

Epidemiology and pathophysiology of obesity as a cause of cancer

Michela Ceschi^a, Felix Gutzwiller^b, Holger Moch^c, Monika Eichbolzer^b, Nicole M. Probst-Hensch^a

^a Molecular Epidemiology / Cancer Registry, Institutes of Social and Preventive Medicine / Surgical Pathology, University of Zürich, Switzerland

^b Institute of Social and Preventive Medicine, University of Zürich, Switzerland

^c Institute for Surgical Pathology, University Hospital Zürich, Switzerland

Summary

According to World Health Organisation estimates 1.1 billion people were overweight or obese worldwide in the year 2000 with the prevalence rapidly increasing. Compelling evidence suggests that excess body weight is a risk factor for several cancer types including cancer of the colon, breast, endometrium, kidney, oesophagus, as well as possibly additional sites. According to previous meta-analyses and systematic literature reviews, an important proportion of cancer has been estimated to be attributable to excess body weight. The extrapolation of a European meta-analysis [1] to the Swiss situation broadly estimates that around 700

cancers could be prevented in the absence of overweight and obesity in this country. The data presented highlights the public health relevance of preventing excess body weight. Several interacting metabolic and hormonal pathways seem to underlie the association between being overweight and cancer with insulin-resistance playing a central role. Since evidence is mounting that excess body weight can also adversely affect cancer prognosis, obesity is a primary target for cancer control programs.

Key words: obesity; cancer; overweight

Introduction

The prevalence of excess weight and obesity is rapidly increasing worldwide. Convincing evidence relates being overweight to the risk for several types of cancer as well as other chronic illnesses, including cardiovascular disease, stroke and diabetes [2] which are responsible for a large percentage of premature mortality [3]. The International Agency for Research on Cancer reviewed the literature on the association between excess body weight and cancer risk. They judged the available evidence as sufficient for a causal link with cancers of the colon, female breast (post-

menopausal), endometrium, kidney (renal cell), and oesophagus (adenocarcinoma). Preliminary evidence also exists to suggest a relationship with additional cancer sites [4].

This report gives an overview on the epidemiological and biological evidence regarding the association between excess weight/obesity and cancer. The specific aim of this publication is to discuss the relevance of obesity for cancer burden and control based on data from several existing and thorough systematic literature reviews and formal meta-analyses.

Abbreviations

BMI	body mass index
FFAs	free fatty acids
IGF-1	insulin-like growth factor
IGFBP-1/-2	insulin-like growth factor binding proteins 1 and 2

IL-6	interleukin-6
PAR%	population attributable risk
SHBG	sex hormone binding globulin
TNF α	tumour necrosis factor α

Overweight and obesity: definition and prevalence

The World Health Organisation (WHO) defines obesity as “an abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired” [5]. The currently accepted classification of obesity for epidemiological purposes defines overweight at body mass index (BMI) levels greater than 25 kg/m² and obesity beginning at BMI of 30 kg/m² [5]. But different cut-off points have been used to define overweight and obesity in some previous studies. For example some Canadian studies defined overweight as a BMI >27 kg/m² [6, 7].

Lifestyle changes with associated increased high fat/energy-rich foods and reduced physical activity have led to a rapid increase in excess weight and obesity worldwide. Worldwide 1.1 billion people are currently estimated to be overweight, at least 300 million of them obese [5]. Between 1992 and 2002 the percentage of the Swiss population that was overweight increased from 25% to 29%; the percentage that was obese increased from 5.5% to 8% [40]. The obesity epidemic observed in children is of special concern [8, 9].

Overweight and cancer: summary of the epidemiological evidence

Worldwide, cancer represents a major health problem with roughly 22 million persons living with cancer in the year 2000 [10]. Currently, obesity follows cigarette consumption in public health relevance as a cause of avoidable cancer in Western society. Bergström et al. [1] estimated that in the European Union excess body weight accounts for 5% of all incident cancers, 3.5% in men and 6.5% in women. This corresponds to additional 27 000 male and 45 000 female cancer cases each year. In addition to increasing the likelihood of developing cancer, obesity has also been associated with cancer mortality. In the largest prospective study to date [11] excess body weight accounted for 14% of all deaths from cancer in men and 20% of those in women, respectively.

