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Review article

Obesity and cancer: at the crossroads of cellular metabolism and proliferation

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Epidemiology

Obesity is associated with increased incidence and mortality of multiple cancers, with risk ratios correlating directly with body mass index (BMI) in a dose-dependent fashion. The relationship between BMI and cancer is nonlinear and amplified at high BMI: the risk ratio for mortality from endometrial cancer, among the highest of all cancers, is 1.5 for overweight women (BMI 25–30), 2.5 for women with class 1 obesity (BMI 30–35), and rises to over 6 in women with class 3 obesity (BMI $>$ 40). Obesity is a particularly strong risk factor for colon, renal, pancreatic, and esophageal adenocarcinomas as well, with similar dramatic increases in risk at high BMI. This high degree of risk translates into a substantial disease burden: obesity is estimated to be a dominant causative factor in 10%–20% of all cases of cancer [1–3].

Although obesity increases the risk of most cancers, exceptions exist. Obesity is associated with a decreased risk of lung cancer and squamous cell cancer of the esophagus [1–4], cancers for which smoking is an important risk factor, confounding analysis of the effect of BMI. Although obesity increases breast cancer risk in postmenopausal women, no such association exists in premenopausal women, in whom some data suggest that elevated BMI may exert a protective effect [2]. Data is conflicting regarding obesity's effects on prostate cancer incidence, with different studies demonstrating a weak positive effect, no effect, or a weak protective effect [5–8]. Lower androgen levels in obese men may explain an observed protective effect, and differences among studies may relate to differences in androgen sensitivity of individual prostate cancers.

Obesity not only affects cancer incidence and long-term cancer-specific mortality, but also affects survival and recurrence among those diagnosed with cancer. Despite conflicting data regarding obesity's effects on prostate cancer incidence, compelling data demonstrate decreased survival among obese patients compared to lean patients who develop prostate cancer [9–11]. Other cancers associated with worse prognosis in the obese include colon [12], lymphoma [13], and breast [14]. Treatment efficacy may underlie some of these observations. Underdosing of chemotherapy, reduced delivery of radiation therapy, and technical challenges associated with extirpative surgery leading to lower rates of R-0 resections are reported in obese patients [15–18]. Biologic effects of adipose tissue may interfere with cancer therapy; for example, aromatase inhibitor therapy is less effective at reducing serum estradiol levels in obese breast cancer patients [19], possibly related to increased aromatase activity from adipose tissue, while other data demonstrate that obesity is associated with decreased efficacy of cytotoxic chemotherapy in breast cancer patients [20]. In contrast to these findings, in some cases obesity appears to exert a beneficial effect on survival in patients diagnosed with cancer, the so-called "obesity

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paradox". Obesity is a strong risk factor for the development of renal cell cancer, but obese patients who develop renal cell cancer experience longer survival compared to lean patients [21,22]. Conflicting data suggest that obesity may be associated with more favorable outcomes in endometrial, head and neck, rectal, and esophageal cancer as well, even after controlling for tumor stage [23–26]. The mechanisms underlying such protective effects are poorly defined. Obesity may be associated with decreased chemo- and radiation-therapy toxicities, which may contribute to increased treatment efficacy in some cases [27,28]. Alternatively, limitations in BMI as a metric for obesity as well as selection bias and other statistical confounders have been proposed to discount the obesity paradox with respect to cancer survival [29,30], which therefore remains controversial.

Multiple variables regulate the obesity-cancer risk equation. Gender and ethnic differences exist; risk ratios for obesity are significantly higher in men than women for colon cancer incidence, for example, Asians suffer increased breast cancer risk at lower BMI compared to non-Asians [30]. Similar to other metabolic diseases, visceral adiposity imparts greater risk than subcutaneous adiposity. Diabetes, hyperlipidemia, and other metabolic diseases are tightly linked to obesity but nonetheless exert independent effects on cancer incidence and mortality, and confound analysis of obesity as an independent predictor of risk. Similar confounding effects are exerted by dietary factors, which are also tightly correlated with obesity but nonetheless exert independent effects on cancer incidence; for example, high fat, low fiber diet, although associated with obesity, is a well-established independent risk factor for colon cancer. Despite these epidemiologic complexities, obesity is clearly a dominant causative agent in the pathogenesis of cancer. An understanding of the diverse molecular and cellular mechanisms underlying this association will drive development of novel diagnostic and therapeutic modalities.

