

Associations Between Obesity and Cancer: The Role of Fatty Acid Synthase

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Obesity is a common metabolic disorder and rapidly becoming a global public health problem in the 21st century. In the United States, the data from Centers for Disease Control and Prevention (CDC) indicates that about one-third (33.8%) of adults and 17% of children and adolescents were obese in 2010 (www.cdc.gov/obesity/data/trends.html). Obesity is associated with an increased risk of several life-threatening diseases such as type 2 diabetes, cardiovascular disease, and multiple types of cancer and may represent a leading preventable cause of death (1). Recent emerging epidemiological data further reveal that obesity is also associated with poor prognosis in patients with breast and colon cancer (2,3).

Obesity is characterized by body mass index (BMI), which closely represents both percentage body fat and total body fat. It is generally assumed that obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) is caused by a combination of excessive consumption of energy-dense foods such as high dietary fat and sugars, lack of physical activity, and occurs in some people because of genetic susceptibility (4). Consistent with these findings, high dietary fat intake is not only associated with obesity, diabetes, and heart disease, but also cancer, especially

with colorectal, liver, breast, pancreatic, and prostate cancer (5). However, the mechanisms underlying the association of obesity with cancer are poorly understood.

Excess adipose tissue is associated with metabolic changes such as reduced high-density lipoprotein cholesterol, elevated triglycerides, hypertension, and insulin resistance (1). Several site-specific mechanisms have been proposed to explain the association of obesity with organ-specific cancers. For example, obesity-induced esophageal reflux, hypertension, insulin resistance, and hormone alternations could contribute to an increased risk in esophageal, kidney, colorectal, and breast cancers, respectively. It is also widely accepted that obesity-associated inflammation contributes to cancer progression in several organs. In this issue of the Journal, Kuchiba et al. (6) offer an additional explanation for the association between obesity and colorectal cancer (CRC) risk in female patients. They investigated whether associations between obesity and risk of CRC varied according to lipogenic enzyme fatty acid synthase (FASN) expression in the ongoing prospective Nurses' Health Study. FASN catalyzes fatty acid synthesis. They

found that obesity (BMI ≥ 30 kg/m²) was positively associated with an increased cancer risk only in the subgroup of patients whose colon tumors had no or low expression of FASN (FASN negative) compared with “normal weight” (BMI = 18.5–22.9 kg/m²) individuals with FASN-negative CRC. In contrast, this association was not observed in the subgroup of patients whose colon tumors expressed FASN at moderate to high levels. Further studies are necessary to determine whether this association also exists in male CRC patients. Their findings indicate that the association of obesity with CRC may depend on cellular FASN status.

Increased de novo lipogenesis contributes to increased fat mass (7). The evidence that expression and/or activity of FASN is elevated in human breast, colorectal, prostate, endometrial, ovary, and thyroid cancers (8–10) supports the hypothesis that FASN responds to exacerbated de novo fatty acid biosynthesis in tumor cells, which is essential for generating cell membranes during tumor cell proliferation (10). Kuchiba et al. (6) showed that the age-adjusted incidence rate of FASN-positive CRC is higher than FASN-negative CRC in the entire study population (n = 109051 women). They postulated that FASN in colonic tumor epithelial cells may serve as a tumor accelerator independent of obesity based on their finding and previous observations that elevation of FASN is associated with a poor prognosis (10,11).

The elevation of FASN expression in cancer is consistent with evidence that metabolism of arachidonic acid (a polyunsaturated fatty acid) by the cyclooxygenase (COX) pathway plays important roles in inflammation and cancer progression (12). The proinflammatory enzyme, COX-2, is elevated in up to 90% of colorectal carcinomas and 50% of adenomas (13,14), and its expression is associated with a lower survival among CRC patients (15). Similarly, COX-2 is also induced in colonic epithelium in patients with active human inflammatory bowel disease (16). Moreover, COX-2 levels are also elevated in other premalignant and malignant solid tumors, and its expression is associated with decreased survival among these cancer patients (17). One group of compounds, among the most promising chemopreventive agents for CRC, is nonsteroidal anti-inflammatory drugs (NSAIDs) that exert some of their anti-inflammatory and antitumor effects by targeting COX-1 and COX-2 enzymes (18). A large body of evidence from population-based studies, case-control studies, and clinical trials indicates that regular use of NSAIDs, including aspirin and selective COX-2 inhibitors, over a 10- to 15-year period reduces the relative risk of developing CRC by 40%–50% (19–21). In particular, aspirin specifically prevents the subgroup of individuals whose colon tumors express COX-2 at higher levels (22). In addition to prevention, regular aspirin use after the diagnosis of CRC at stage I, II, and III improves overall survival, especially among individuals with tumors that overexpress COX-2 (23). Therefore, metabolism of a fatty acid such as arachidonic acid by COX-2 provides one potential mechanism for explaining pro-tumor effects downstream of FASN. Based on the results of the study by Kuchiba et al. (6), which indicated that FASN-positive epithelial cells may progress to cancer independent of other effects related to obesity, we postulate that FASN is not a driver in cancer development but rather accelerates tumor growth. Another possibility is that FASN may

