre-diagnostic leptin was associated with higher colon cancer risk only in men, while in women no association was observed [72]. A positive association between pre-diagnostic circulating leptin concentrations and risk of colon cancer in men was also observed in a study from Norway [73]. A higher risk of colorectal cancer in women with high pre-diagnostic leptin concentrations was observed in the Japan Collaborative Cohort Study [74] and in the WHI cohort [75]. In a meta-analysis including six prospective studies, higher leptin concentrations were significantly associated with higher risk of colorectal cancer [76]. Interestingly, soluble leptin receptor (sOB-R), which determines the bioactivity of leptin, was strongly inversely associated with risk of colorectal cancer in EPIC [72]. In two US cohorts, soluble leptin receptor was not associated with higher overall colorectal cancer risk in either men or women, although high sOB-R concentrations were associated with higher rectal cancer risk in women [56]. A positive association between genetic variation in *LEP* and colorectal cancer risk has been observed [77], but so far no Mendelian Randomization study has been conducted to improve causal inference.

Less epidemiological studies have been conducted to elucidate whether leptin may play a mediating role in the association between obesity and other types of cancer, and the few studies on breast cancer, endometrial cancer and pancreatic cancer were not conclusive so far [69].

4.3 Other Adipokines

There is limited evidence on the association between pre-diagnostic concentrations of other adipokines such as resistin and cancer incidence. Resistin is a relatively newly discovered adipokine that may mediate the association between obesity and cancer through insulin and inflammatory pathways [76]. In the WHI, resistin was associated with nonsignificantly higher risk of colorectal cancer but the positive association was mainly accounted for by insulin concentrations [75]. With respect to postmenopausal breast cancer, no associations with resistin were observed [60]. In a cohort of male smokers, no association between resistin and risk of renal cell carcinoma was reported [61]. The investigation of the role of novel adipokines deserves further attention in future research in obesity and cancer.

5 Inflammatory Markers

There is convincing evidence that obesity is associated with chronic low-grade inflammation triggered by adipocyte-derived production of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin-6) which stimulate the hepatic secretion of acute-phase proteins, such as C-reactive protein (CRP) [4]. In 1863 Rudolf Virchow postulated inflammation as the origin of cancer based on his clinical observations that cancer often arises from sites of local chronic inflammation, which is observed also nowadays [78]. There is plausible evidence that chronic inflammation plays an etiologic role in colorectal carcinogenesis, as it has been consistently observed that individuals with chronic inflammatory bowel diseases have a higher risk of colorectal cancer [79, 80]. In addition, the use of aspirin and other anti-inflammatory drugs has been associated with a lower risk of colorectal cancer, which gives further support for a role of inflammation in colorectal carcinogenesis [81–84]. Obesity-associated chronic low-grade inflammation [4] may play an important role in colorectal carcinogenesis through fostering cell proliferation, cell survival and migration [85]. Therefore, at least part of the positive association between obesity and colorectal cancer may be explained by inflammatory processes. In support of this hypothesis, it was shown that diet-induced weight loss reduced chronic inflammation in the colorectal mucosa of obese individuals accompanied by downregulation of inflammatory and cancer gene pathways [86]. A number of epidemiological studies investigated the association between biomarkers of chronic inflammation, particularly CRP and colorectal cancer risk. High blood concentrations of CRP have been associated with moderately higher

CRC risk in several prospective studies [87–89] including in the EPIC study [90]. However, findings from observational studies relating circulating CRP to cancer risk may not necessarily reflect causal associations. Despite a prospective study design, it is possible that pre-clinical disease leads to inflammatory processes before symptomatic disease diagnosis, which may result in false-positive associations due to reverse causation. Furthermore, residual confounding cannot be excluded. In a Mendelian Randomization analysis within EPIC, genetically determined higher CRP concentrations due to four SNPs in the *CRP* gene were associated with higher risk of colorectal cancer, which is in line with the hypothesis that CRP plays a causal role in colorectal carcinogenesis [91]. Interestingly, very similar results were obtained in a Mendelian Randomization study employing 20 CRP-related SNPs within a US cohort with colorectal cancer, whereas no association was observed for breast cancer [92]. Genetically determined higher CRP concentrations were not associated with higher risk of overall cancer in another Mendelian Randomization analysis [93]. However, all these studies had limited sample size for deriving robust evidence from Mendelian Randomization. Therefore, larger Mendelian Randomization studies on inflammatory markers and cancer risk are warranted. Other inflammatory cytokines such IL-6 have been less often investigated, but a meta-analysis of six prospective studies of circulating IL-6 found a borderline statistically significant positive association with colorectal cancer risk [94].

There is less evidence for inflammatory markers playing a role in other types of obesity-related cancer. However, in the EPIC study, pre-diagnostic concentrations of both IL-6 and CRP were positively associated with hepatocellular carcinoma [63]. Furthermore, in the WHI, CRP was associated with higher risk of postmenopausal breast cancer and the association between BMI and postmenopausal breast cancer was substantially attenuated after adjusting for CRP, which indicates a mediating role in the obesity–breast cancer association [60].

6 Mediating Effect of Biomarkers in the Obesity–Cancer Association

Although there is a variety of studies investigating specific obesity-related biomarkers and their association with cancer incidence, only few investigations took various biomarkers in the obesity pathway simultaneously into account and formally examined their mediating role in the obesity–cancer association.

In a case–cohort analysis within the WHI, the mediating effects of estradiol, insulin and CRP in the association between obesity and risk of postmenopausal breast cancer were evaluated [60]. The results showed that the association between BMI and breast cancer risk was completely attenuated after adjustment for circulating estradiol, insulin and CRP, with insulin and CRP being the most important mediators. In another case–cohort investigation of the WHI, the positive association between waist circumference and risk of colorectal cancer was by 50 % attenuated after adjustment for leptin and insulin concentrations [75]. These first investigations

taking the large spectrum of biomarkers simultaneously into account give important insights into which factors are the most promising targets for prevention of obesity-associated cancer morbidity. More such comprehensive analyses are warranted.

7 Conclusions

The molecular epidemiologic research of the past decades has provided important insights into potential metabolic mechanisms linking obesity with higher risk of cancer. However, as to date, the underlying mechanisms of the obesity–cancer association are not fully understood. The metabolic pathways insulin/IGF-1, sex-steroid hormones, adipokines and inflammation are likely to explain part of the positive association between obesity and higher risk of certain types of cancer. The insulin/IGF-1 axis has been implicated to play an important role in the association between obesity and risk of pancreatic, colorectal and prostate cancer. Obesity-associated pre-diagnostic elevations of endogenous sex-steroid hormone concentrations, in particular estrogen and progesterone, play an important role in postmenopausal breast cancer and endometrial cancer. The adipokines adiponectin and leptin and adipocyte-mediated chronic low-grade inflammation represented by the acute-phase CRP may explain a substantial part of the association between obesity and risk of colorectal cancer. Whether these obesity-related biomarkers really play a causal role in carcinogenesis deserves further investigation, ideally through adequately powered Mendelian Randomization studies utilizing knowledge on genetic determinants of obesity-related biomarkers derived from genome-wide association studies. In addition, more studies investigating various implicated obesity-associated biomarkers simultaneously in order to quantify their individual mediating role will pave the way for targeted pharmacological or lifestyle interventions aiming at obesity-associated cancer prevention through modification of the most important biomarkers.

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Biological Mechanisms for the Effect of Obesity on Cancer Risk: Experimental Evidence

Mauricio Berriel Diaz, Stephan Herzig and Tobias Schafmeier

Abstract

Multiple epidemiological studies demonstrated that overweight and obesity significantly increase the risk of several types of cancer. As the prevalence of obesity is dramatically rising, it is expected that it will represent one of the major lifestyle-associated risk factors for cancer development in the near future. Numerous recent studies expanded knowledge about key players and pathways, which are deregulated in the obese state and potentially promote cancer initiation, progression and aggressiveness via remote and local effects. These players include (but are not limited to) insulin/IGF, adipokines and inflammatory signaling molecules as well as metabolites. Nevertheless, the detailed mechanisms linking obesity and malignant transformation at the systemic, cellular and molecular level still demand further investigation. Additionally, dysfunctional molecular metabolic pathways appear to be specific for distinct cancer entities, thereby yet precluding definition of a common principle. This chapter will present an overview of the current knowledge of molecular nodes linking obesity and cancer and will briefly touch upon potential therapy options addressing metabolic cancer etiologies.

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1 Introduction

The worldwide prevalence of overweight and its severe form obesity has reached pandemic dimensions with nowadays 500 million people being obese. In addition to its negative impact on quality of life and physical fitness, obesity commonly progresses into deleterious and often fatal pathologies, including type 2 diabetes, cardiovascular diseases and several types of cancer [1–3].

