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"Obesity-Associated" Breast Cancer in Lean Women: Metabolism and Inflammation as Critical Modifiers of Risk

Gerald V. Denis[1] and **Julie R. Palmer**[2]

[1]Cancer Center, Boston University School of Medicine, Boston, Massachusetts

[2]Slone Epidemiology Center at Boston University, Boston, Massachusetts

Abstract

Why is obesity only weakly associated with certain "obesity-driven" cancers? Recent population studies identify cohorts of high body mass index (BMI) subjects with unexpectedly reduced risk for breast and colon cancer, and normal BMI subjects with unexpectedly elevated risk for breast cancer, provoking hard thinking about cellular and molecular mechanisms that most strongly couple obesity to cancer occurrence or progression. Emerging work suggests that abnormal metabolism and its associated chronic inflammation make the difference. Type II diabetes, for example, is a chronic inflammatory disease with specific imbalances in T-cell and myeloid-origin cytokines. Inflammation is elevated systemically, measured through blood biomarkers, and locally in adipose tissue. Here, cytokines and chemokines likely modify tumor microenvironments in dangerous ways. High BMI subjects with low inflammation and less disturbed metabolism appear to have reduced risk for certain obesity-associated cancers, whereas lean or slightly overweight subjects with high inflammation and metabolic abnormalities have elevated risk. This latter phenotype is prevalent among South Asian adults and suggests we are not monitoring certain normal weight adults sufficiently for risks of "obesity-associated" cancers. Profiling of patient metabolism and inflammation should accompany measures of body composition when considering cancer risk; the evidence base for these refinements must be extended through new, prospective observational studies.

After smoking, obesity is now thought to be the most important modifiable cause of cancer. Overweight and obesity [body mass index (BMI) 25.0–29.9, or ≥30 kg/m^2, respectively) are associated with increased risk of colorectal cancer, post-menopausal breast cancer, and cancers of the endometrium, gall bladder, pancreas, kidney, and liver. The alarm was first raised in 2003 with a series of epidemiologic analyses led by Eugenia Calle and colleagues at the American Cancer Society (1, 2). Nearly 25% of the relative contribution to cancer has since been attributed to overweight and obesity; the American Society of Clinical Oncology in 2014 (3) joined a 2007 consensus report of the World Cancer Research Federation and

Corresponding Author: Gerald V. Denis, Boston University School of Medicine, Room K520, 72 East Concord Street, Boston, MA 02118. Phone: 617-414-1371; Fax: 617-638-5673; gdenis@bu.edu.

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American Institute of Cancer Research (Washington, DC; ref. 4), reinforcing concern. Not all cancers are linked with obesity; interesting exceptions include acute myeloid leukemia, retinoblastoma, glioblastoma, and osteosarcoma. In premenopausal women, higher BMI is associated with lower risk of breast cancer rather than higher risk. The molecular mechanisms that underlie stratification of risk are not well understood and have prompted intensive molecular and cellular investigation of the functional links between obesity and cancer.

One of the challenges for such molecular studies is that many local and systemic factors are simultaneously elevated in obesity, including insulin, IGF-1, proinflammatory cytokines, blood glucose, free fatty acids, and leptin, while other factors are reduced, such as the cardioprotective adipokine adiponectin. Some research supports the hypothesis that ratios of proinflammatory to anti-inflammatory factors, or of adiponectin to leptin, are also important to tumor cell proliferation, survival, and invasiveness. Despite numerous animal and cellular models for obesity-associated cancer, such as exposing mice with genetically engineered, carcinogenic lesions to a high-fat diet in an acute setting, it remains unclear which of the several comorbidities of obesity are the most important drivers of increased cancer risk. Obesity *per se* does not appear to have a mutagenic mechanism, unless one considers metabolic stress that alters mitochondrial metabolism and increases the production of reactive oxygen species. One important area of interest has been the role of chronic inflammation, a prominent feature of insulin-resistant obesity, as a modifier of the tumor microenvironment and potential driver of cancer incidence and metastasis. In postmenopausal breast cancer, investigators have identified metabolically abnormal adipocytes (which are typically larger and insulin resistant) in breast adipose tissue that are surrounded by $CD68^+$ proinflammatory macrophages in histologically distinct features, called "crown-like structures" (CLS) because they encircle the stressed adipocytes. These CLS-Bs (5) associate with increased expression of aromatase and blood biomarkers of chronic inflammation, linking breast and blood inflammation to increased breast cancer risk.