simply be a bystander during cancer progression. Additional research is needed to determine the precise role of FASN in cancer formation and progression.

Kuchiba et al. (6) observed that obesity is only associated with an increased risk of FASN-negative CRC in female patients; however, the study included only women, so it is not known whether this also affects male CRC patients. The findings of this study makes us wonder if FASN-negative tumor epithelial cells may depend on obesity-associated inflammation and insulin resistance for progression. One plausible hypothesis is that obesity-induced chronic inflammation and insulin resistance coordinately promote cancer progression. Excess adipose tissue secretes growth factors and cytokines such as adiponectin, leptin, plasminogen activator inhibitor-1, vascular endothelial growth factor, tumor necrosis factor- α , resistin, interleukin -6, and interleukin-8 (24). Particularly, infiltrating immune cells found in adipose tissue secrete high levels of circulating inflammatory cytokines (25,26) that contribute to obesity-associated chronic inflammation and insulin resistance. A recent study showed that diet-induced weight loss in 10 obese premenopausal women statistically significantly reduced colonic inflammation ($P < 0.05$) (27). Obesity-associated inflammation is thought to be one of the most important factors connecting obesity to cancer (1). This hypothesis is supported by an epidemiological study showing that a daily dose of 325 mg of aspirin more effectively reduced a risk of recurrent colorectal adenomas in patients with obesity than patients with overweight and normal weight (25). An in vivo study revealed that obesity-induced hepatocellular carcinoma was dependent on elevation of proinflammatory cytokines interleukin-6 and tumor necrosis factor- α , which cause hepatic inflammation and activation of the oncogenic signal transducer and activator of transcription 3 (28).

Insulin resistance signaling pathways, including ligands such as insulin and insulinlike growth factor 1 and 2 (IGF-1 and IGF-2), receptors such as insulin receptor isoform A and B (IR-A and IR-B), IGF-1 and IGF-2 receptors (IGF-1R and IGF-2R), and high-affinity IGF-binding proteins (IGFBP-1 to IGFBP-6), have also been proposed to mediate the contribution of obesity to cancer (1). In humans, IGF-1 polymorphisms are correlated with an increased risk for developing colorectal adenomas and carcinomas (29,30). Several in vivo studies showed that insulin resistance signaling pathways promoted azoxymethane-induced colon carcinogenesis (31,32) and accelerated liver metastasis by activating and sustaining liver inflammation in a mouse model of obesity (33). Interestingly, investigators showed that cross talk exists between COX-2-derived prostaglandin E₂ and IGF-1 signaling pathways in colon cancer cells (34). Collectively, these findings support the hypothesis that obesity-induced chronic inflammation and insulin resistance synergistically promote CRC progression.

An entirely new approach referred to as personalized cancer prevention and treatment is likely to play an important role in developing effective chemopreventive strategies and/or agents against obesity-associated CRC. The current study by Kuchiba et al. (6) and previously published results suggest that further investigation of NSAIDs as chemopreventive agents is needed in obese patients with high risk for developing CRC.

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Funding

This work is supported, in part, by the National Institutes of Health (R37 MERIT grant DK47297, RO1 grant DK 62112, NCI P01 grant CA77839; all to RND) and Cancer Prevention and Research Institute of Texas (CPRIT RP100960 to RND and DW).

Notes

We thank the National Colorectal Cancer Research Alliance (NCCRA) for its generous support (to RND).

The authors declare no conflict of interest.

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