Breast cancer

Weight gain during adult life has consistently been associated with breast cancer risk. The relationship varies according to the menopausal status. While overweight seems to produce a protective effect in premenopausal women, it is consistently associated with an increased breast cancer risk after menopause [12, 13], especially among those who have never used of hormone replacement therapy [14]. The relevance of obesity as prognostic factor in breast cancer patients has not been conclusively elucidated. Available information suggests an independent association of overweight with higher risk of tumour recurrence and poorer overall survival in both, pre- and postmenopausal women [12, 15, 16]. Overall, the strength of this relationship seems to be modest. More recent evidence suggests that excess body weight adversely affects outcome especially in specific subpopulations of breast cancer patients, as reported for pre- or perimenopausal women [17], for women who have never smoked [18], and for women with oestrogen receptor-negative breast cancers or breast cancers diagnosed at early stages [19].

Endometrial cancer

The association between overweight (BMI >25 kg/m²) and endometrial cancer has been demonstrated consistently in several studies and estimates ranged between a 2- and 5-fold risk increase (reviewed in: [4, 20]). Contrary to breast cancer, the effect of obesity on endometrial cancer risk seems to remain constant throughout adult life independent of menopausal status. Although overweight and obesity were consistently related to increased endometrial cancer risk, the few analyses reporting results on their relevance as prognostic factor are contradictory [4, 11].

Colorectal cancer

Studies reviewed by the International Agency for Research on Cancer [4] indicated an association between excess body weight and/or abdominal fat and risk for colorectal cancer. Relative risk estimates ranged from 1.2 to 2.0. Obesity may influence the development of colorectal cancer at an early stage in tumorigenesis as suggested by studies showing an association between BMI and incidence as well as recurrence of adenomatous polyps, precursor lesions of colorectal cancer [21-25].

A gender difference has been described with an increased risk for colon cancer in men but not consistently in women [20, 26, 27]. Reasons for this gender difference are not known, but several hypotheses have been reported. A stronger relationship between central adiposity, more common in men, and colon cancer risk has been proposed [20]. Alternatively, oestrogen produced in greater amount by obese postmenopausal women may exert a protective effect leading to a diminished obesity-related risk in women [4]. However, a recent analysis [28] found the increased colon cancer risk to be restricted to obese women who were “oestrogen positive” (premenopausal women or women using hormone replacement therapy). The authors hypothesised that oestrogen up-regulates the insulin like growth factor system in the colon

thereby increasing susceptibility to obesity-induced insulin.

There is also evidence for an interaction between excess weight/obesity and physical activity, which is a strong protective factor against colon cancer. Slattery et al. [29] reported the greatest risk of development of colon cancer among men with large BMI if they were in the least physically active group and in the group with the highest energy intake suggesting that energy balance as a whole seems to be associated with risk of colon cancer. The role of excess body weight as a prognostic factor for colorectal cancer is inconclusive. Calle et al. [11] found a statistically significant positive linear trend of mortality with increasing BMI in men and less strongly in women.

Renal-cell cancer

Epidemiological studies consistently reported an increased risk of renal cell carcinoma among individuals, especially women, with high BMI independent of other risk factors such as hypertension and diabetes (reviewed in: [1, 4, 20, 30]).

Calle et al. [11] found an increased mortality rate in overweight men and women with a dose-effect relationship. Patients with renal cell carcinoma have a more favourable prognosis if they are obese, both in terms of recurrence-free and overall survival [31–33]. These results await confirmation by large scale analyses.

Oesophageal cancer

In Western countries the incidence of oesophageal adenocarcinoma, but not of squamous-cell carcinoma has been rapidly increasing during the last decades [4]. Only a limited number of studies have analysed the relationship between excess body weight and oesophageal carcinoma, but have consistently shown a 2–3-fold increased risk of adenocarcinoma of the oesophagus and to a lower extent of the gastric cardia with increasing BMI [20, 30]. The relationship of obesity with a higher

incidence of gastro-oesophageal reflux has been proposed as putative causal mechanism [4].