A causal connection between adiposity and increased cancer risk has been hypothesized based on obvious evidence from multiple epidemiological studies [4]. Notably, the tumor-promoting effects of excess body weight vary between distinct cancer entities and genders [4]. Additionally, several components of obesity might be independent risk factors, including elevated body weight per se as indicated by the BMI, but also weight gain and body fat distribution [5–8]. Thus, multiple mechanisms appear to be involved in obesity-associated cancer development.

Already in the early 1950s, first experimental evidence for an obesity-driven promotion of breast cancer appearance resulted from animal studies [9]. Numerous studies have since then been performed, which contributed significantly to understanding the risk connection between increased body weight and tumor development. However, a universal concept mechanistically defining the metabolic etiology of cancer still seems to be far from being achieved. As numerous players have been identified to date, it is questionable that a general mechanism exists which can explain the interconnection of obesity and cancer. It is rather very likely that the collective of pathophysiological changes in body homeostasis that occur during obesity cumulatively increase cancer risk. In essence, these changes can be grouped into altered inter-tissue cross talk on the one and generation of a tumor-promoting metabolic profile on the other hand. As a consequence, several hormones and metabolites display abnormal levels in the circulation and in the tumor microenvironment during obesity, eventually promoting tumor cell growth and invasiveness.

In this chapter, we will review the current state of the art, concerning the pathophysiological alterations caused by adiposity, which are potential molecular mediators of metabolic tumor promotion.

2 Tissue Communication

Communication between tissues and cells in our bodies occurs via hormones, cytokines and metabolites that are sensed through a variety of cellular mechanisms. Inter-tissue cross talk is vital for proper function of a biological system. As a consequence, dysfunction of tissue communication precipitates into various diseases.

Obesity primarily affects the white adipose tissue, which faces the challenge of dealing with a constant energy surplus and thus lipid overload of the adipocytes and eventually pathological expansion and cell death. Beside the adipocyte fraction, the tissue consists of several cell types with distinctive functions, as a whole summarized as stromal vascular fraction (SVF). The SVF, which contains, e.g., progenitor cells as well as cells of the immune system, has specific functions for adipose tissue integrity and thus is crucial for energy homeostasis. Dysfunctional adipocytes exert effects on cells of the SVF, such that the function of both adipose tissue fractions is compromised during obesity. The pathological consequences of adipose tissue dysfunction and their implications for cancer are outlined below.

2.1 Adipose Tissue

2.1.1 Endocrine Effects of Adipose Tissue

Adipose tissue is not considered being solely a calorie-storing depot. Nowadays it is seen as a huge endocrine organ that secretes a multitude of bioactive factors (adipokines), thereby locally and remotely regulating energy homeostasis on multiple levels [10]. In an obese setting, the body fat mass is not only markedly increased, but adipose tissue becomes also functionally impaired upon overloading of adipocytes with lipids and massive invasion of immune cells. As a result, adipose tissue dysfunction manifests in an altered signature of adipokines, particularly in visceral adipose tissue. Changes in the adipokine profile during obesity are exemplified by elevated release of leptin, resistin and pro-inflammatory cytokines, as well as reduced secretion of adiponectin [11]. Strikingly, certain cancer cells express adipokine receptors in high amounts and are therefore particularly responsive to an altered adipose secretome. The molecular pathways affected by adipokine signaling and their implications for tumor development, progression and metastasis thus required further discussion.

Leptin

Leptin is a 167 amino acid peptide hormone that activates anorexigenic and inhibits orexigenic neurons in the hypothalamus, and increases the sympathetic tone, thereby controlling food intake and energy expenditure, respectively [12]. Loss-of-function of one of the genes encoding either leptin (*OB*) or its receptor (*LEPR, OB-R*) results in severe hyperphagia in mice and men, and consequently leads to development of extreme obesity [13]. Leptin levels in the blood are

proportional to the amount of (visceral) adipose tissue. As a consequence of leptin resistance during obesity, the production and secretion of leptin are disproportionately increased, thereby precipitating in a vicious circle of progressively aggravating hyperleptinemia.

The leptin receptor is abundant in a number of peripheral tissues. Notably, malignant cells frequently express particularly high levels of OB-R. In line with this, specific SNPs in the leptin receptor gene were linked to an enlarged risk of certain cancers [14], altogether highlighting the significance of leptin signaling for tumor development. Despite being obese, leptin-deficient *ob/ob* mice were protected from developing specific types of cancer, whereas other tumors occurred more frequently, indicating that leptin has a role in a specific subset of obesity-associated cancer entities [15].

Epidemiologic studies indicate a connection between elevated circulating leptin levels and occurrence of (postmenopausal) breast cancer [16]. Furthermore, plasma leptin concentration is significantly correlated with poor clinical outcome in breast cancer [17]. Importantly, leptin plays a role in development of the mammary gland and the leptin receptor is thus highly expressed in mammary epithelia [18]. In the majority of human mammary tumors, leptin as well as leptin receptors is overexpressed, which provides an explanation for the increased breast cancer risk in obese women [18, 19]. Concordantly, ablation of leptin signaling suppressed tumor development in murine breast cancer models [20–22]. Given that obesity is a risk factor mainly for postmenopausal breast cancer, whereas obese young women seem rather to be protected from malignancies of the breast, increased leptin signaling is unlikely to be the sole reason for risk enhancement. At least in specific subtypes of mammary tumors in elderly women, leptin might work in synergy with estrogen, which is produced in high amounts by adipose tissue after menopause (see below). Notably, leptin potentially induces adipose tissue aromatase activity, resulting in an increased production of estrogen [17].

A connection between leptin and cancers of the gastrointestinal tract has been proposed based on several studies involving human samples. Specifically, leptin receptor expression has been observed in human colon cancer cell lines as well as colon biopsies and resected colonic adenocarcinomas [23, 24]. Besides promoting proliferation and migration/invasion, leptin-induced metabolic reprogramming by inhibition of mitochondrial respiration has been observed in human colon cancer cell lines [25], which is in accordance with observations that have been made earlier in a breast cancer mouse model [26]. Notably, whereas circulating leptin levels were found to be decreased in colon cancer patients, they were negatively correlated with tumor aggressiveness [27]. It is unclear though if decreased serum leptin levels in patients with aggressive colon cancer were secondary effects caused by the tumor disease, e.g., upon cancer-associated weight loss.

More recently, leptin signaling has been shown to be involved in pancreatic cancer by in vitro and in vivo studies. While pancreatic tumor cells were shown to express distinct isoforms of the leptin receptor, leptin accordingly stimulated tumor growth, migration and metastasis formation [28, 29]. Clinical relevance of these observations still needs to be demonstrated.

Evidence exists that leptin also promotes growth and invasiveness of cholangiocarcinomas, gliomas and thyroid tumors [30–32]. However, epidemiological data supporting an association between obesity and these tumor entities are yet lacking.

Leptin signaling has been recently reported to be centrally involved in the development of chemotherapy resistance in glioblastoma, gastrointestinal- and breast cancer [33–35], thereby worsening the clinical outcome of anticancer therapies in obese subjects. Importantly though, a present study provides evidence for an increased response of colon cancer patients with high circulating leptin to treatment with Vascular Endothelial Growth Factor (VEGF) inhibitors [36]. Altogether, these data indicate that leptin levels might be an indicator for therapeutic responsiveness, thereby representing a potential biomarker for patient stratification.

Leptin acts via a group of signal transduction pathways that have been shown previously to have tumor-promoting effects [32, 37]. Upon binding by its ligand, OB-R induces several intracellular signaling pathways through interaction with the cytoplasmic kinase janus kinase (JAK) 2. Whereas the short receptor isoforms activate PI3K-Akt signaling via phosphorylation of insulin receptor substrates (IRS), the long isoform (OB-Rb) induces phosphorylation of the mitogenic transcription factor signal transducer and activator of transcription (STAT) 3. In addition, leptin induces MAP kinase signaling pathways and promotes neovascularization through activation of angiogenetic factors. In colonic epithelial cells, leptin treatment resulted in p42/44 MAP kinase activation, thereby inducing their proliferation in vitro and in vivo [23]. Furthermore, migration and invasiveness of colon cancer cell lines derived from particularly aggressive human tumors were potentiated by leptin-dependent stimulation of PI3K and Src signaling pathways, which subsequently activated Rho GTPases, Cdc42 and Rac1 [24]. In pancreatic cancer cells, leptin was able to promote proliferation and migration through activation of PI3K-AKT signaling and enhanced expression of matrix metalloproteinase-13 [28, 29].

Altogether, clinical and experimental evidence exists that leptin signaling affects a large number of distinct tumor entities, thus being one of the foremost links between obesity and cancer risk. On a cellular level, leptin promotes signaling pathways involved in proliferation, survival, migration and angiogenesis, as well as inhibition of apoptosis, all of which are key determinants of tumor development and progression.