One of the perplexing questions has been how to leverage our understanding of interactions among chronic inflammation and metabolic abnormalities, which underlie cardiovascular disease in obesity, to understand risks for specific cancers. The obesity field is experiencing significant controversy about how risks for obesity-associated diseases should be defined with respect to components of the metabolic syndrome. For example, risks for ischemic stroke or cardiovascular death vary depending on how the association is tested [e.g., with different combinations of elevated fasting glucose, hypertension, hypercholesterolemia, hypertriglyceridemia, the homeostatic model assessment for insulin resistance (HOMA-IR), or other factors like waist circumference (WC) or waist-to-hip ratio (WHR); ref. 6]. Similar arguments could be applied to breast cancer risk.

New work by Iyengar and colleagues (7) suggests that even in normal BMI women, systemic markers of inflammation may be associated with elevated breast adipose inflammation and aromatase. Therefore, obesity alone may be a poor risk factor for breast cancer, and some women may be at increased risk due to metabolic factors without being overweight or obese. The insights should be of great value for physicians who seek to counsel patients who do not have obvious obesity or clinically overt, abnormal metabolic

markers, but might nevertheless experience elevated breast cancer risk. Iyengar and colleagues found that fasting glucose, hypertension, and hypercholesterolemia were not associated with CLS-B or elevated aromatase, whereas HOMA-IR and hypertriglyceridemia were associated with this inflammation in normal BMI women, although numbers of subjects are small. WC and WHR were not reported in their study. The report deepens the urgency of the question of how clinicians should best leverage available clinical biomarkers for cardiovascular risk and noninvasive measures in a nonsurgical population to evaluate breast cancer risk.

Although elevated BMI is associated with estrogen receptor positive–breast cancer in postmenopausal women, interesting "off-diagonal" populations have also become the subject of informative studies. One group of adults shows high BMI but relatively low risk for type II diabetes, cardiovascular disease, and other complications of obesity (8), including cancer (9, 10). This group of insulin-sensitive (11), so-called "metabolically healthy obese" subjects (12) also tends to have reduced blood biomarkers of inflammation (13), suggesting that some of the signal transduction mechanisms of proinflammatory cytokine production or signaling are attenuated, yet within the normal range. Yet another "off-diagonal" population includes adults who have relatively normal BMI or are overweight, yet have high risk for cardiovascular disease and type II diabetes. Such adults, who have been termed "metabolically obese but normal weight" (14), often have ectopic deposition of adipose tissue (intrahepatic, perirenal, visceral accumulation outside of the normal anatomic depots), and also tend to be chronically inflamed. The numbers of such women in Caucasian, Latina, or African American populations are small, but the phenotype is common in South Asia.

India is currently undergoing a well described shift in disease patterns for cardiometabolic disease (15). Macroeconomic forces, such as urbanization and rising incomes, are driving reductions in physical activity (16) and increases in consumption of high-glycemic index foods. Together, these promote obesity and diabetes. Chronic inflammatory conditions like cardiometabolic disease are increasingly dominating the disease pattern in South Asia (17). Metabolic complications arise in South Asian adults at much lower BMI values than in U.S. adults (18); the International Diabetes Federation now includes ethnic-specific criteria for the definition of abdominal obesity (19). Breast cancer rates in India have been rising rapidly in all population-based cancer registries and shifting to more aggressive presentation among younger women (20). Metabolic disease may drive progression of these cancers through chronic systemic and adipose inflammation that likely promotes dangerous shifts in the tumor microenvironment. As cardiometabolic diseases, such as type II diabetes, dyslipidemia, hypertriglyceridemia, and hypertension, are increasing around the world, although not necessarily accompanied by morbid obesity as observed in U.S. endocrinology practice, it is likely that the incidence of "obesity-associated" cancers will rise, tracking the rise in metabolic disease.

The impact of this recent thinking is that elevated BMI alone is a poor predictor of obesity-associated cancer risk, and specific blood and clinical biomarkers should supplement BMI-based assessment for cancer risk. It is unlikely that a limited set of common biomarkers will be useful to predict risk for all obesity-associated cancers, but that each cancer type will have ethnic and race-specific biomarkers. These biomarkers may also change as a function

of age and specific cardiovascular complications. Large prospective cohort studies should help identify the populations most at risk for cancer and the most informative sets of biomarkers. The expected worldwide increase in diabetes and metabolic disease demands urgent public health responses to the anticipated increase in cancer burden.

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