

What Links Obesity to Cancer?

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Abstract

The predominant cancers associated with obesity include breast, endometrial and prostate cancer which all have a hormonal basis. Several studies have shown that obesity also increases the risk for cancers of the colon, oesophagus (adenocarcinoma), pancreas, gall bladder, liver, cervix, ovaries, kidney, as well as Hodgkin's disease and non-Hodgkin's lymphoma. The mechanism of increased cancer risk in obese populations is unclear, but nutritional and dietary factors, and lack of exercise may have a role. The conversion of androstenedione, which is secreted by the adrenal gland, into oestrone by aromatase in adipose tissue stroma provides an important source of oestrogen for postmenopausal women. Leptin may be a possible link between Western lifestyle and the transition from pre-malignant lesions to overt cancer through the induction of tumour angiogenesis. Insulin and IGF-I may be the biological mediators of cell growth. The increased release of cytokines by the adipocyte may play a role in the inflammatory state associated with obesity.

Introduction

Obesity and its attendant health risks constitute a growing global epidemic. It is well known that obesity increases the risk of cardiovascular diseases, but its role in oncogenesis is less understood. The most widely used index of body weight for these assumptions is the body mass index (BMI) calculated by dividing the body weight in kilograms by the square of the person's height in metres (kg/m^2). According to the World Health Organisation a BMI of 18.5 to 24.9 is considered normal weight, 25 to 29.9 overweight and ≥ 30 is obese [1]. The risks of site specific cancers associated with obesity are less well established. The relative risk of developing certain cancer types in Europe with relation to BMI is shown in Table 1 [2]. A landmark study on the relationship between cancer and obesity was conducted by the American Cancer Society over a 13-year period from 1959 to 1972. After adjusting for the effects of age and cigarette smoking, people whose body weight was 40% higher than average had an overall increased risk of cancer death (33% increase in men and a 55% increase in women). Overweight males experienced significantly higher rates of colorectal and prostate cancer; whereas, overweight women experienced higher rates of gallbladder, breast, cervical, endometrial, uterine and ovarian cancers [3]. More recently Wolk et al. [4] have evaluated

Table 1. Overweight and obese people and cancer in Europe

Cancer site	RR (overweight vs. normal)	RR (obese vs. normal)
Breast (postmenopausal)	1.12	1.25
Colon	1.15	1.33
Endometrium	1.59	2.52
Prostate	1.06	1.12
Kidney	1.36	1.84
Gallbladder	1.34	1.78

Table 2. Obesity and cancer in Sweden (SIR with 95% CI)

Cancer site	Men SIR	Women SIR	All SIR
Colon	1.2	1.3	1.3
Liver	3.6	1.7	2.4
Gall bladder	0.9	1.7	1.6
Pancreas	2.4	1.1	1.5
Breast	3.0	1.1	1.1
Endometrium	–	2.9	–
Ovary	–	1.2	–
Prostate	1.0	–	–
Renal	2.0	2.4	2.3
NHL	0.7	1.6	1.3
Hodgkin's	3.3	0.9	1.8

the relationship between obesity and the risks for various forms of cancer in a population-based cohort of 28,129 hospital patients (8165 men, 19,964 women) in Sweden from 1965 to 1993. Cancer risk was estimated using the standardised incidence ratio (SIR, with 95% confidence interval), which is the ratio of the observed number of cancers to that expected. Overall, a 33% excess incidence of cancer was seen in obese persons, 25% in men and 37% in women. Significant risk elevations were observed for many cancer sites and these are presented in Table 2. [4].

Breast Cancer

Obesity is associated with increased oestrone production and a reduced level of sex-hormone binding globulin (SHBG) in young and older women as well as in men [5]. The source of the increased oestrogen appears to be the conversion of androstenedione, secreted from the adrenal gland, by aromatase in the adipose tissue stroma. In severe obesity, androstenedione production itself may be increased, providing extra pre-hormone for conversion to oestrogens. Alterations in SHBG may further

lead to changes in “free” oestradiol, which may play a role in target organ stimulation. Women with a predominance of upper body fat have lower SHBG levels and an increased percentage of free sex hormones [6].

An increase in breast cancer risk is associated with higher BMI levels and this association is restricted to women with ER+/PR+ tumours. Only recently, total body size and not just body size in young adulthood was associated with risk of ER+/PR+ tumours in postmenopausal women [7]. Oestrogen has been shown to be an important growth factor for cells of the breast and ovary and has been implicated in cancer of reproductive tissues. Postmenopausal women also produce less progesterone [8]. Thus, overweight, postmenopausal women may be exposed to relatively more oestrogen, which could increase breast cancer risk. It has been proposed that in pre-menopausal women obesity may protect against breast cancer by causing more frequent anovulatory menstrual cycles. This would result in decreased oestradiol and progesterone levels and lower luteal phase progesterone levels in the ovulatory cycles. However the level of obesity needed to induce sufficient anovulatory cycles, such that breast cancer risk is decreased, is unclear [9].

