Re: Insulin, Insulin-like Growth Factor-I, and Risk of Breast Cancer in Postmenopausal Women

Gunter et al. (1) reported results of a large prospective case–control study, confirming that hyperinsulinemia is an independent risk factor for postmenopausal breast cancer. They also discussed a variety of possible mechanisms for breast cancer promotion by hyperinsulinemia and concluded that lowering insulin levels may be a possible strategy for reducing the risk of breast cancer in postmenopausal women.

We strongly agree with these conclusions. However, we would like to comment on some slightly different mechanisms that may better explain the biology of the insulin effect in breast cancer cells and, perhaps, suggest possible strategies for reducing the cancer-promoting effect of insulin. First, it is well recognized that insulin promotes breast cancer cell proliferation (ie, it has mitogenic activity), but there is no evidence that it promotes breast cancer initiation (ie, that it has mutagenic activity). In only a few experimental models is insulin able to induce a transformed phenotype that has some but not all of the characteristics of malignant cells. For example, in both mouse NIH/3T3 fibroblasts (2) and human 184B5 breast cells in permanent culture (3), overexpression of the insulin receptor is a prerequisite for insulin-mediated

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transformation. By contrast, extensive in vitro and in vivo data indicate that insulin may promote breast cancer progression through its mitogenic effect. Therefore, the well-established association between insulin level and breast cancer risk is likely to be the result of hyperinsulinemia promoting growth and progression of subclinical breast cancers rather than a direct effect of insulin on new breast cancer initiation.

A second issue concerns the observation that even a modest fasting hyperinsulinemia (two- to threefold increase over normal) is associated with a statistically significantly increased risk of breast cancer. Gunter et al. did not mention that most breast cancers display increased expression of the insulin receptor (eg, the average increase in insulin receptor expression in 159 human breast cancer specimens compared with normal breast tissue was more than sixfold) (4). This receptor overexpression plays an important role in the tumor biology: in 584 node-negative breast cancers, the insulin receptor level was the strongest independent predictive factor for disease-free survival (5).

Finally, most human breast cancers not only overexpress the insulin receptor but also preferentially express the insulin receptor isoform A (IR-A), which has a mitogenic rather than metabolic effect when activated by insulin (6). IR-A is also a high-affinity receptor for insulin-like growth factor (IGF)-II and a component of the insulin IGF-I hybrid receptor that is overexpressed in breast cancer cells (7). Hybrid receptors mediate the mitogenic signaling of IGF-I and, to a lesser extent, of IGF-II and thus contribute to the stimulation of malignant breast cell growth by both circulating and locally produced growth factors. In summary, the complex relationship between insulin and breast cancer involves not only the high levels of the hormone itself but also the overexpression of both total insulin receptor and IR-A in the malignant tissue. Targeting insulin levels, therefore, may be an insufficient approach for preventing the negative effects of insulin on breast cancer promotion.

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Notes

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