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Overview

Obesity and cancer

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Abstract

Epidemiologic evidence associating obesity and cancer accumulated over last two decades pointing to potentially preventable forms of cancer disease. Observational prospective analyses point to breast and colon cancer as most influenced by obesity-linked lifestyle habits. Other tumor-types can comprise to this group as well (endometrium, esophagus, liver, stomach, thyroid, pancreas, and prostate cancer), according to epidemiological data, but with lesser level of certainty. Randomized studies of lifestyle interventions are still scarce in this area of research, despite being urgently needed. Different pathophysiological mechanisms for obesity-cancer link are proposed in literature. Endocrine factors, deregulated signaling cascades, oxidative stress, and chronic inflammation are implicated as obesity-related carcinogenic processes. Considering growing prevalence of obesity, expert recommendations for lifestyle change (healthy nutrition, physical activity) are widely suggested as a main strategy in primary and secondary prevention of adiposity-related cancers.

INTRODUCTION

Body fat accumulation represents evolutionary advantage for survival in natural habitat due to its many physiologic roles (energy storage, thermoregulation, endocrine regulation etc.). On the other side, pathophysiological effect of excess body fat (especially abdominal, visceral fat) on overall risk of death and cardiovascular mortality in particular, is well elaborated in literature. Increasing body of scientific evidence corroborates additional etiopathogenetic roles of adiposity in carcinogenesis and mortality from malignant diseases in general and from death of cancers of various specific organs.

TABLE 1

Body fat composition description with Body Mass Index (BMI) according to Word Health Organization (WHO) criteria.

	Body Mass Index (kg/m^2)
Underweight	Below 18,5
Overweight	25 to 30
Obese	30 and more

BMI is calculated by dividing body mass in kilograms by the square of height in meters. This is the most frequently used variable for body fat composition description. It is considered a crude but reliable measure. Abdominal or visceral fat (most pathophysiologicaly active part of fat-tissue compartment) is sometimes better described with waist circumference. Accurate measurement of visceral fat is performed with computed tomography.

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Obesity increases general cancer-death risk

Epidemiologic data on obesity association with cancer had accumulated and gradually matured over a period of more than two decades, arising from smaller, heterogeneous and largely retrospective studies to larger-sampled, focused and more often prospective observational trials, with elaborated multivariate statistical backup. Calle EE and coworkers *(1)* summarized data from prospective cohort that included nearly 60000 cancer-death cases during 16 years of follow-up. Association of obesity and death from breast, uterus, and ovary cancer was found in women, and from stomach and prostate cancer in men. Both sexes' cancer-deaths in obese individuals were more frequent for esophagus, colon, liver, gallbladder, pancreas and kidney cancer-cases. The quantum of scientific information regarding association of body fat with malignancy grew sufficiently in following years to reach higher levels of evidence (as much as can be expected from epidemiologic data), especially in case of breast and colon cancer. To date there are several epidemiological reports that summarize different aspects on obesity–cancer association. A comprehensive report was issued in 2007 by panel of experts *(2)* finding a clear connection between obesity and breast, colon, endometrial, esophageal, kidney and pancreatic cancer. Probable association was presumed for prostate and gallbladder cancer. Published risk variables for each cancer-site tested vary considerably between studies, depending on population under research, applied anthropometric measures and their timing, tobacco consumption, sex, as well as other possible covariates *(3)*. Most elaborated explorations are available for breast and colon cancer, providing epidemiologic evidence for association with obesity that is considered convincing (breast and colon cancers are among most frequent cancers so the numbers of analyzed patients are greatest – a total of several hundred thousands of patients are included in the meta-analyses up to now).

TABLE 2

Solid tumors of different sites associated with obesity.

Tumor origin
Breast
Colon
Esophagus
Endometrium
Kidney
Pancreas
Rectum
Prostate
Gallbladder
Thyroid
Liver

Epidemiologic association between risk of cancer and obesity vary a lot for majority of cancers among different studies. Level of evidence is considered as 'convincing' only for breast and colon cancer, due to vast amount of accumulated prospective data. List provided here should not be considered as definitive due to large number of ongoing studies in this area of research. Data in table are summarized from references 1–5.

Obesity and breast cancer

Among corner-stone studies for breast cancer (BC) are results from van der Brandt *(4)* concluding from prospective data that overweight postmenopausal women are at significantly higher risk for BC development – relative risk (RR) was 1.43 for 27–29 vs. <21 kg/m^2 BMI-group. Moreover, recent meta-analysis from Chan DS *(5)*; (N≈500000) showed a significant association between adiposity and risk of death from BC after surgery and oncologic therapy (RR 1.34 and 1.7 in BMI-cohorts 25–30 or 35–40 kg/m^2 versus patients with normal body mass index). The influence of excess BMI and increased risk of death from BC appears to be linear (RR increase of 0.14 for each 5 kg/m^2 BMI). In other words, obese women (according to BMI) despite complete oncological treatment have larger risk of death from recurrence/dissemination for at least 25% (range 25–68%) than patients with normal BMI. Association between body-fat and BC appears to extend for both pre- and postmenopausal disease *(6)*. The link between adiposity and worse BC prognosis can partly be explained with higher incidence of unfavorable disease-stage (lymph node involvement, higher grade, larger tumors, and more hormone-receptor negative disease) that is more often seen in obese women in some studies *(7)*. On the other hand multivariate analysis confirmed obesity as independent prognostic factor, after correction for worse disease stage. It is still a matter of debate whether phenomenon applies in the same way (or even exists) also for estrogen receptor (ER) negative disease (about 20 to 30% of all breast cancer patients). Described data on postmenopausal women appear to apply to male breast cancer patients but with much less certainty due to very small number of patients and consecutive paucity of reliable study data *(8)*.

