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RE: Circulating Adipokines and Inflammatory Markers and Postmenopausal Breast Cancer Risk

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Obesity is a risk factor for breast cancer in postmenopausal women. In their recent article, Gunter et al. found that associations between breast cancer risk and circulating levels of adipokines were null to modest. Importantly, they underscored that adipokines primarily function in a paracrine manner. Hence, adipokine plasma levels might be a poor surrogate for breast tissue levels (1). This is reminiscent of the situation observed with vitamin D. Obesity is inversely associated with vitamin D levels (2), and vitamin D inadequacy is observed in postmenopausal women (2). Moreover, 1,25-dihydroxyvitamin D (1,25D), the active metabolite of vitamin D, limits adipose tissue inflammation and suppresses leptin stimulation of cancer growth (3). As for adipokines, studies that have investigated the association between circulating levels of vitamin D and breast cancer risk gave mixed results (4,5). Could vitamin D and adipokines be two faces of the same coin?

Vitamin D is barely active and requires two successive hydroxylations to produce 1,25D. The first hydroxylation is catalyzed in the liver by CYP2R1, the second one in the kidney by CYP27B1. This is the vitamin D endocrine system in which 1,25D is released in blood circulation and controls calcium homeostasis and skeletal health. Circulating 25(OH)-vitamin D levels between 50 and 75 nmol/L are considered indicative of vitamin D sufficiency.

A paradigm shift recently occurred with the discovery of autocrine/paracrine vitamin D signaling in many tissues. In autocrine/paracrine systems, molecules are produced, act, and are degraded locally. Therefore, the autocrine/paracrine vitamin D signaling does not affect circulating levels of vitamin D metabolites. Two important features of the autocrine/paracrine vitamin D system are: 1) the regulation of CYP2R1 and CYP27B1 expression by inflammatory stimuli (6) and 2) the local storage of vitamin D in fat tissue (6). Hence, hydroxylated metabolites of vitamin D can be produced locally in response to inflammatory stimuli if sufficient local storage of vitamin D exists. Note that vitamin D

storage in fat might require circulating levels of 25(OH)-vitamin D higher than 100 nmol/L (6). In other words, adequate functioning of the vitamin endocrine and autocrine/paracrine systems might require different vitamin D inputs. Shifting our thinking from endocrinology to paracrinology provides the missing link to unify in the same paradigm obesity, adipokines, vitamin D, inflammation, and cancer.

In the autocrine/paracrine paradigm, adipokine-induced inflammation would promote the local expression of the vitamin D activating enzymes CYP2R1 and CYP27B1. This converts local vitamin D into its active metabolite 1,25D. This locally produced 1,25D would in turn control obesity-associated inflammation because of its anti-inflammatory potential.

Adipokines and vitamin D can now be viewed as two faces of the same autocrine-paracrine signaling pathway whose dysfunction can participate in postmenopausal breast cancer risk. A necessary but not sufficient requirement of the system is the presence of adequate stores of vitamin D in breast fat tissue. For that reason, both local vitamin D and adipokine concentrations should be considered in addition to plasma levels. This provides a possible explanation for the mixed results obtained when plasma concentrations are used to investigate associations between adipokines or vitamin D and breast cancer risk.

The authors have no conflicts of interest to declare.

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