

# Obesity and Cancer

## Part 1 of the Diabetes and Cancer Mini-Review Series

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### Key words

- cancer
- estrogens
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### Abstract

Epidemiological studies have suggested that obesity is associated with increased risk of several cancer types including colon, esophagus, breast (in postmenopausal women), endometrium, kidney, liver, gallbladder and pancreas. Suggested mechanisms include increased intake of potentially carcinogenic food ingredients along with excessive amount of calories, loss of cancer protective effects due to reduced physical activity,

carcinogenic factors released from increased adipose tissue mass and “secondary” associations via “precursor” condition such as gallstones. The increased cancer risk in patients with obesity is a neglected topic which deserves more scientific attention. Because of its extreme chronicity and co-association with numerous other conditions true causality and underlying mechanisms are difficult to study. Nevertheless, a large body of literature is already available which provides concepts for future research.

“Corpulence is not only a disease itself, but the harbinger of others” Hippocrates wrote 2500 years ago, recognising that obesity is both a medical disorder and a cause for many other co morbidities. Since the early 1960, when obesity was a minor problem epidemiologically, with the accelerating increase in its prevalence during the 80s and 90s, the mean BMI increased by 3 BMI units approximately in both genders. This translates into an increase of 9 kg while average height only increased by less than 2 cm. Alarmingly, the same trend applies to children [1]. Excess bodyweight is the sixth most important risk factor contributing to the overall burden of disease worldwide. 1.1 billion adults and 10% of children are now classified as overweight or obese. Current epidemiologic trends in obesity suggest that the steady rise in life expectancy during the past two centuries may soon come to an end [2]. In a 40-year-old obese person the average life expectancy is already diminished by 7 years. The relationship between excess body weight and morbidity including cardiovascular disease, type 2 diabetes mellitus, hypertension and osteoarthritis has been firmly established. Several forms of cancer, including endometrium, colon, renal cell and oesophageal cancer are also associated with obesity [3,4]. The WHO International Agency for Research on Cancer estimated that overweight

and inactivity account for a about a quarter of these cancers [5]. The mechanisms that link obesity and cancer have not been fully elucidated and are being intensively investigated in many fields of basic science. The topic has been covered by a number of excellent reviews [6,7]. While the mechanism linking obesity with metabolic and cardiovascular disease seem to be operative on a more accessible time scale, those involved in cancer are probably more subtle and slower. Clearly, any individual cancer is far less prevalent than coronary heart disease or type 2 diabetes, for example. Therefore, establishing epidemiological and mechanistic associations between obesity and cancer is challenging.

### Epidemiologic Evidence

Epidemiological studies have suggested that overweight and obesity are related to increased risk of several cancer types, including colon cancer, adenocarcinoma of the esophagus, breast cancer (in postmenopausal women), endometrial cancer and kidney (renal-cell) cancer. Epidemiological evidence also indicates that cancers of the liver, gallbladder and pancreas are obesity related, and that obesity might also increase the risk of some hematopoietic cancers and aggressive

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forms of prostate cancer [8]. Data from other cancers have been inconsistent [9]. Estimates suggest that 14% of all cancer deaths in men and 20% of all cancer deaths in women are attributable to overweight and obesity [10].

Obesity has been consistently associated with higher risk of colorectal cancer in both case-control and cohort studies [3]. Similar relationships are seen for colonic adenomas which are considered carcinoma precursors. Obese men are more prone to develop colorectal cancer than obese women, a consistent observation across studies and populations. Abdominal adiposity is thought to account for this difference. Obese women have a 30–50% higher risk of breast cancer in postmenopausal years [11, 12]. There is convincing and consistent evidence from both case-control and cohort studies that overweight and obesity are strongly associated with endometrial cancer [10, 13]. Studies of populations worldwide have revealed that the risk of kidney cancer (specifically, renal-cell cancer) is 1.5–3 times higher in overweight and obese individuals than in people of normal weight [14, 15].