Obesity and colon cancer

Colon cancer also develops more frequently among obese individuals *(9)* (risk-increase varies from 14 to 41% depending on fat burden measured as BMI). Population of treated obese colon cancer patients also appear to be at higher risk of colon cancer-related death than survivors with normal BMI *(10)* (RR 1.35 for BMI cohort >30 kg/m^2 versus normal body weight). Aforementioned phe-

nomena do not apply or at least applies to a lesser extent to rectal cancer *(11)*. Furthermore, there is a difference in the effect on right- and left-sided (distal) colon cancer, with stronger association of the former (colon descendens or left part of transversum) with obesity-induced carcinogenesis *(12)*. There is still no plausible explanation for these differences.

Alternative possibilities for explanation of described obesity-cancer mortality association include suboptimal therapy (under-dosing, complicated course of treatment, less-effective regimens) *(13)*, and the possibility of enhanced tumor resistance to therapy due to the adiposity *(14)*.

Hypothesized mechanisms of action

Reports on exact mechanisms of obesity and tumorigenesis association are still highly speculative and equivocal despite emanating from area of extensive research. Bioactive factors derived from adipose tissue or under its influence could change (pre)malignant target cells or tissue affecting their proliferation or differentiation- potential, survival, metabolism or migration thus triggering or promoting chain of events that could lead to neoplasia *(15)*.

Endocrine factors are among must studied putatively tumorigenic molecules directly associated with obesity. These include estrogen, insulin, insulin-like growth factor – 1 (IGF-1), leptin, decreased adiponectin. Mainly the anabolic i.e. growth-stimulatory effects in direct or indirect manner are hypothesized to promote tumorigenesis by these mediators *(16)*. Leptin is also supposed to exert indirect proangiogenic function as well, by activation of vascular endothelial growth factor (VEGF) *(17)*.

Disturbed endocrine milieu can even go beyond obesity, concerning carcinogenesis, as recent confirmatory data point out that metabolic syndrome (fasting blood glucose level, high blood pressure, hypertriglyceridemia) are independent risk factors for endometrial cancer development even after correction for obesity in multivariate analysis *(10, 18)*.

Besides extracellular signals, subsequent intracellular signal transduction, can become disarranged and contribute to pro-neoplastic events in connection with obesity. For example mTOR signaling pathway and the AMP-kinase system may in the context of adiposity lead to disturbance of the cell cycle and cancer-promotion *(19)*.

There is also indirect evidence of impaired immune response *(20)*, deregulation of oxidative stress *(21)* and stimulation of chronic pro-inflammatory stimulation by factors secreted from immune and inflammatory cells infiltrating adipose tissue (for instance cytokines like IL-6, TNF-α) with carcinogenic potential *(22)*.

Need for interventional research of "adiponcosis"

Aggregate result of observational studies should pave the way for intervention studies that further analyze proven statistical association of cancer with obesity. Unfortunately, comprehensive cancer incidence estimation in prospective, randomised setting would claim for very long follow-up and large number of participants in order to detect significant effect, so interventional studies to date are usually based on indirect biomarkers of potential tumorigenesis (like precancerous lesions) *(11, 23)*. Only indirect preliminary data of small studies and meta-analyses point to a more favorable course after the reduction of body weight or adoption of positive lifestyle-change *(24)*. For example, methods of bariatric surgery (stomach banding, insertion of a balloon, intestinal bypass etc.) appear to be associated with lowering the risk of colorectal cancer *(25)*. In addition, lifestyle-changing interventions able to produce sustainable lowering of BMI, could not easily be tested for anti-carcinogenic potential in prospective, randomized setting *(26, 27)*. Considering vastness of published epidemiological data some authors propose neologism "adiponcosis" for etiopathogenetic conundrum found between obesity and cancer *(28)*.

CONCLUSIONS

According to the described body of evidence guidelines for changing the lifestyle of obese patients are promoted by different expert societies (American Cancer Society *(29)*, National Comprehensive Cancer Network *(30)*). Patients treated especially for breast and colon cancer should thrive to reduce excess body fat, or at least keep present body weight after oncological therapy of localized cancer. Methods to achieve such a goal should include multimodal approach and be based on motivational support and follow-up (healthy diet, regular physical activity, support by regular personal, written or telephone consultation) *(24, 25, 31)*.

Given the increasing incidence and prevalence of excessive body mass index in the population of Western civilization *(32)*, the motivation for positive change in lifestyle of healthy and already diagnosed persons, should become a priority task for physicians as well as other professionals in biomedical field.

A reasonable assumption is that the reduction of overweight by effective lifestyle adaptation will significantly improve primary and secondary prevention of cancer diseases, quantitatively comparable with the overall results of the current curative oncological methods *(33, 34)*.

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