Inflammation, nutrient excess, and cancer

Since Virchow first observed lymphocytes populating tumors in 1863 [31], thousands of reports have implicated inflammation in the pathogenesis of cancer. Inflammatory bowel disease, primary sclerosing cholangitis, hepatitis, and pancreatitis are but a few of many chronic inflammatory diseases associated with an increased risk of cancer in involved tissues. Immune leukocytes, including macrophages, neutrophils, monocytes, T-cells, β-cells, and natural killer (NK) cells, utilize multiple cytotoxic molecules, such as reactive oxygen species, free radicals, antibodies, and cytolytic proteins, to mediate inflammatory responses. Leukocytes also secrete cytokines, which potentiate leukocyte activation, proliferation, and inflammatory responses via autocrine and paracrine effects, and exert multiple effects on nonimmune cells, including regulating proliferation and apoptosis. The specific mechanisms underlying the association between inflammation and cancer remain poorly defined, but at a conceptual level, increased mutagenesis resulting from exposure of cells to inflammatory weapons combined with increased cell turnover secondary to tropic effects of cytokines create a perfect storm for carcinogenesis.

Obesity is associated with a state of chronic systemic inflammation. The link between nutrient excess and inflammation is rooted in the chemical nature of nutrients, bioenergetic molecules capable of participating in energy-intensive reactions that are potentially damaging to cells. Cells have evolved protective systems designed to sequester and limit exposure to these molecules, including the endoplasmic reticulum (ER), a complex organelle present in all cells that meters exposure to nutrients. When inundated with nutrients beyond the capacity of the ER to manage, cells mount an ER stress response, which leads to apoptosis. An inflammatory response is in turn generated to scavenge apoptotic cells. Cells damaged by excess nutrients are thus removed, limiting nutrient-mediated injury and protecting the organism as a whole. Excess nutrients, including free fatty acids, glucose, and downstream metabolites such as diacyglycerol, ceramides, and advanced glycation end-products, directly trigger leukocyte-mediated inflammation: free fatty acids are ligands for Toll-like receptors (TLR), which are expressed on innate immune cells and trigger inflammatory responses, while advanced glycation end-products bind leukocyte receptors for advanced glycation end-products (RAGE) with similar effects. TLR and RAGE ligands represent direct molecular links between metabolism and inflammation.

Adipose tissue in health acts as a nutrient buffer, protecting other tissues by storing excess nutrients in adipocytes in the form of lipid. As adipocytes reach hypertrophic capacity in overweight and obese patients, ER stress ensues, and leukocytes are recruited to scavenge apoptotic adipocytes. The resulting adipose tissue inflammatory leukocyte infiltrate is dominated by macrophages, but also involves T-cells, β-cells, NK cells, and other immune cell subtypes. In early obesity, nutrient excess, ER stress, and inflammation remain confined to adipose tissue. With progressive obesity, adipocyte storage capacity is overwhelmed, nutrient buffering capacity is exceeded, and excess nutrients and metabolites overflow into the systemic circulation. Nutrient- and metabolite-induced cell stress spreads beyond adipose tissue, establishing a low grade inflammatory state in all tissues that underlies the pathogenesis of malignant and nonmalignant metabolic disease.

Cytokines are central mediators of the link between inflammation and cancer. Tumor necrosis factor-alpha (TNF-α, a dominant inflammatory cytokine expression of which is elevated in obesity, promotes cancers of the skin, liver and lymphoid system in murine models, while TNF-α knockout mice are protected from chemically-induced skin and colon cancers [32–36]. Similar murine models