Calle et al. [11] reported a linear increase of death rates with higher BMI in men. The same trend was found in women, however without reaching statistical significance.

Prostate cancer

The International Agency for Research on Cancer summarised available data on the relationship between obesity and prostate cancer from a large number of studies as controversial and not suggesting any association [4]. These contrasting results may reflect a complex relationship between excess weight and prostate cancer which can differ in subpopulations of cancer patients. For example, the association seems to vary by cancer aggressiveness [34, 35] and patients' age at diagnosis [36, 37]. Obesity may play a more important role in prostate cancer progression as opposed to aetiology [11, 38, 39].

Gallbladder cancer

Only a limited number of small studies analysed the effect of being overweight on the risk of gallbladder cancer. According to Calle et al. [20] cancer risk increases two-fold in overweight subjects. Because of the small study populations available the IARC-working group defined the data currently available as inconclusive [4].

Excess weight has been related to higher mortality rates of gallbladder cancer in both men and women, the latter showing a stronger relationship [11].

Others

Some studies reported enhanced cancer risks related to excess body weight for several additional cancer sites, including pancreatic, ovarian- and cervical cancer and cancers of the haematopoietic system. The available evidence in this respect is too limited to be conclusive [4, 20, 30].

Excess weight and cancer: attributable risk

Table 1 shows the estimates of the proportion of cancers attributable to excess weight and obesity as reported by Bergström et al. [1] for Europe. We extrapolated these estimates of the attributable cancer fraction to the Swiss population by using National Health Survey data on the overweight and obesity prevalence in the Swiss population [40]. The meta-analysis by Bergström et al. [1] was based on the systematic analysis of the epidemiological literature for six cancer sites (colon-, postmenopausal breast-, endometrium-, renal-, prostate- and gallbladder-cancer) and estimated summary relative risks. We did not consider prostate- and gallbladder-cancers for the extrapolation to the Swiss situation because at present

this sites lack strong evidence for a casual link between excess weight/obesity and cancer development.

Overall, due to the higher obesity prevalence, Europe presents a higher proportion of attributable cancer cases than Switzerland. According to these estimates the greatest proportion of cancers attributable to excess body weight is expected for endometrium and renal cancers. Due to their low incidence however, they account for only a small number of additional cancer cases. The largest number of attributable cases is expected for colon cancer. From a gender-specific perspective the largest absolute impact of obesity is expected for postmenopausal breast cancer in women and for

Table 1

Population attributable fractions (PAF%) according to excess body weight in Europe and Switzerland (incl. number of cancer cases) for overall and site-specific cancer incidence, based on a meta-analysis by Bergström et al. [1].

Cancer site	RR for overweight ¹ vs. normal weight [1]	RR for obese ² vs. normal weight [1]	PAF% in EU population [1]	PAF% in CH population	Nr. of cases in CH population
Cancer incidence					
Colon men	1.15	1.33	11.1	7.6	157
Colon women	1.15	1.33	10.7	5.5	101
Breast in postmenopausal women ³	1.12	1.25	8.5	6.2	172
Endometrium	1.59	2.52	39.2	19.5	160
Renal cell	1.36	1.84	25.0	15.6	101
Total cancers			4.2	2.0	691

¹ Overweight, 25 ≤ BMI < 30

² Obese, BMI ≥ 30 RR = Relative Risk (source for RR estimate ranges: [1])

³ Women ≥ 55 yrs only. PAF% in EU derived from [1].

The population attributable fraction (PAR%) for the Swiss population was calculated using the following equation [71]:

$$PAR\% = PF1 \{RR1-1\} + PF2 \{RR2-1\} / 1 + PF1 \{RR1-1\} + PF2 \{RR2-1\}$$
 PF1 denotes the proportion of the total population in the overweight category, and PF2 the proportion of people who are considered as obese.