Adiponectin

Adiponectin is a 244 amino acid peptide secreted by adipocytes. It exists in several multimeric forms and induces signaling via its two receptor isoforms [38]. By augmenting the insulin response, adiponectin contributes to coordination of glucose and lipid metabolism [39]. Adiponectin secretion is induced by oxidation of fatty acids. In line with this, obese adipose tissue usually displays a markedly reduced adiponectin production [40]. Given its beneficial effects on insulin sensitivity and its inverse correlation with body weight, adiponectin is considered the “good guy” among the adipokines.

Several epidemiological studies provide evidence for a tumor-suppressing action of adiponectin, since its levels inversely correlate with cancers of the colon, mammary gland, endometrium and kidneys [41–43]. Accordingly, a high leptin/adiponectin ratio has been associated with poor survival in colorectal cancer patients [44]. Kaklamani et al. [45] found specific SNPs in the adiponectin and adiponectin receptor gene loci to be associated with either increased or decreased colorectal cancer risk in Caucasians. A recent meta-analysis provided evidence for an association of three SNP in the adiponectin gene with colorectal cancer in Asians, whereas there was no evidence for a significant correlation in the white ethnicity [46]. Overall, efforts to identify adiponectin SNPs associated with increases colorectal cancer risk provided inconsistent results to some degree [47]. Thus, significance of the proposed association remains a matter of debate.

Epidemiological evidence is supported by in vitro studies, demonstrating that adiponectin has anti-proliferative effects on distinct cancer cell lines [48, 49]. These data were confirmed by observations obtained in vivo using tumor mouse models. Growth of various subcutaneous and chemically induced tumors was promoted in adiponectin knockout mice, which particularly was observed under high-fat diet feeding [50, 51]. In line with this finding, adiponectin administration inhibited epithelial proliferation and development of neoplastic foci in colons of obese adiponectin-deficient mice [51]. In breast cancer mouse models, adiponectin haploinsufficiency resulted in early onset of mammary tumors as well as faster progression and enhanced metastasis formation compared to control animals [52].

Although the exact mechanisms underlying its protective function are still a matter of investigation, several mechanisms of anti-carcinogenic action of adiponectin have been convincingly demonstrated, including but not limited to restriction of macrophage recruitment [50], AMPK and LKB1 activation [49, 53], as well as inhibition of mTOR, STAT3 and AKT pathways [51, 52, 54]. Overall, the biological functions of adiponectin antagonize specific aspects of leptin action.

Others

The *VEGF* family controls development of the vascular system during embryogenesis and induces angiogenesis in response to hypoxia. In solid cancers, VEGF is frequently highly expressed to promote vascularization, thereby ensuring nutrient and oxygen supply, which is vital for tumor growth. Consequently, the VEGF pathway is one of the most promising therapeutic targets in oncology. VEGF- and VEGF-receptor-directed therapies are available on the market and approved for treatment of renal, prostate, pancreatic and gastrointestinal tumors. Treatment of further cancer entities is currently being tested in phase II and III studies [55].

Adipose tissue is an important source for circulating VEGF, and leptin activates VEGF expression (see above). As hypoxia occurs in obese adipose tissue, neovascularization is required, resulting in enhanced VEGF expression [56]. In consistency with this, circulating VEGF levels were twofold elevated in centrally obese versus normal weight subjects and VEGF expression was significantly upregulated in visceral compared to subcutaneous adipose tissue in the obese group [6]. Furthermore, VEGF serum levels were elevated in a mouse model of postmenopausal

obesity concomitant with enhanced growth of orthotopically implanted breast tumors compared to lean controls. Notably, in this study, VEGF expression in the subcutaneous adipose tissue was found to be higher than in visceral fat [57]. Conditioned media from visceral adipose tissue obtained from obese donors significantly promoted proliferation of esophageal adenocarcinoma and colorectal carcinoma cell lines, which was rescued by neutralization of VEGF using a specific antibody [6]. In genetically obese mice, VEGF signaling is involved in adipose tissue inflammation, which has additional implications for obesity-linked tumor promotion [58]. Altogether, these data suggest tumor-promoting actions of adipose tissue-derived VEGF through angiogenesis induction and beyond.

In summary, adipose tissue secretes a pattern of bioactive molecules, with implications for tumor development and/or progression as they control signaling pathways involved in cell proliferation, angiogenesis and migration. The composition of the adipose tissue secretome depends on the metabolic health of the adipose organ. A considerable number of studies have revealed potential molecular mechanisms that could explain how alterations in leptin and/or adiponectin levels might increase cancer risk in an obese setting. As these adipokines have basically antagonistic functions, not only their absolute levels might be of relevance for tumor development, but also their ratio should be taken into account. It should be noted that adipose tissue secretes a number of further molecules (e.g., resistin, visfatin, nesfatin, lipocalin-2 and others). Although they have not yet been as intensively investigated with respect to cancer as the above described factors, changes in their serum levels have been associated with cancer development. For example, high levels of resistin have been observed to correlate with tumor and inflammatory markers, but not with anthropometric variables in a breast cancer cohort [59]. Moreover, adipocytes secrete pro-inflammatory cytokines, which are discussed in detail below. Altogether, it might be worth considering the entire adipokine signature of an individual as prognostic factor to assess cancer risk and the clinical outcome [60]. In addition, obesity and insulin resistance are associated with increased circulating levels of adipose tissue-derived fatty acids and other lipid species, which can serve as substrates for enhanced tumor growth (see below).

2.1.2 Cancer-Associated Adipocytes (CAAs)

Besides the role of adipose tissue as an endocrine organ exerting systemic effects, adipocytes are increasingly recognized as important component of the tumor microenvironment, particularly in tumors growing in close proximity to adipocytes [61]. For instance, human and murine breast cancer cells showed increased invasive capacity when co-cultivated with mature adipocytes [62]. Conversely, the adipocytes exposed to the tumor cells exhibited a modified phenotype favoring delipidation and overexpression of proteases, including matrix metalloproteinases 11 and proinflammatory cytokines such as interleukin (IL)-1beta and IL-6, the latter of which was shown to contribute to the proinvasive effects in tumor cells. Importantly, the presence of such modified adipocytes was shown in human breast tumors and tumor size was associated with increased IL-6 expression in the surrounding adipocytes [62]. In a recent study, the secretion of the chemokine CCL7 by

periprostatic adipose tissue was found to be enhanced during obesity. Elevated CCL7 levels stimulated directed migration of CCR3-positive prostate cancer cells. As a result, obese individuals are at higher risk of particularly aggressive forms of prostate cancer [63]. Notably, CCR3 expression was associated with poor prognosis in human patients [63]. Thus, even in tumor entities without an obvious correlation between obesity and tumor risk, exemplified by prostate cancer, adipocytes in the tumor microenvironment potentially affect disease progression by secretion of pro-inflammatory mediators.

2.2 Other Tissues

2.2.1 Insulin and IGF Signaling

Constantly elevated levels of circulating insulin as a consequence of the development of insulin resistance, which can be observed in the majority of obese individuals, are associated with progression and aggressiveness of several types of cancer [64, 65]. This relationship has been validated in a vast number of studies using animal models of hyperinsulinemia and insulin resistance [66]. Likewise, levels of the insulin-related peptide hormone insulin-like growth factor (IGF) 1 were interpreted as biomarkers for cancer development [67]. Notably, insulin induces hepatic IGF1 expression in a growth hormone-dependent manner, and enhances IGF1 bioavailability by repression of IGF binding proteins [4, 64]. Thus, hyperinsulinemia goes hand in hand with elevated circulating IGF1 levels.

Insulin and IGFs activate heterotetrameric tyrosine kinase receptor complexes, namely insulin receptor (IR) and IGF1 receptor (IGF1R), respectively. Whereas IGF1R is ubiquitously expressed and activates proliferative and anti-apoptotic pathways, IR expression is mainly found in rapidly dividing cells (isoform A) as well as metabolically active tissues, including liver, muscle and adipose tissues (isoform B). Thus, IR-B mediates the metabolic functions of insulin. Importantly, the mitogenic IR-A and IGF1R were found to be highly expressed in tumor cells [68]. Due to their high homology, IR and IGF1R potently form hybrid receptors. Notably, IGFs have a substantially higher affinity to IR/IGF1R hybrids than insulin, resulting in IGF1 occupation and consequently enhanced proliferation of cells expressing both receptors. Consistently, accumulation of hybrid receptors is characteristic for several cancer types [64, 68].

The major downstream effectors of IR/IGF1R are the PI3K/AKT and MAPK signaling pathways. Whereas PI3K mediates metabolic functions of insulin in liver, muscle and adipose tissue, both pathways have been linked to proliferation in various cancers [64]. As these pathways can be targeted with small molecule inhibitors, they became attractive for specific anticancer therapies. Inhibiting the PI3K/AKT/mTOR axis resulted in reduced growth of mammary tumors in hyperinsulinemic mice in a similar way as previously demonstrated for tyrosine kinase inhibitors blocking IR/IGF1R activity [69–71]. Of note, the anti-diabetic drug metformin, which among other effects activates AMPK and inhibits mTOR, and

eventually attenuates hyperinsulinemia, has been shown to suppress tumor activity [72].