The incidence of adenocarcinoma of the esophagus has been rapidly increasing in western countries in recent decades [16]. Independent of obesity, gastro-oesophageal reflux disease (GERD) has been associated with oesophageal adenocarcinoma and with its metaplastic precursor, Barrett's oesophagus [17]. Obesity has therefore been proposed to increase the risk of adenocarcinoma of the oesophagus indirectly, by increasing the risk of GERD and Barrett's oesophagus [18]. Results from many recent studies indicate that obesity is associated with an almost twofold increased risk of pancreatic cancer [19, 20]. The majority of studies on liver and gallbladder cancer found an increased risk among obese individuals [21, 22].

### Suggested Mechanisms

Obesity is a state of increased body fat mass caused by a prolonged positive energy balance. This is accompanied by a wide range of physiological and biological alterations. The mechanisms and pathways involved in obesity-related carcinogenicity are multifaceted and difficult to extricate. We have defined four groups of mechanisms: 1) increased energy intake, 2) decreased energy output, 3) increased adipose tissue mass and 4) "secondary" associations. Intake includes both the amount of consumed calories and the dietary composition. Energy output is equivalent to energy expenditure and can be viewed as a cancer protective mechanism. Increased adipose tissue as a potential source of metabolic and endocrine modulators of oncogenic cascades will be described in more detail and finally two examples for indirect or secondary associations will be given (◻ Fig. 1).

#### Increased energy intake

Diet is one main determinant of body composition and dietary factors are thought to account for about 30% of cancers in Western countries [1]. Thus, diet is second only to tobacco as a modifiable cause of cancer. Not only the quantitative caloric intake but also the composition of consumed food has potential carcinogenic effects. The majority of case control and prospective studies imply a causal relationship between increased caloric intake and breast, colon and prostate cancer [23]. Caloric restriction has never prospectively examined as a preventive intervention in humans. Obesity virtually by definition is a result of overeating, not only of energy-rich compounds such as fat, but of

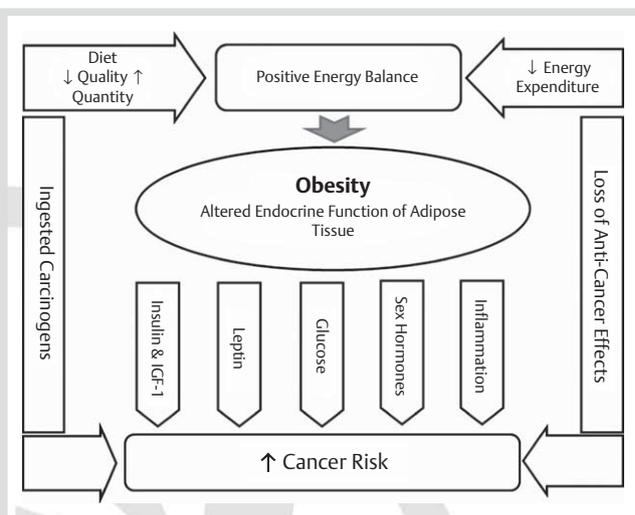


Fig. 1 Obesity and cancer: suggested mechanisms.

pretty much everything contained in modern food including complex proteins, toxins and artificial food additives whose metabolic derivatives (e.g., toluols, nitrites) may contribute to large bowel carcinogenesis and other malignancies [24].

#### Decreased energy output

In addition to reduction of adipose tissue mass and its detrimental metabolic and endocrine consequences, especially reduced pro-inflammatory cytokine expression, physical activity is independently associated with reduced mortality from cancer. Potential mechanisms include the reduction of oxidative stress and the increase of protective cytokines [25].

#### Increased adipose tissue mass

The endocrine function of adipose tissue is altered when it becomes hypertrophic or hyperplastic. Both conditions, but more so the former, can result in significant changes in hormone and growth factor secretion. This can have complex consequences on intracellular pathways involved in inflammation, cell proliferation, oxidative stress and carcinogenesis.

#### Insulin and IGF-1 pathways

Chronic hyperinsulinemia and insulin resistance increases risk for several malignancies [6, 26–28]. The mechanisms are not fully understood but may involve direct growth promoting effects of insulin or indirect effects via stimulation of the IGF-1 receptor or modulation of the release of other hormones. Both insulin and IGF-1 act in vitro as growth factors to promote cancer cell proliferation and decrease apoptosis [26]. This topic will be covered in more detail by a separate mini-review in this series.