Prevalence estimates for overweight and obesity in the Swiss population are derived from the latest Swiss National Health Survey [72]. Specific risk estimates describing the association between overweight / obesity and cancer risk in the Swiss population (RR₁ and RR₂) are not available. Subsequently, in order to estimate the impact of excess body weight on cancer burden in Switzerland, we used relative risk estimates for the most relevant cancer sites reported in a recent extensive review [1]. Number of cases in CH estimated relating PAF% with the total number of new cancer cases reported by the Association Swiss Cancer Registries (www.vskr.ch).

colon cancer in men. Overall, Bergström et al. [1] estimated that 4.2% of all cancers could be avoided in the EU population. This amounts to 2.0% in the Swiss population, corresponding to additional 700 cancer cases. Several aspects must be considered in the interpretation of this estimate. First, the estimation of the excess number of cancer cases in the Swiss population could be underestimated because data on the prevalence of obesity is based on self reporting in the National Health Survey. Second, the assumption of a causal relationship between excess body weight and cancer underlies the calculation of the attributable disease fraction. As outlined above the International Agency for Research on Cancer judged the available evidence as sufficient for a causal link with cancers of the colon, female breast (postmenopausal), endometrium, kidney (renal cell), and oesophagus (adenocarcinoma); preliminary evidence also suggests a relationship with additional cancer sites [4]. As we

considered only cancer sites for which strong evidence for a causal relationship with excess weight is available, the above estimates may be a conservative approximation of the true attributable numbers. Third, confounding of the obesity-cancer associations may have led to an overestimation of the attributable fractions. Whenever possible Bergström et al. [1] restricted the inclusion of studies for their meta-analysis to the ones accounting for major confounders of the obesity-cancer association at each site. However, to avoid a major loss of information, some summary RRs used for the estimation of the attributable fractions were derived from studies not accounting for major confounders. Therefore, we cannot rule out a certain proportion of the estimated excess risk as being due to residual or unmeasured confounding rather than a true causal impact of excess weight/obesity on cancer development [41].

Excess weight and cancer: pathophysiological mechanisms

Mechanisms by which excess weight/obesity induce carcinogenesis and their respective relevance are likely to vary by cancer site. At present the biological mechanisms which link excess weight/obesity and cancer are well understood only for cancer types with an endocrine component such as breast- or endometrium cancer. These and other, less understood biological pathways proposed in the literature, are briefly discussed below.

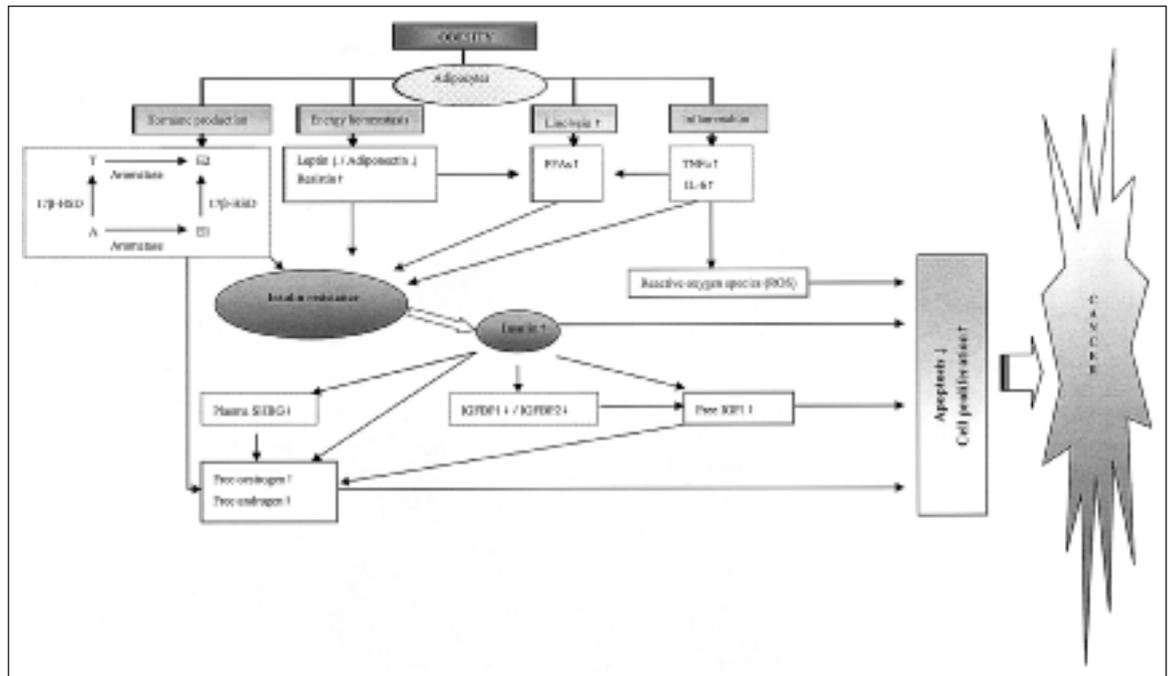
The adipose tissue, known for its primary function as energy storage organ, has been more recently identified as an important endocrine organ reacting to different signals and secreting a wide range of factors (ie, adipokines). Some of these mediators, perturbed in obesity, have been