There is a decreased breast cancer risk associated with increasing levels of physical activity (Table 3) for all ER/PR subtypes in both pre-menopausal and postmenopausal women [7]. It is well established that intense and chronic or sustained physical activity can result in menstrual cycle disturbances including secondary amenorrhoea and anovulatory menstrual cycles [10]. These changes are thought to reduce endogenous oestrogen exposure and have been hypothesised to reduce breast cancer risk [11]. Subjects who did not report participation in college athletics were nearly twice as likely to report a history of breast cancer as women who had been on

Table 3. Physical activity and cancer prevention (adapted from Friedenreich CM, Orenstein MR: Physical Activity and Cancer Prevention: Etiologic Evidence and Biological Mechanisms. Suppl: Intl Res Conf Food, Nutrition Cancer. Am Soc Nutr Sci, J Nutr 2002;132:3456S–3464S)

Cancer site	Risk reduction (%)	Scientific evidence level
Colon	40–50	Convincing
Breast	30–40	Convincing
Prostate	10–30	Probable
Endometrium	30–40	Possible
Lung	30–40	Possible
Testis	10–30	Insufficient
Ovary	20–30	Insufficient

sports teams in college [12]. A study, limited to premenopausal breast cancer of women aged 40 and younger, found a linear trend toward reduced risk with increasing hours per week spent in physical exercise during a woman's reproductive life [13].

There is no evidence of a positive association between total dietary fat intake and the risk of breast cancer. Results of the Nurses' Health Study which followed 89,500 women for 8 years indicated that total fat intake did not affect breast cancer incidence [14]. A growing body of epidemiological literature suggests that the dietary fat-breast cancer association may be a result of the type of fat consumed rather than total fat intake [15]. International comparisons indicate that diets high in omega-6 (n-6) polyunsaturated fatty acids (n-6 PUFAs) are associated with increased breast cancer risk. In contrast consumption of monounsaturated fatty acids and n-3 PUFAs do not increase or may even reduce risk of breast cancer [16]. There was no reduction in risk even among women whose energy intake from fat was less than 20% of total energy intake. Lowering the total intake of fat in midlife is unlikely to reduce the risk of breast cancer substantially [17].

Endometrial Cancer

Endometrial cancer is the seventh most commonly diagnosed cancer world-wide [18]. Most cases of endometrial cancer are diagnosed in older women, but some studies report that obese younger women are more likely to develop endometrial cancer than leaner ones [8]. Epidemiological studies indicate that oestrogens, both endogenous and exogenous have a major role in endometrial carcinogenesis [19]. Obesity, especially abdominal obesity, is associated with insulin resistance and therefore hyperinsulinaemia. It has been hypothesised that insulin decreases the levels of circulating SHBG, thus increasing free circulating oestrogen levels [20].

A second proposed mechanism is that insulin decreases hepatic insulin-like growth factor binding protein-3 (IGFBP-3) and consequently increases circulating insulin-like growth factor-I (IGF-I). There are IGF-I receptors in the endometrium and IGF-I stimulates cell proliferation *in vitro*. Insulin is also a weak analogue of IGF-I in the endometrium [21]. Mechanisms by which obesity itself raises risk for endometrial cancer are not fully elucidated. Increased oestrogen alone is not sufficient to explain the positive association of endometrial cancer with BMI [22].

Prostate Cancer

Unlike breast and endometrium, prostate cancer has not been associated consistently with BMI, although continuing exposure to growth hormones and sex hormones have been proposed to increase prostate cancer risk [23,24]. The two prospective Cancer Prevention Study Cohorts have supported the hypothesis that obesity is associated with higher prostate cancer death rates [25]. The increased prostate cancer mortality rate may be related to the effect of obesity, particularly abdominal obesity, on the progression of the existing disease. Abdominal obesity is closely associated with insulin resistance and hyperinsulinaemia [26] and the exposure to elevated blood levels of insulin and IGFs may increase prostate cancer progression [27]. Slowing of tumour progression and increased apoptosis has been achieved in mice by lowering IGF-1 levels through dietary restriction [28].

Leptin is a hormone secreted by the adipocytes and positively correlated by BMI. Higher levels of leptin among obese men could adversely affect survival in prostate cancer patients. *In vitro* and *in vivo* experiments have revealed that leptin can promote angiogenesis [29]. Because the degree of angiogenesis within prostate cancer tumours can predict the probability of metastasis, higher BMI may be associated with increased mortality with this pathway [30].

Many studies support the observation that energy restriction augments apoptosis. Energy imbalance likely increases the production IGF-1, which through the type 1 insulin growth factor receptor (IGF-1R) may promote proliferation and inhibit apoptosis in a forming prostate tumour. Energy imbalance may also enhance the production of Vascular Endothelial Growth Factor (VEGF), possibly through the increased production of IGF-1. VEGF promotes the generation of new blood vessels in the growing prostate tumour, contributing to tumour survival and ability to metastasise [31].