2.2.2 Signaling via Sex Hormones

Sex hormones are involved in specific cancer entities, exemplified by the implications of estrogen and androgen signaling in breast and endometrial, as well as prostate cancer, respectively. Obesity increases the risk of development of postmenopausal breast cancer, whereas the risk of premenopausal breast cancer appears to be reduced [73]. It is evident that the adipokine leptin, which correlates with the grade of obesity, is involved in breast cancer development and progression. However, an exclusive role of leptin is unlikely, given the apparent protective function of obesity in the context of premenopausal breast cancer. After menopause, adipose tissue is the main source for estrogen production. Thus, circulating levels of estrogens directly correlate with the amount of body fat. Moreover, in obese adipose tissue, expression of aromatase, the enzyme that converts androgens to estrogens is further induced by excess of pro-inflammatory cytokines, thereby further promoting hyperestrogenemia [74]. Notably, obese women are at higher risk of developing mammary tumors derived from cells that express the estrogen receptor (ER-positive breast cancer), which applies to a high number of postmenopausal breast cancers [75]. Estrogens have many modes of action, which could contribute to tumor promotion, including mitogenic effects, mediation of genetic instability and inhibition of apoptosis [76].

Androgens play a key role in prostate cancer development and progression. According to epidemiological studies, there is no significant increase in relative prostate cancer risk in obese men [4]. This is in line with the observation that obesity correlates with low testosterone and sex hormone-binding globulin levels [77]. However, disease progression and mortality are significantly enhanced in obese patients [4]. In this context, a recent study has demonstrated that periprostatic adipose tissue-derived inflammatory signals might determine aggressiveness and invasiveness of prostate tumors under obese conditions (see above and [63]).

2.2.3 Immune Cells and Pro-inflammatory Signaling

Whereas the immune system has significant tumor-suppressing functions, cancer often develops in local environments where persistent inflammation occurs [78]. Chronic inflammatory states generally have pro-tumorigenic potential as they promote proliferation and cell survival by inducing mitotic and anti-apoptotic pathways [79]. Moreover, tumors frequently exhibit characteristics that are typically associated with inflammatory processes including activation of pro-inflammatory signaling pathways, angiogenesis and tissue remodeling [79].

Obese adipose tissue undergoes a substantial remodeling process. In this context, massive infiltration of adipose tissue by cells of the innate immune system takes place. Indeed, formation of distinctive “crown-like structures” by macrophages surrounding dying adipocytes is a hallmark of adipose tissue inflammation during obesity [80, 81]. Moreover, whereas adipose tissue-resident macrophages predominantly exhibit an anti-inflammatory M2 phenotype under lean conditions,

pro-inflammatory M1 polarized macrophages become more abundant during obesity. Macrophage reprogramming might be driven by free fatty acids and inflammatory mediators released from dysfunctional adipocytes [82]. Enhanced secretion of an array of pro-inflammatory cytokines by immune cells and adipocytes can be observed in an obese setting. Specifically, release of tumor necrosis factor (TNF) α, interleukin (IL)-1beta and IL-6, as well as CC-chemokine ligands (CCL), is markedly increased during obesity, thereby aggravating adipocyte dysfunction and promoting systemic insulin resistance [82–84]. Altogether, under obese conditions, infiltration of adipose tissue by macrophages, mast cells and lymphocytes, as well as alterations in the adipose tissue secretome, precipitates into a persistent local and systemic subclinical inflammatory state.

Pro-inflammatory cytokines have been shown to be involved in tumor development and/or progression, thus providing a possible direct link between adipose tissue inflammation and cancer. Notably, they also induce expression of chemokines and prostaglandins, resulting in recruitment and activation of immune cells, ultimately establishing an inflammatory feed-forward mechanism [78]. TNFα promotes tumor progression through activation of transcription factors controlling proliferative and anti-apoptotic pathways, particularly NF-κB and AP-1 [78, 85]. It has been also shown to be involved in mutagenesis and epithelial to mesenchymal transition, the latter of which is a critical event in metastasis formation [86]. IL-6 promotes expression of genes involved in oncogenic pathways, mainly via Jak-STAT activation [85]. In this context, the Karin laboratory demonstrated that TNFα and IL-6 directly promote tumor growth in a STAT3-dependent manner in a carcinogen-induced liver cancer mouse model. Notably, the tumor-promoting effect of pro-inflammatory signaling was amplified in obese animals. Accordingly, loss of either the IL-6 receptor or TNF receptor 1 largely prevented tumor development even under obese conditions [87]. A more recent study demonstrated that under obese conditions, HCC was promoted through stabilization of the E3 ligase Mcl-1. Of note, IL-6 regulates Mcl-1 turnover, which was disrupted during obesity, resulting in an IL-6 independent HCC promotion in obese mice [88]. TNFα signaling was found to be central for progression of PanIN lesions toward pancreatic cancer in obese mice, supporting a general role of pro-inflammatory signaling in obesity-associated tumor development [89].

Specific tumor-suppressing immune cells are quantitatively reduced during obesity, which has implications for cancer risk. In mice and men, obesity is associated with dysfunction of the innate and adaptive immune system, which manifests for instance in reduced numbers of natural killer (NK) and cytotoxic $CD8^+$ T cells [86]. These cells have direct antitumor effects as they mediate cytotoxicity to cancer cells [78]. In line with this, exercise was shown to induce infiltration of distinct tumors by NK cells, thereby inhibiting tumor growth [90]. Additionally, a reduction in regulatory T (Treg) cells could be observed in the abdominal fat of obese mice and humans [91]. Whereas Treg cells play a role in immune evasion of tumor cells, they probably have antitumor function as well as suppressive effects on chronic inflammatory states.

Several other types of immune cells have tumor-promoting or tumor-suppressing activities, including neutrophils, B-lymphocytes and T-helper cells [78]. It still needs to be shown in detail if and how these cells are affected by obesity and may link metabolic dysfunction to cancer manifestation.

3 The Gut Microbiome

Microorganisms have been threatening human health at all times. While bacteria-associated infectious diseases have mostly lost their terror due to the discovery of vaccination and antibiotics, microbes have gained attention as pathogens also in non-communicable diseases. In this context, a number of bacterial species have been designated as carcinogenic [92].

The vast majority of the human microbiota resides in the digestive tract, which provides optimal growth conditions for various bacterial species, e.g., constant temperature and availability of nutrients. Actually, the gastrointestinal tract of an average healthy adult contains more than 1 kg of bacterial mass [93]. Metagenomic analyses based on 16S rRNA sequences have revealed an unexpectedly high complexity of gut bacterial communities and that their composition depends on several parameters [94]. The symbiotic relationship between the intestinal microflora and its host results in mutual benefits for both organisms.

As gut-resident bacteria are involved in digestion and absorption of macronutrients, they have a key function in regulating metabolism of their host. However, despite being generally advantageous and health promoting for the host, the gut microbiota might as well contribute to several pathologies. In the other direction, metabolic status and diet composition potentially have significant impact on the composition of the intestinal microflora [95–97]. While Firmicutes and Bacteroidetes are the most abundant bacterial phylae under healthy conditions, Enterobacteriaceae were found to be enriched in the intestinal tracts of obese humans and rodents [98]. This family of Proteobacteria, which is hardly detectable in healthy microbiomes, is known to release large amounts of lipopolysaccharide (LPS), thereby locally and systemically leading to a pro-inflammatory milieu [99]. Accordingly, circulating LPS levels were found to be 2–3 times elevated in obese mice compared to lean controls [100]. Thus, by constantly triggering an innate immune response, a modified gut microbial community potentially might contribute to the low-grade chronic inflammatory state that is observed under obese conditions.

Obesogenic diets that contain high amounts of fat while being poor in fiber were reported to cause lowering of microbial diversity (dysbiosis) in the gut, which has been linked to cancer [101, 102]. In line with this, transfer of wild-type microbiota to dysbiotic mice reduced tumor burden in a colorectal cancer model [102]. Notably, eradication of the microbiota through germ-free housing or antibiotic treatment resulted in tumor reduction in various rodent models of colorectal cancer, leading to the assumption that no microflora at all might be better than dysbiosis

[101]. As inhibitory effects of gut microbiota elimination could be observed on tumors of the liver, the lung and the mammary gland, it is plausible that intestinal bacteria also potentially promote remote oncogenesis [101].