linked to obesity-related morbidity known as "metabolic syndrome" [42-44]. A major molecular consequence of obesity and principal pathophysiological feature of the metabolic syndrome is the insulin-resistance, a metabolic state in which muscle and liver tissues present a reduced response capacity to insulin (fig. 1).

Nutritional insulin resistance associated with obesity may be a reflection of the lipotoxic effects of fatty acids as well as of an adipokine imbalance, two pathways interacting in a vicious circle. The elevated basal lipolysis and the consecutively increased plasma concentrations of free fatty acids (FFAs) accounts for their increased intracellular accumulation which can impair nonadipose cells in their normal function and insulin signaling. This

Figure 1

Mechanisms linking excess weight to increased cancer risk. 17 β -HSD, 17 β -hydroxysteroid dehydrogenase; T, Testosterone; A, Androstenedione; E1, oestrone; E2, oestradiol; FFAs, free fatty acids; TNF α , tumour necrosis factor α ; IL-6, interleukin-6; SHBG, sex-hormone-binding globulin; IGFBP 1 / 2, insulin-like growth factor binding protein 1 / 2; IGF I, insulin-like growth factor I.



phenomenon is referred to as “lipotoxicity” [45]. Lipotoxicity is additionally associated with an altered secretory profile of adipokines. For example the impaired function of leptin, adiponectin and resistin (which have a major role in the control of food intake and energy expenditure) by obesity has been correlated with a decreased insulin sensitivity [45]. Furthermore, in the insulin-resistant state pro-inflammatory mediators such as tumour necrosis factor- α (TNF α) and interleukin-6 (IL-6) are upregulated in adipose tissue [45]. TNF α can exacerbate the insulin resistance through a direct paracrine inactivation of the insulin receptor as well as through elevation of circulating FFAs level [46].

Hyperinsulinaemia / Insulin-like growth factor-I

Insulin resistance is correlated to a subsequent compensatory overproduction of pancreatic insulin. Chronic hyperinsulinaemia has been linked to carcinogenesis and related to colon [47, 73], endometrium [49], pancreas [47, 50] and breast cancers [47, 48]. Both, the direct impact of insulin on target cells and the indirect effect through secondary metabolic and endocrine changes can underlie its carcinogenic effect. Insulin enhances the Insulin-like growth factor (IGF-1) synthesis and its bioavailability. The insulin-induced decreased production of the insulin-like growth factor binding proteins-1 and -2 (IGFBPs-1 and -2) results in the subsequent rise of plasma levels of free IGF-I. Both, insulin and IGF-I are anabolic molecules that can promote tumour development by inhibiting apoptosis, and by stimulating cell proliferation [47, 51, 52]. High concentrations of IGF-I have been related to an increased risk of prostate and premenopausal breast cancer [51, 53].