#### Hyperglycemia

Although difficult to separate from diabetes mellitus, hyperglycaemia per se, including transient and mild forms such as in obesity-related pre-diabetic states, is considered to possess carcinogenic potential. Like in diabetic complications increased levels of reactive oxygen species and accumulation of advanced glycation end products (AGEs) may play a role. Bound to their receptor, AGEs induce inflammation by activating the transcription factor NF-κB and inducing the formation of intracellular ROS [29]. This may adversely interfere with DNA-repair mechanisms, for example.

**Table 1** Malignancies associated with obesity (modified from reference 6).

Malignancy Type	Relative risk with BMI > 30 kg/m <sup>2</sup>	Possible mechanisms
colon	1.5 female 2.0 male	– pro-inflammatory and pro-carcinogenic effects of abdominal obesity – local effect of animal meat and derivatives (nitrites, iron, carbon derivatives) – local effect of artificial sweeteners
breast (postmenopausal)	1.5	– increased endogenous estrogen production and decrease levels of SHBG – increased levels of insulin and IGF
endometrium	3.0	– increased endogenous estrogen production and decrease levels of SHBG – increased levels of insulin and IGF
renal cell	2.5	– unknown
esophagus (adenocarcinoma)	3.0	– local inflammation provoked by GERD
pancreas	1.7	– indirect effects of insulin?
liver	1.5–4.0	– NAFLD, NASH
gallbladder	2.0	– local inflammation provoked by cholestasis
gastric cardia	2.0	– unknown

### Inflammation

Hypertrophied adipose tissue has been shown to release inflammatory adipocytokines including IL-1, TNF- $\alpha$  and plasminogen-activator inhibitor-1 (PAI-1) [30] which affect cell growth, survival, proliferation and angiogenesis. The association between chronic inflammation and cancer has been studied in greater depth in other conditions such as inflammatory bowel disease which carries an increased risk of colonic cancer [31].

### Leptin

This hormone is secreted from adipocytes and links fat cells and positive energy balance to satiety, fertility and other endocrine and metabolic pathways. Obesity is associated with high circulating levels of leptin, probably as a consequence of central leptin resistance. Consistent findings link hyperleptinemia to colon cancer [32]. In vitro, leptin stimulates proliferation of multiple types of preneoplastic and neoplastic cells [33]. The Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway is the main downstream channel through which leptin exerts its metabolic and proliferative effects, in addition to activation of AMPK in muscle and liver [34]. There are increasing data suggesting crosstalk between the JAK/STAT family of transcription factors, the insulin/IGF-1/Akt pathway and AMPK [35]. Leptin also functions as an inflammatory cytokine and appears to influence immune function, possibly by triggering release of interleukin-6 and other cytokines [33].

### Sex hormones

Adipose tissue aromatase converts androgenic precursors produced in adrenals and gonads to estrogens. Increased insulin and bioactive IGF-1 levels that typically accompany obesity down-regulate levels of sex hormone binding globulin (SHBG), resulting in an increased fraction of bio available estradiol and possibly testosterone. The epidemiologic literature suggests this increased bioavailability of sex hormones, especially estrogen, is strongly associated with risk of endometrial and postmenopausal breast cancers [13]. This link is attributed to the direct proliferative and anti-apoptotic effect of estrogen on its main target organ: endometrium and breast and through an indirect effect via induction of increased production of IGF-1 and consequently increased growth promoting effects on these tissues.

### “Secondary” associations

In addition to the described systemic processes, some more indirect or “secondary” associations between obesity and cancer also need to be considered. Two such examples are cholelithiasis and gall bladder carcinoma or gastroesophageal reflux and esophageal carcinoma. Both precursor conditions are more common among overweight and obese people than in normal weight population due to stasis and disrupted balance of bile acids and increased intra-abdominal pressure, respectively. Both pathologies involve localized chronic inflammation which in turn may lead to cancer through various pathways not necessarily specific for obesity (see Table 1).

### Conclusion

▼ The increased cancer risk in patients with obesity is a neglected topic which deserves more scientific attention. Because of its extreme chronicity and co-association with numerous other conditions true causality and underlying mechanisms are difficult to study. Nevertheless, a large body of literature is already available which provides concepts for future research.

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