Specific gut-resident microbes break down dietary fiber into bioactive short-chain fatty acids (SCFA), mainly acetic, propionic and butyric acid. Whereas butyrate can be used by colonocytes as an energy substrate, SFCA are generally known to have anti-inflammatory effects [103, 104]. Moreover, butyrate was shown to have tumor-suppressing functions in neoplastic colon cells under defined dietary and microbial conditions [105]. By contrast, in colonocytes with mutations in the *Msh2* and *Apc* genes, butyrate production by microbes resulted in enhanced proliferation [106]. Furthermore, gut bacteria have important functions in bile acid metabolism. It has been recently demonstrated that mice fed a high-fat diet exhibited elevated levels of the secondary bile acid deoxycholic acid (DCA), concomitant with significant alterations of the gut microbiota [107]. It has been shown in the same study that DCA promotes development of hepatocellular carcinomas through induction of DNA damage, which could be prevented by antibiotic elimination of gut bacteria [107]. The carcinogenic effect of DCA can be at least partially explained by its cytotoxic and genotoxic potential [108]. Thus, disrupted bile acid homeostasis provides another connection between obesity, gut microbiota and cancer.

It is accepted that the connection between dysbiosis and cancer is caused not only by toxic actions of specific pathogens, but also by an impaired host–microbe interaction. However, the underlying molecular mechanisms are only partially resolved. Dysbiosis potentially results in barrier failure of the intestinal mucosa and subsequent inflammatory response. It has been hypothesized that a healthy microflora (eubiosis) might at a low-level activate receptors of the innate immune system, which are presently in the focus of tumor-suppressing immune therapies [109]. It is questionable though, if the degree of activation of the innate immune response is sufficient to induce anti-tumor effects [101]. Also, this is somewhat counterintuitive and contradictory to the tumor-promoting effects of LPS, which acts through stimulation of the innate immune system. Also, in disagreement with the hypothesis that induction of a (low level) innate immune system response could exert anti-tumorigenic effects, activation of Toll-like receptors resulted in pancreatic inflammation and subsequent carcinogenesis [110].

There is consensus that the gut microbiota contributes to health and disease in many respects. By mediating inflammatory responses, accumulation of toxic compounds, and/or provoking barrier failure, a dysbalanced microbiota might link obesity to certain cancers. Regardless of whether alterations of the microbiota are cause or consequence of obesity, promoting a healthy microbiome composition in the gut might not only help to maintain general wellbeing, but also could provide to a certain degree protection from cancer. Thus, diets rich in fiber as well as pre- and probiotic nutritional supplementation should always be taken into account when we think about lifestyle modifications aiming toward cancer prevention.

4 Tumor Cell Metabolism

Already in the 1920s, the German biochemist Otto Warburg hypothesized that a metabolic switch from respiration to increased glucose consumption for lactic acid fermentation (a process termed aerobic glycolysis or the Warburg effect) represents a main event in the transformation of a normal to a tumor cell and that cancer cells could be defeated by targeting their energetic requirements [111]. Although widely neglected for a long period of time, the field of cancer metabolism achieved enormous attention by researchers in the past decade. Consequently, Warburg's concept mainly focused on increased glucose consumption has been extended by the definition of a plethora of specific changes referred to as the metabolic reprogramming of cancer cells [112]. As both direct and indirect consequence of oncogenic mutations, cancer cell metabolism is considered a prerequisite for maintaining viability and fulfilling the biosynthetic demands associated with cell proliferation. However, the precise metabolic program of cancer cells might depend on their specific oncogenic mutations, the tissue context and other factors, including macro- and microenvironmental components. Nevertheless, most cancer cells display several of the six hallmarks of cancer metabolism, which have been defined in a recent review based on known cancer-associated metabolic changes [112]. Some of the metabolic features of cancer cells might contribute to the risk association between obesity and cancer. These include (1) the increased uptake of glucose, which might be favored by hyperglycemia under diabetic conditions, (2) the opportunistic modes of nutrient acquisition enabling tumor cells to benefit from increased lipid availability under obesity conditions and, at least in part related to the latter, (3) the metabolic interactions with the environment, e.g., neighboring adipocytes.

4.1 Hyperglycemia

As a central component of metabolic reprogramming, cancer cells take up high amounts of glucose, which is utilized for ATP production by aerobic glycolysis and generation of building blocks for nucleotide, amino acid and lipid biosynthesis. This suggests that increased concentrations of glucose in the circulation (hyperglycemia), as a hallmark of type 1 and type 2 diabetes mellitus (DM) could contribute to tumorigenesis. Indeed, a number of epidemiological studies suggest that DM is associated with higher prevalence as well as increased mortality for certain types of cancer, including liver, pancreas, colorectal, kidney, bladder, endometrial and breast cancers [113, 114]. Notably, type 2 diabetes represents approximately 90 % of total diabetes cases and arises from insulin resistance under obesity conditions. Therefore, given that cancer occurs preferentially in the older population, in which type 1 diabetes is less frequent, it can be assumed that the increased cancer risk associated with DM refers to mainly to type 2 diabetes [114]. Like for obesity, the risk connection between DM and cancer is complex and might be based on

various mechanisms including increased levels of pro-inflammatory cytokines as well as oncogenic effects of hyperglycemia which are not directly linked to glucose as an energy substrate, e.g., anti-apoptosis, induced cell migration and invasion as well as hyperglycemic memory effects [115]. However, hyperglycemic conditions in vitro have been shown to trigger increased glucose uptake in choriocarcinoma cells by inducing expression of the glucose transporter isoforms GLUT1 and GLUT3 [116]. Also, hyperglycemia has been shown to contribute to hypoxia-inducible factor (HIF)-1 alpha stabilization [117], which in turn can induce the expression of glycolytic enzymes further enhancing glucose utilization. However, the direct effects of hyperglycemia on cancer development are widely unexplored, also due to technical difficulties in studying the effects of high glucose levels on cancer in vivo without interfering with the effects of absence or induction of insulin signaling.

4.2 Lipid Metabolism

As part of the metabolic reprogramming of cancer cells, fatty acids are generally considered to serve as building blocks for biosynthesis of membranes and signaling molecules, as well as to support other aspects of the transformed phenotype of rapidly proliferating cells [118]. Consequently, there are numerous examples showing that oncogenic pathways re-activate de novo lipid synthesis, in part through increased expression and activation of the required metabolic enzymes, including fatty acid synthase (FASN) [118, 119]. Along this line, inhibition of fatty acid availability by different modes could offer novel opportunities in cancer therapy [120].

Despite the observation that cancer cells acquired increased capacity for de novo lipid synthesis to enable proliferation, it is conceivable that under obesity conditions, the increased availability of exogenous lipids from the circulation and from cancer-associated adipocytes could promote tumor development. In support of this idea, Nomura et al. showed that inactivation of the lipolytic enzyme monoacylglycerol lipase (MAGL) markedly impaired the tumorigenic capacity of different aggressive human cancer cell lines representing melanoma, breast and ovarian cancer. They identified MAGL in a proteomic analysis in which this lipase was consistently elevated in the aggressive cell lines compared with their non-aggressive counterparts from the same cancer entity. Knockdown of MAGL in the aggressive or overexpression in the non-aggressive cell lines impaired or induced oncogenic features, respectively, including migration, invasion and in vivo growth. Strikingly, the reduced in vivo growth of xenograft tumors upon knockdown of MAGL in the implanted cells could be rescued by feeding the mice a HFD, suggesting a pro-tumorigenic effect of the availability of exogenous fatty acids [121]. Another study showed that the proliferation of breast cancer and sarcoma cells expressing Lipoprotein Lipase (LPL) and CD36 is accelerated upon treatment with triglyceride-rich lipoproteins. Since LPL and CD36 are involved in lipoprotein-associated triglyceride lipolysis and fatty acid uptake, respectively, this

suggests that these cells are capable to acquire fatty acids from the circulation or other sources to fuel their growth [122]. In addition, providing prostate cancer cells, which are characterized by high lipogenic capacity, with LPL and TG-rich lipoproteins prevented the growth inhibitory effects of fatty acid synthesis inhibition [122]. Interestingly, there is also evidence that under hypoxic conditions or Ras activation, certain cancer cells can switch from de novo lipogenesis to scavenging of serum fatty acids to meet their lipid requirements [123]. Similarly, another study demonstrated in a panel of cell lines and in tumors that exogenous palmitate could be incorporated into both structural and oncogenic signaling lipids [124]. Furthermore, dietary lipids potentially also act as ligands for nuclear receptor transcription factors. In this context, a recent study showed that high-fat diet promotes stemness and induced the capacity for tumor initiation of intestinal progenitor cells via activation of PPARδ and subsequent induction of WNT/β-catenin signaling [125].

Also, more direct interactions between adipocytes and cancer cells might contribute to metabolic adaptations promoting tumor growth and aggressiveness. For instance, co-culturing of primary adipocytes with ovarian cancer cells led to the direct transfer of lipids by induced lipolysis in the adipocytes and beta oxidation in the cancer cells, suggesting that adipocytes can act as an energy source to promote tumor growth [126]. Interestingly, ovarian cancer metastasis to the omentum, an organ primarily composed of adipocytes, was induced by adipokines characterized by induced fatty acid binding protein (FABP) 4 expression, indicating a modified lipid metabolism phenotype.

Although further research is required to elucidate the interaction between cancer cell metabolism and the altered metabolic macro and microenvironment in metabolic diseases, the described examples might point to the implication of such mechanisms in the connection between obesity and cancer and guide further studies in this direction in the future.