Endogenous sex steroids

Obesity has been associated with lower levels of sex hormone-binding globulin (SHBG) and plasma total and bioavailable androgens and oestrogens. Sex steroids are mitogens that can stimulate cell proliferation, inhibit apoptosis, and therefore potentially increase the chance of malignant cell transformation, particularly of endometrium and breast [49, 54, 55] but possibly also at other organ sites (eg, prostate- [56], colorectal cancer [57]). Several mechanisms may link obesity with the level of sex steroids. First, insulin and IGF-I stimulate the synthesis of sex steroids in ovarian, testicular or adrenal tissue, and inhibit the hepatic synthesis of SHBG, increasing their free circulating levels and bioavailability to tissues [47, 52]. The increased production of androgen from the ovarian thecal cells and possibly from the adrenal gland [58] leads to anovulatory cycles and lower progesterone levels. This syndrome, named polycystic ovary syndrome (PCOS), is a metabolic disorder also associated with insulin resistance. It has been related to a higher risk for endometrial cancer [49]. Finally, adipocytes express sex hormone metabolising enzymes and are the main site of oestrogen production in postmenopausal women. Obese women show higher aromatisation of androgenic precursors to oestrogens with BMI positively correlated with circulating sex-hormone levels [55, 59].

Inflammation and oxidative stress

Obesity is related to a condition of chronic inflammation characterised by abnormal production of inflammatory cytokines with local (eg, TNF α) or systemic effects (eg, IL-6) that can contribute to the development of malignant disease [45, 46, 60]. Chronic inflammation induced by obesity can affect both tumour initiation and tumour progression. Iyengar et al. [61] described for example that

adipocyte-conditioned medium can promote tumorigenesis in breast cancer cells, including cell proliferation, invasive potential, angiogenesis and the induction of the cross-talk between cancer cells and the surrounding extracellular matrix [62–65]. 1863, Rudolf Virchow suggested a connection between inflammation and cancer after the observation of lymphoreticular infiltrate in neoplastic tissues [62]. In recent years, improved understanding of the inflammatory microenvironment of malignant tissues has supported this hypothesis. Over-expression of TNF α and IL-6, as well as other cytokines is common in malignant and/or stromal cells in several malignancies such as breast, prostate, colorectal, and ovarian cancer [62]. Animal models produced direct evidence for the carcinogenic potential of these cytokines. For example mice lacking the gene for TNF α are resistant to skin cancer development [66]. Several molecular mechanisms have been proposed to explain the carcinogenic effects of chronic inflammation and inflammatory markers. First, reactive oxygen species (ROS) are often generated by inflammatory cells and cytokines in order to destroy patho-

genic agents in the acute defence reaction. However, as demonstrated in vivo and in vitro [67, 68], obesity causes a chronic overproduction of ROS which can induce mutagenic changes and may damage DNA repair proteins contributing to cancer development [69]. Second, pro-inflammatory adipokines can improve insulin resistance as discussed above.

The process relating obesity to cancer development is multifactorial and involves a network of metabolic and immunological factors. The differential role of the biological mechanisms in various cancer sites has to be defined and mechanisms related to the imbalance of adipokines by obesity need to be further elucidated in future research. In addition, the interaction of body weight (as well as of additional indicators for excess weight, ie, waist-hip-ratio) with lifestyle, environmental and genetic factors in determining cancer incidence, survival and mortality must be investigated in the different cultural contexts. These investigations would permit to identify susceptible target groups in various populations for future obesity interventions.

Conclusion

The excess weight epidemic represents a big challenge for national health care systems [70]. The cancer-related estimates presented in this report further highlight the public health relevance of preventing excess weight. They stress the fact that obesity must be a central aspect of cancer research and cancer control.

Correspondence:

PD Dr. Nicole Probst

Cancer Registry / Molecular Epidemiology

University Hospital

Vogelsangstrasse 10

CH-8091 Zürich

Switzerland

E-Mail: Nicole.Probst@usz.ch

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