Epidemiological studies have provided little support for the hypothesis that prostate cancer risk is increased in men with elevated total or bioavailable testosterone (T). Overweight, which is generally associated with moderate reductions in both total and bioavailable plasma T, appears to be unrelated to any significant increase or decrease in prostate cancer risk. However, significant increases in risk have been observed for men with a taller body stature, or with elevated plasma IGF-1. IGF-1 down regulates the synthesis of SHBG, and enhances sex steroid synthesis. Therefore, it is not entirely ruled out

that an elevation of plasma IGF-1 levels, men at increased risk of prostate cancer, also have mildly elevated plasma bioavailable T [32].

A recent study suggested that physical activity, later in life, might be related inversely to prostate cancer [33]. Overall, epidemiologic data do not strongly support an appreciable association between physical activity and risk of prostate cancer, but the data are limited and further study is needed to confirm this conclusion (Table 3).

Colon Cancer

Most studies have shown that obese men are at higher risk of colon cancer, but that obese women are not [34,35]. The reason for this gender difference is not known. One hypothesis is that men are more likely to accumulate fat tissue in the abdomen [36] and abdominal fat is more biologically active. Many studies have shown that obese adults have much higher insulin levels in their blood than leaner people. Insulin and insulin-like growth factors (IGFs) also have been linked to cell development and proliferation. IGFs have been identified as growth factors for colonic mucosal cells. They also play a role in the development of colonic carcinoma cells [37].

Colon cancer has been associated consistently with increased consumption of red meat and some types of fats, decreased consumption of vegetables, and physical inactivity [36,38]. The evidence for a protective influence of physical activity is most clear for colon cancer, although exercise does not appear to protect against rectal cancers (Table 3). A decrease in colon cancer risk has been observed in individuals who work at occupations that require high degrees of physical exertion. Also, studies of self-reported exercise and recreation [36] have indicated a lower risk of colon cancer among more physically active individuals. Exercise increases the rate in which stool transits through the intestine and, as a result, contact with the potential carcinogens in the stool may be minimised. Exercise has numerous other benefits, such as increasing the level of high-density lipoprotein (HDL) and reducing blood sugar and insulin levels. Although a reduction in colon cancer risk through physical activity is very likely, the magnitude of the benefit is not well quantified.

Adenocarcinoma of the Oesophagus

One risk factor that has emerged as being associated with the risk of adenocarcinoma of the oesophagus is

obesity. Lagergren et al. [39] showed a strong dose-dependant relation between BMI and oesophageal adenocarcinoma in Sweden. Obese people had an odds ratio of 16.2 (95% CI, 6.3–41.4) compared with the leanest (BMI < 22) people [39]. The carcinogenic mechanism involved may be related to the gastro-oesophageal reflux disease (GERD) that is common in obese patients. Several causes of GERD have been proposed in the obese. One of them is that obese subjects are more sensitive to acid in the oesophagus. Secondly, hiatus hernia (which is capable of promoting GERD) is more prevalent among obese individuals. Thirdly, increased intra-abdominal pressure in the obese displaces the lower oesophageal sphincter and increases the gastro-oesophageal gradient. Moreover, vagal abnormalities associated with obesity may cause a higher output of bile and pancreatic enzymes, which makes the refluxate more toxic to the oesophageal mucosa [40]. It has been shown that GERD is a risk factor for Barrett's oesophagus which is a metaplastic precursor to oesophageal adenocarcinoma, and this may explain the increase in the adenocancer of the oesophagus in the obese [41].

Kidney Cancer

There is an independent dose response relation between BMI and the risk of kidney/renal cell cancer and between diastolic and systolic blood pressure and the risk of renal cell cancer (Table 4) [42]. A large population-based case control study was designed specifically to examine the association of renal cell carcinoma with the use of diuretics and hypertensive agents and its association with the conditions that call for the use of these drugs. In this study obesity and a history of hypertension were strong and independent risk factors for renal cell carcinoma in both men and women. Anti-hypertensive intake did not increase the risk of renal cell cancer [43].

Table 4. Combined effect of diastolic blood pressure and BMI on the relative risk of renal cell cancer

	Diastolic blood pressure		
	<79	80–99	>100
BMI	RR (95%CI)	RR (95%CI)	RR (95%CI)
≤22.85	1.0	1.3	1.2
22.86–25.95	1.2	1.8	2.3
≥25.96	1.8	2.3	2.7

Conclusion

It is likely that obesity in conjunction with other risk factors (such as menopausal status, low activity level and exposure to high insulin, IGF-I and leptin which can lead to distortion of the normal balance between cell proliferation, differentiation and apoptosis) places men and women at higher risk of oncogenesis. Physical activity lowers risk of colon cancer in both men and women. Some evidence suggests that physical activity could help prevent breast cancer, but the evidence is still inconclusive.

Epidemiological studies of body weight are subject not

only to biases of sampling, selection and confounding but also to marked difficulties in definition and measurement. Bearing in mind the methodological shortcomings, there is a distinct and reproducible association between obesity and endometrial and post-menopausal breast cancer. The studies of cancer of the colon, oesophagus, prostate, kidney, pancreas, gall bladder, liver, cervix, ovaries, as well as Hodgkin's disease and non-Hodgkin's lymphoma are too inconclusive to elucidate whether obesity implies an increased risk. It is concluded that obesity, especially in females, should be avoided as a part of the general cancer preventive effort.

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