5 Outlook and Open Questions

Obesity increases the risk of several cancer entities by triggering multiple (patho-) physiological alterations in local and remote fashions. Given its pandemic prevalence, obesity is expected to become one of the main lifestyle-associated risk factors for cancer development in the near future. Knowledge of the underlying molecular principles will be crucial, as it will open new opportunities for "metabolocentric" cancer treatment and prevention. Such options would include targeted therapies affecting deregulated pathways under obese conditions, exemplified by inhibition of inflammatory and growth factor signaling. Importantly, interventions targeting obesity and metabolic dysfunction in a more general way might have (immediate) effects on cancer risk independent of actual weight loss: Exercise triggers the release of potentially tumor-suppressing myokines, such as oncostatin and SPARC [127, 128]. Bariatric surgery instantly results in metabolic improvements

independent of body weight loss, including elevated adiponectin levels and alleviation of hyperinsulinemia [129–131]. Pre- and probiotics could be an option for supporting a healthier intestinal microflora [132]. Noteworthy, transplantation of healthy microbiota showed antitumor effects at least in murine cancer models [102]. Major future challenges will include the tumor entity-specific definition of metabolic complications and/or obesity-associated comorbidities, including type 2 diabetes, insulin resistance and dyslipidemia that determine increased tumor progression and/or aggressiveness in affected patients. Of particular interest will be the question to which extend metabolic dysfunction cannot only trigger tumor promotion but might also serve as an initiating event in the malignant transformation of a normal to a cancer cell, independent of classical gene mutations in oncogenes or tumor suppressors. Clinical and experimental studies in this direction can be anticipated to shed light onto this exciting field of biomedicine to overcome metabolism-driven tumorigenesis in the future.

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Obesity as an Avoidable Cause of Cancer (Attributable Risks)

Andrew G. Renehan and Isabelle Soerjomataram

Abstract

Excess body weight, commonly categorised as overweight (body mass index, BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) is an established risk factor for increased incidence of several adult cancers. As body weight is modifiable, there is a potential for cancer prevention. Calculation of attributable risk (here expressed at population attributable fraction, PAF) offers an estimate of the burden of excess cancers attributable to elevated BMI in populations, and thus an approximation of avoidable cases and the opportunity for prevention. Using counterfactual methods, the estimated PAF worldwide attributed to elevated BMI is 3.6 % or nearly half a million new cancer cases in adults (aged 30 years and older after a 10-year lag period). PAFs are higher in women compared with men (5.4 % vs. 1.9 %). Endometrial, post-menopausal breast, and colon cancers account for nearly two-thirds of cancers attributable to elevated BMI. Globally, excess body weight is the third commonest attributable risk factor for cancer (after smoking and infection); in western populations such as the UK, excess weight ranks as second commonest risk factor.

Keywords

Population attributable fraction · Burden of disease · Avoidable cancers · Cancer prevention

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In this chapter, we discuss the epidemiological background linking obesity and cancer risk, the rationale, methodology and model assumptions underpinning attributable risk estimations, and then summarise recent analyses that estimated the excess burden of cancers attributed to excess weight at a global level. In this manuscript, we use the term 'obesity' in a general common sense (as in the title) to denote excess body fatness. In sections on the epidemiology and modelling, we will indicate the specific exposure measure of body fatness. For almost all examples, this is BMI.

1 Epidemiology

Excess body weight, commonly categorised as overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2), is an established risk factor for increased incidence of several adult cancers [1]. Other anthropometric measures of body fatness, such as waist circumference (WC), are less well studied but are generally associated with increased cancer risk with similar patterns and strengths as those for BMI [2]. The most comprehensive and systematic evaluations of the associations between measures of body fatness and cancer risk have been undertaken through the World Cancer Research Fund (WCRF) continuous update project, which now links excess weight or body fatness to 11 cancers [3]. In 2016, an expert working group of 21 scientists from eight countries gathered under the auspices of the International Agency for Research on Cancer (IARC), to specifically evaluate the preventive effects of avoidance of excess body fatness on cancer risk. This group extended the list of obesity-related cancer, for which *sufficient* evidence exists, to thirteen malignancies as follows: cancers of the colon and rectum, oesophagus (adenocarcinoma), kidney (renal cell), breast (post-menopausal), endometrium, gastric cardia, liver, gall bladder, pancreas, ovary, thyroid, multiple myeloma and meningioma [2]. For the majority of these cancers, there are plausible (hypothesised) biological mechanisms to explain these links. These candidates are three hormonal (systemic) systems, namely circulating sex hormones; the insulin and the Insulin-like Growth factor system; and circulating adipokines and subclinical systemic inflammation [4]. In addition, the local peri-tumour adipose micro-environment or local ectopic fat is likely to be important [4, 5].

It has become clear over the past five years that, in addition to the common effect modifier such as age and sex, there are other effect modifiers of the above BMI–cancer associations. Two clear examples are smoking status [6] and hormonal replacement therapy [4, 7], and these need to be taken into account in attributable risk modelling. For example, studies show a higher risk of pancreatic cancer due to elevated body weight among never and ex-smokers as compared to current smokers with the same BMI [8]. Meta-analyses generally show inverse associations between BMI and smoking-related cancers such as lung cancer and oesophageal squamous

cell carcinoma. When these analyses are stratified by smoking status, null associations were generally observed in the never smoker strata. In the example of HRT use, meta-analyses of prospective studies evaluating the associations between BMI and subsequent risk of post-menopausal breast, endometrial and ovarian cancers stratified by HRT use demonstrate that per incremental increase in 5 kg/m^2, and there are increased risks of 18, 90 and 10 %, respectively, in never HRT users. Among ever HRT users, there are no associations between BMI and post-menopausal breast ($P_{interaction} < 0.001$) and ovarian ($P_{interaction} < 0.001$) cancers, and an attenuated association (18 % increase per 5 kg/m^2) for endometrial cancer ($P_{interaction} = 0.003$) [4].

2 Why Estimate Attributable Risk

There are broadly four reasons to estimate attributable risk. First, it is an estimate of the burden of a public health problem in a population. Such information is helpful for policy makers planning health strategies and resources. In specific circumstances, this information can be instrumental in bringing about legislative changes. Two examples are told in Table 1—the smoking ban in Ireland [9, 10] and the implementation of the 'sugar tax' in the UK [11, 12]. In both examples, the uses of attributable risk estimation were key drivers in the implementations of these legislations.

Second, estimation of attributable risk facilitates ranking of the burden of an 'exposure' of interest versus other exposures. This is illustrated later in this review by the recent initiatives by Cancer Research UK, the largest cancer charity organisation in the world, which drew a fresh focus on the link between obesity and cancer, and recognised that this risk factor was the second commonest cause of cancer (in the UK) after smoking, which had been a key preventive focus of the charity for the preceding decades [13].

Third, estimation of attributable risk across many cancer types allows identification of specific 'hot spots' and targeting of specific exposure–disease associations. A specific example of this might be the link between excess body weight and endometrial cancer. Here, the (PAF: calculation detailed below) is approximately 50 % [14], and indeed points to some sub-populations of women (e.g. women undergoing bariatric surgery) as potential targets for screening for atypical endometrial hyperplasia, a precursor lesion of endometrial cancer [15].

Finally, in principle (with caveats detailed below), estimation of attributable risk can be used to project future cancer incident trends, (again) important for planning health strategies and resources—for example, future colon cancer incidence in various European countries might be greatly reduced by decreasing BMI level in men; whereas in women, physical activity probably offers a better intervention to curb the future colon cancer problem [16].

Table 1 Case studies to illustrate the uses of attributable risk as key drivers to the implementation of legislative process

The 'smoking ban' in Ireland In March 2004, Ireland became the first European country to implement legislation creating smoke-free enclosed workplaces including bars and restaurants [10], commonly known as the 'smoking ban'. At the time, this was ground breaking and of huge public health importance. Reports during the 1990s recognised that second hand smoking or passive smoking in the workplace was harmful, but legislation to prohibit smoking was voluntary and had little effect. Momentum after 2000 drew in international expertise to 'shout for the cause' of hospitality workers. Of particular note was the input from James Repace [9], a renowned US health physicist, who had already been instrumental in the banning of smoking in US airlines. He used attributable risk calculations and estimated that 'up to 150 Irish bar workers could be dying annually as a result of their exposure to second hand smoke'. In a country with a population of only 3.5 million, this figure struck a chord with politicians and policymakers and helped to argue this bill to implementation through the Irish parliament
The 'sugar tax' in England In March 2016, the UK announced a new taxation system on sugary drinks, which has caused a lot of stirs-up, either positive and negative ones. In addition to combat, the growing proportion of obesity in the UK especially among children, this initiative will also ultimately have a large impact on various chronic diseases in adults such as diabetes, cardiovascular disease as well as cancer. This is ground breaking and of huge public health importance The consumption of sugary drinks has been increasing worldwide, and its relation to the epidemic has been previously made [11]. Yet, opposition from the industry has been tremendous, keeping implementation of such tax at bay for most nations globally. The momentum is now stronger than ever, led by various publications reporting the population attributable fraction supported by various WHO reports including the Global status report on NCDs in 2014 [12] Of particular note was the input from Jamie Oliver, a renowned English chef and entrepreneur, who had already been instrumental in the promoting healthier nutrition especially in children. Other countries around the world are starting (or have already started) taking similar actions: for example in Europe France and Hungary have adopted a tax on sugary drinks in 2011 and 2012, respectively. Outside of Europe Chile and Mexico have implemented similar sugar tax. Early study has shown a positive impact of taxation to reduce sales, but its health impact remains to be assessed

3 Estimation of Attributable Risk

Details on the methodologies behind the calculations of PAF have been detailed by the authors previously [7] and are summarised here. The standard approach includes modelling estimates of prevalence of the exposure (P_e) and relative risk (RR) with the simplest formula for such a model described half a century ago by Levin [17] and shown in Table 2. The derived PAF is defined as the proportion of all cases that would not have occurred if the exposure had been absent and is thus relevant in cancer prevention research.

