Letters to the Editor

Insulin-Like Growth Factor–Binding Protein-3, Breast Cancer Risk, and Different Serum Assays[1]

To the Editors: We are concerned about the potential misleading interpretations in the recently published study by Rinaldi et al. (1). In 2004, we reported the results of a systematic review determining the relationships between circulating total insulin-like growth factor-I (IGF-I) and total IGF-binding protein-3 (IGFBP-3) concentrations and cancer risk at several sites, including premenopausal and postmenopausal breast cancers (2). Using predetermined inclusion criteria and doing statistical analyses at two levels (a baseline meta-analysis and a meta-regression analysis of the study-specific dose-response slopes), we showed that higher concentrations of total IGF-I and IGFBP-3 were significantly and positively associated with a modest increased risk of premenopausal but not postmenopausal breast cancer. Three subsequent systematic reviews, using different approaches, broadly came to the same conclusions (3, 4).

Rinaldi et al. (1) recognized that the type of IGFBP-3 assay used and the extent of serum IGFBP-3 proteolysis may influence cancer risk associations. Consequently, they used three different assays for measuring IGFBP-3 concentrations and calculated risk associations for breast cancer in young women separately for each assay type. Two of these assays measured total IGFBP-3, whereas the third was an unreferenced immunoassay measuring ''functional'' IGFBP-3. An appreciation of IGFBP-3 physiology highlights that there is difficulty in the interpretation of the different risk associations found with these measures. Conventionally shown on a Western immunoblot, IGFBP-3 is proteolyzed as intact IGFBP-3, a doublet band at 38 and 42 kDa, and as fragments at 30, 20, and 16 kDa. Total IGFBP-3 equates to the sum of intact and fragmented moieties. Under normal conditions, there is an appreciable but variable level (30-40%) of IGFBP-3 proteolytic activity in serum. The functional assay used in this study measured only moieties that are able to bind the IGF ligand (i.e., intact IGFBP-3), and to some extent, the 30-kDa fragment (5). However, all fragments may be biologically active in an IGF-independent manners; thus, the term *functional* IGFBP-3 is misleading (5).

Given this background physiology, not unexpectedly, the risk estimates determined by the assays measuring total IGFBP-3 differed from that measuring functional IGFBP-3. More interestingly, the lack of association for the functional IGFBP-3 assay in the face of the positive association for the total IGFBP-3 assays suggests that the smaller (unmeasured) fragments may be the most relevant aspect of IGFBP-3 physiology in the assessment of premenopausal breast cancer risk. Future epidemiologic studies need to be carefully designed using standardized laboratory methods based on a thorough understanding of the physiology of this complex molecular system.

Potential Conflict of Interest. Andrew G. Renehan has received hospitality from Diagnostic Systems Laboratories and a lecture honorarium from Eli-Lilly.

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References

1. Rinaldi S, Kaaks R, Zeleniuch-Jacquotte A, et al. Insulin-like growth factor-I, IGF binding protein-3, and breast cancer in young women: a comparison of risk estimates using different peptide assays. Cancer Epidemiol Biomarkers Prev 2005;14:48–52.
2. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–53.
3. Renehan AG, Egger M, Minder C, O'Dwyer ST, Shalet SM, Zwahlen M. IGF-I, IGF binding protein-3 and breast cancer risk: comparison of 3 meta-analyses. Int J Cancer 2005;115:1006–7.
4. Fletcher O, Gibson L, Johnson N, et al. Polymorphisms and circulating levels in the insulin-like growth factor system and risk of breast cancer: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14:2–19.
5. Baxter RC. Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities. Am J Physiol Endocrinol Metab 2000; 278:E967–76.

[1] The authors of the original article were invited to respond but did not do so.