However, there are several limitations of the Levin methods. First, the Levin formula only partially adjusts for confounding and does not allow the inclusion of effect modification into the model. In turn, this results in biased PAF estimates (generally overestimated), as has been extensively described by Flegal et al. [18].

Table 2 Formulae

$\mathrm{PAF} = \frac{P_e(RR-1)}{P_e(RR-1)+1}$ Levin's Formula (1953)
$\mathrm{PAF} = \frac{\int RR(x)P(x)dx - \int RR(x)P^*(x)dx}{\int RR(x)P(x)dx}$ Counterfactual method where $P(x)$ is the population distribution of BMI, $P^*(x)$ is the distribution of theoretical minimum BMI, $RR(x)$ is the RR of cancer associated with BMI and dx indicates that the integration was done with respect to BMI

Second is a limitation of specific relevance to the relationship between elevated BMI and disease risk. Specifically, the categorisation of the BMI distribution into normal weight (18.5–24.9 kg/m^2), overweight and obesity cause the parameter to become trichotomous or polychotomous. This approach risks double counting the exposure, as individuals who were obese, also had a previous exposure to overweight exposure. Furthermore, using polychotomous categorical distributions to calculate PAF may cause a non-linear result [19] and overestimations of PAFs. There are methods described to overcome some of these limitations, such as those described by Hanley [20].

Against the above limitations, the currently preferred method for the calculation of PAF is the use of counterfactual methods. The contribution of a risk factor to a health measure is estimated by comparing the current or future level of the health measure under alternative hypothetical scenarios including the absence of the exposure. This hypothetical scenario is referred to as *counterfactual analysis*. The derivation of PAF is shown in Table 2 where $RR(x)$ is the RR of the exposure level x, $P_e(x)$ is the population distribution of exposure, $P_{ne}(x)$ is the counterfactual distribution of the exposure (hypothetical rather than to the actual condition) [21] and m is the maximum exposure level. A key component of this method is to determine the *theoretical minimum risk*—this is the exposure distribution, here BMI, that would result in the lowest population risk, here of cancer. In the example of smoking, this would be straightforward and would be defined by the never smokers population. In the example of BMI, things are less simple as there are hazards associated with low as well as high BMI, and this needs to be taken into account. Because of these considerations, the WHO has advised a theoretical minimum value of 21–22 kg/m^2 for BMI [22]. We have used single values of 22.5 kg/m^2 [14] and 22.0 kg/m^2 [23], in our respective analyses (detailed below). The difference in the theoretical minimum risk group or reference group is one of the causes of the variations of estimations of cancer risk attributed to excess body weight.

Importantly, counterfactual modelling handles BMI as a continuous distribution and that distribution might take a different form and parameterisation for the whole population and that of the theoretical minimum risk population. This also better captures changes in BMI distributions with time.

4 Model Assumptions Relevant to Obesity-Related Cancers

There are a number of model assumptions that require discussion. Again, these have been detailed elsewhere by the authors [7] and summarised here.

4.1 Assumptions About Causality

A central assumption in all this discussion is that the associations between obesity and increased cancer risk are causally linked. There are a number of authoritative reports from the WCRF [3] and IARC [2] to support this and are covered elsewhere in this Book [24]. One of the present authors has specifically addressed this in a systematic manner [25], evaluating BMI–cancer associations against the nine Bradford-Hill criteria (strength of association; consistency; specificity; temporality; biological gradient; plausibility; coherence; experimental evidence; and analogy) that offers a starting point, and also what have become to be known as the Bristol criteria [26] of appropriate adjustment for key confounding factors; measurement error; assessment of residual confounding; and lack of alternative explanations add a further dimension for assessing the causality of the evidence. The BMI–cancer associations hold up robustly for the majority of these criteria.

4.2 Assumptions About BMI Distributions

The simplest approach to estimate PAF is to use categorical BMI data, yet limitation of such approach needs to be acknowledged and understood. For example, if an increasing mean BMI is modelled over time, the corresponding prevalence based on the commonly used WHO overweight and obese categories will increase. Yet, with further increases in mean BMI, the prevalence of overweight declines as the prevalence of obese continues to increase. Simple formulae to estimate attributable risk, such the Levin formula, are inadequate in this setting. A second approach that is generally quite simple using current statistical tools is the use of a normal BMI distribution. Furthermore, with increasing mean BMI in a population, the BMI distribution changes from a normal to a gamma distribution [27], where the commonly observed skewed distribution of risk factors is converting into a more flat distribution with a growing population being overweight or obesity. These dynamics are best dealt with using the counterfactual modelling analysis.

4.3 Relative Risks

The outputs from the PAF equation—whether using the classical Levin method or contemporary counterfactual modelling—are very sensitive to changes in the RR

[14]. Wherever possible, conservative RRs (typically the most adjusted RRs) should be used from overview analyses that have derived RRs and their confidence intervals (CIs) using standardised approaches. Credible intervals for PAFs can be derived using Monte Carlo simulations [23]. The term credible intervals is used here, because of the false reassurance that confidence interval might give. The many underlying assumptions that have to be taken when estimating PAF combined with unavailability of a truly population-based prevalence of the exposure (here obesity) for many low and middle income countries means that cancer burden estimations with CIs is challenging and often impossible.

A note on linearity of relation is worth discussion. In general, PAF is derived as one risk function assuming linearity in the model. Although this model is often justified, we showed that this is not always the case [28]—thus, the risk of endometrial cancer increases exponentially with increasing weight, and risk function should be adjusted for calculating PAR for the higher BMI level, otherwise PAF might be underestimated.

Finally, another assumption in calculating PAF, using the general formulas described earlier, is risk reversibility. For smoking and cancer, risk reversibility has been reported before, i.e. stopping smoking at a young age reduces cancer risk compared to that of non-smokers [29]. Yet, for obesity evidence of reversibility remains limited, mostly because large weight loss is difficult and hard to maintain [30]. Risk reversibility and also accumulation of risk have led to various research avenues assessing the role of 'obese years' on cancer risk and also the PAF related to time spent with overweight or obesity [31, 32].

4.4 Assumptions About Lag Periods

For many common epithelial adult malignancies, tumour development is a multi-step process over many years or even decades. It is generally held that the influence of 'obesity exposure' on increased cancer risk probably plays out over at least a decade, and perhaps up to four decades with neoplastic processes such as colorectal cancer [33]. In the two published analyses [14, 23] from the authors, detailed below, a lag period of ten years has been assumed for all cancer types. Reasons are twofold, one being the fact that cohort studies for which risk estimates are taken from have on average a follow-up time of 10 years [25]. Secondly, case studies from bariatric surgery patients, with expected decreases in body weight, show a decreased risk of cancer 10 years following the intervention [34]. Nonetheless, the lag period probably varies between different cancers for the same exposure, and currently, this is not integrated into models.

5 Key Papers on the Estimation of Burden of Cancer Attributed to Elevated BMI

Using the above assumptions, the authors have published two analyses evaluating the excess new cancer cases attributed to elevated BMI—the first analysis in 30 European countries [14]; the second, as a global analysis [23]. For the former, PAFs were calculated using European- and gender-specific risk estimates from a published meta-analysis [1] and gender-specific mean BMI estimates from a World Health Organisation Global Infobase. Estimates were calculated for oesophageal adenocarcinoma, thyroid, colon, rectal (only men), renal, gall bladder (only women), pancreatic (only women), post-menopausal breast, endometrial, prostate cancers and malignant melanoma (only men), multiple myeloma, leukaemia, and non-Hodgkin lymphoma. Country-specific numbers of new cancers were derived from GLOBOCAN 2002. A ten-year lag period between risk exposure and cancer incidence was assumed. We used Monte Carlo simulations to derive 95 % CI, recognising that in today's nomenclature, the term credible intervals are preferred (see above). For 2002, there were 2,171,351 new cancers diagnosed in the 30 countries of Europe. Estimated PAFs were 2.5 % (95 % CI 1.5–3.6 %) in men and 4.1 % (2.3–5.9 %) in women or a total of 70,288 new cases. Sensitivity analyses revealed estimates were most influenced by the assumed shape of the BMI distribution in the population and cancer-specific risk estimates i.e. RR. In a scenario analysis for a 2008 population, the estimated PAFs increased to 3.2 % (2.1–4.3 %) and 8.6 % (5.6–11.5 %), respectively, in men and women. Endometrial, postmenopausal breast and colorectal cancers accounted for 65 % of these cancers.

For the worldwide analysis [23], we derived PAFs using RRs and BMI estimates in adults by age, sex, and country. Again, we assumed a 10-year lag period and calculated PAFs using BMI estimates from 2002 and used GLOBOCAN 2012 data to estimate numbers of new cancers. We selected ten obesity-related cancers, namely oesophageal adenocarcinoma, colon, rectum, pancreas, gall bladder (only women), postmenopausal breast, corpus uteri, ovary, kidney and thyroid cancers. We also calculated the proportion of cancers that were potentially avoidable had populations maintained their mean BMIs recorded in 1982 i.e. 30 years prior to the present day analysis. We did sensitivity analyses to estimate the effects of HRT use and smoking. In total, we estimated that almost a half million or 481,000 new cancers in adults (aged 30 years and older) in 2012 were attributable to high BMI. This was a PAF of 3.6 %. PAFs were greater in women than in men (5.4 % vs. 1.9 %) (Table 3). The burden of attributable cases was higher in countries with very high and high human development indices (HDIs; PAF 5.3 and 4.8 %, respectively) than in those with moderate (1.6 %) and low HDIs (1.0 %). As in our European-based analysis, endometrial, postmenopausal breast and colon cancers accounted for almost two-thirds of cancers attributable to high BMI. As an assessment of the changes in prevalence of excess body weight globally over the past three decades, we found that a quarter (about 118,000) of the cancer cases

Table 3 Estimated numbers and PAFs of cancer cases associated with high BMI in women and men in 2012 by cancer sites

	Men		Women	
	Numbers	PAF	Numbers	PAF (%)
Oesophageal adenocarcinoma	13,569	33 %	3862	34
Colon	55,608	13 %	29,451	8
Rectum	17,804	6 %	7160	4
Pancreas	14,845	8 %	12,269	8
Gall bladder	NA	NA	32,346	32
Breast (post-menopausal)	–	–	113,767	10
Corpus uteri	–	–	107,172	34
Ovary	–	–	8948	4
Kidney	34,231	17 %	30,179	26
Thyroid	11,615	19 %	18,108	9

Source Arnold et al. [23]

related to high BMI in 2012 could be attributed (and hence avoidable) had BMI distributions remained as they were in 1982.

As an extension of the worldwide analyses, we published further analyses on the relation between recent trends in BMI and the changing profile of cancer worldwide [35]. By examining seven selected countries, each representing a world region, a pattern of increasing BMI with region and gender-specific diversity was noted: increasing levels of BMI were most pronounced in the Middle East (Saudi Arabia), rather modest in Eastern Asia (India) and generally more rapid in females than in males. This observation translated into a disproportionate distribution of cancer attributable to high levels of BMI, ranging by sex from 4 to 9 % in Saudi Arabia and from 0.2 to 1.2 % in India.

6 The Ranking of Obesity as a Risk Factor

By following principles and assumptions outlined above, it is possible to now start to compare and rank across different risk factors. Table 4 shows that, at a global level, excess body weight is the third commonest attributable risk factor for cancer (after smoking [36] and infection [37]); in western populations such as the UK, excess weight ranks as second commonest risk factor [38]. The exercise that is done in the UK has helped government to prioritise prevention programmes and also increase population awareness on the risk factors for cancer. The UK initiative has also pushed other nations globally to performing similar analyses, for example, in Australia, overweight and obesity are the 4th major cause of cancer following smoking, solar radiation and inadequate diet [39].

Table 4 Estimated PAFs by major risk factors for cancer at a global level and for the UK

	PAF% [ranking]	
	Worldwide	UK[d]
Smoking	21.0 % [1][a]	19.4 % [1]
Infections	16.0 % [2][b]	3.1 % [6]
Overweight and obesity	3.6 % [3][c]	5.5 % [2]
Alcohol		4.0 % [3]
Occupation		3.7 % [4]
Radiation—UV		3.5 % [5]

[a]*Source* Ezzati et al. [36]
[b]*Source* de Martel et al. [37]
[c]*Source* Arnold et al. [23]
[d]*Source* Parkin et al. [38]

7 Future Directions/Integrating Other Obesity-Related Diseases

So far, most of the focus has been on changes in BMI that have already occurred. There are opportunities to predict for changes in the future. Thus, by illustration, CRUK and the UK Health Forum [13] recently reported in *Tipping the Scales: Why Preventing Obesity Makes Economic Sense* that 72 % of adults in the UK are predicted to be overweight or obese by 2035—including 45 % in the lowest-income quintile. The uplift in obesity is predicted to increase the number of new cancer cases in the next 20 years. It is estimated that if these numbers were reduced by only 1 % every year from the predicted trend, about 64,200 cancer cases could be avoided over the next 20 years [13]. At present, insufficient use is made of existing data to underpin obesity-related interventions and assess their potential impact on the future cancer of cancer

With the growing work on PAF, there is an ongoing movement to estimate future attributable fraction based on current and historical trends of obesity, as well as projects assessing the values of different intervention programmes to reduce future burden of cancer. In such exercise, the assumptions that are generally taken in PAF (as outlined above) are bound to be expanded including assumptions on future occurrence of cancer and also future distributions of BMI. The largest driver of the future cancer burden is the changing population structure: the older the population the higher the number of new cancer cases [40]. Global ageing alone will drive up the total number of cases estimated for 2012 i.e. 14 million by 58 % in 2035 i.e. 24 million [41]. Accordingly, the most important aspect that should be taken into account in future prediction of cancers is incorporation of demographic changes in the analysis. Furthermore, whenever possible, especially when projections are longer than 10–20 years, changes in the disease rate overtime and also other causes of deaths should be taken into account to reduce bias in disease estimate and impact of intervention, if the latter were to be incorporated [42].

In Europe, a previous model, PREVENT [43], has been reconstructed to fit the natural history of cancer and incorporates the previously mentioned aspects of modelling future burden of disease. A study in seven representative countries for each European region has estimated the possible long-term impact of continuous increase in BMI over the next decade against the status quo where BMI remains at its baseline level. The study shows that such increase will cause about 4 % increase in the number of cases in 2040, and if body weight were to decrease to a healthy weight, colon cancer might reduce by up to 11 % (in Spanish men) [44]. Such analysis has indeed provided the additional perspective needed in provision of valuable information for researchers and policy makers to quantify the impact of policies targeting BMI (or any other risk factor) on future burden of cancer.

A further dimension is evaluation of the impact on disease (here cancer) where there are two risk factors changing with time, and into the future. This is illustrated in Fig. 1, which might be typical of many western countries—a fall in prevalence of smoking, and a rising in prevalence of obesity. The hypothesis is that currently, smoking is the commonest cause of cancer; but perhaps within the next decade (for example, in women), obesity or more specifically, elevated BMI, might become the commonest cause of cancer.

The proportion of cancer that is avoidable or preventable has been a preoccupation for public health researchers and health makers for many decades. These estimates have started to provide valuable motivations to implement legislative changes. Readers in this field should find the methodologies discussed here, their limitations, and the summarised findings informative.

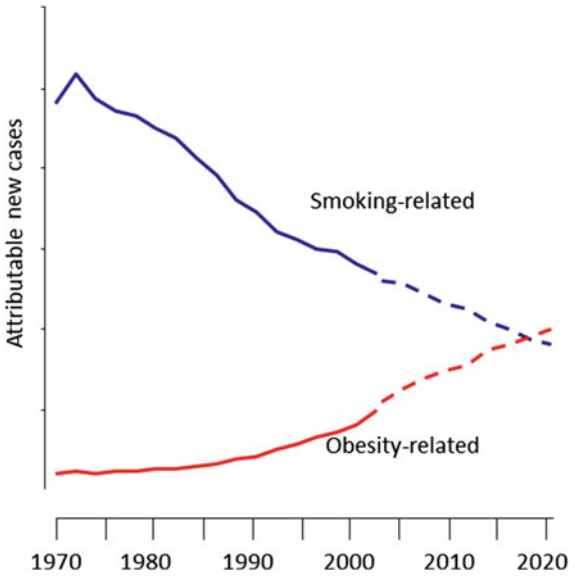

Fig. 1 A schematic representation of future trends in smoking-related versus obesity-related cancers

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