Letters to the Editor

Insulin-Like Growth Factor-I and Mammographic Breast Density

To the Editor: Diorio and colleagues recently (1) reported a direct association of the percentage of mammographic density with plasma insulin-like growth factor-I (IGF-I) in a large cross-sectional study. As in previous studies (2, 3), this association was stronger in premenopausal women, and findings were interpreted as support for the hypothesis that elevated plasma IGF-I increases breast cancer risk in young women. It seems, however, that these findings could be strongly confounded by the effects of adiposity on IGF-I levels.

An elevated body mass index (BMI; adiposity) is generally associated with a modest decrease in plasma IGF-I concentrations, compared with nonobese women, and moderately increased levels of IGFBP-3. BMI generally also correlates strongly with the area of the nondense region on mammogram (largely reflecting adipose tissue), which in turn is strongly correlated with total breast area. Thus, the percentage of mammographic density—calculated as the ratio of dense tissue area divided by the total area—generally correlates strongly and inversely with BMI. Given these various interrelationships, one would expect a weak positive correlation between IGF-I and the percentage of mammographic density, especially when adjusting for IGFBP-3, and this is what the study by Diorio et al. showed. We recently also observed a positive correlation ($r = 0.13$) between the IGF-I/IGFBP-3 molar ratio and the percentage of mammographic density (4). This correlation, however, could be entirely accounted for by the correlation of IGFBP-3 ($r = 0.20$), and hence, the inverse correlation of the IGF-I/IGFBP-3 ratio ($r = -0.19$), with the nondense area.

When Diorio et al. adjusted their analyses for IGFBP-3, the correlation of IGF-I with the percentage of density was substantially strengthened. This adjusted correlation was very much weakened, however, when analyses were further adjusted for BMI. As BMI provides only an approximate measure of adiposity (studies have indicated a correlation of ~0.6-0.7 between BMI and body fat percentage), it cannot be ruled out that the association remaining after BMI adjustment was due to residual confounding by adiposity. To diminish the risk of confounding by adiposity, due to the relationships described above, one should preferably examine the relationships of IGF-I with absolute area of dense breast tissue, instead of the percentage of density. Some studies suggest an equally strong association of breast cancer risk with absolute dense area as with percentage of density (5, 6), and the absolute dense area provides a direct measure of the amount of (epithelial) breast tissue susceptible to malignant transformation and tumor development.

Rudolf Kaaks
Nutrition and Hormones Group,
International Agency for Research on Cancer,
Lyon, France

References

1. Diorio C, Pollak M, Byrne C, et al. Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. Cancer Epidemiol Biomarkers Prev 2005;14:1065–73.
2. Byrne C, Colditz GA, Willett WC, et al. Plasma insulin-like growth factor (IGF) I, IGF-binding protein 3, and mammographic density. Cancer Res 2000; 60:3744–8.
3. Boyd NF, Stone J, Martin LJ, et al. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876–82.
4. Maskarinec G, Williams AE, Kaaks R. A cross-sectional investigation of breast density and insulin-like growth factor I. Int J Cancer 2003;107:991–6.
5. Maskarinec G, Meng L. A case-control study of mammographic densities in Hawaii. Breast Cancer Res Treat 2000;63:153–61.
6. Kato I, Beinart C, Bleich A, Shaun S, Kim M, Toniolo P. A nested case-control study of mammographic patterns, breast volume, and breast cancer (New York City NY, United States). Cancer Causes Control 1995;6:431–8.

doi:10.1158/1055-9965.EPI-05-0607

In Response: We thank Dr. Kaaks for his interest in our published article on insulin-like growth factors (IGF) in relation to mammographic breast density (1). In his letter to the editor, Dr. Kaaks raises the possibility that associations of IGF-I levels with percent density could suffer from residual confounding by adiposity because both percent density and IGF-I levels are associated with adiposity measurements. To counter this problem, he suggests that levels of IGF-I should be examined in association with absolute area of dense tissue on the mammogram (absolute density) instead of with percent density.

In our data, after adjustment for age, body mass index, and IGF binding protein-3 levels, the strength of the correlation of IGF-I levels with percent density was similar to the one observed between levels of IGF-I and absolute density ($r_s = 0.083$, $P = 0.021$ and $r_s = 0.076$, $P = 0.034$, respectively). The similarity of results with percent and absolute density was also observed by Boyd et al. ($\beta = 0.01$, $P = 0.03$ and $\beta = 0.01$, $P = 0.05$, respectively; ref. 2) and Maskarinec et al. ($r_s = 0.11$, $P = 0.06$ and $r_s = 0.11$, $P = 0.09$, respectively; ref. 3).

As Dr. Kaaks, we were also concerned about residual confounding by adiposity, as well as by other factors potentially associated with percent density and/or levels of growth factors. We had considered further adjustment for several factors, including waist-to-hip ratio (an indicator of abdominal fat), and observed similar correlation of IGF-I levels with percent density after such adjustment ($r_s = 0.082$, $P = 0.025$). Thus, level of IGF-I is still positively associated with percent density even if more than one measure of adiposity is taken into account in the analysis.

In our view, it is still unclear whether or not we can learn more about breast cancer etiology by focusing on absolute rather than percent breast density (4). However, whether absolute or percent density is used, adequate adjustment for measures of adiposity (and age) is important in studies evaluating the relation of breast density to factors that are even weakly correlated with adiposity (or age).

Caroline Diorio
Jacques Brisson
Unité de recherche en santé
des populations, Centre hospitalier
affilié universitaire de Québec,
Department of Social and Preventive Medicine,
Laval University, Quebec, Canada

References

1. Diorio C, Pollak M, Byrne C, et al. Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. Cancer Epidemiol Biomarkers Prev 2005;14:1065–73.
2. Boyd NF, Stone J, Martin LJ, et al. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876–82.
3. Maskarinec G, Williams AE, Kaaks R. A cross-sectional investigation of breast density and insulin-like growth factor I. Int J Cancer 2003;107:991–6.
4. Maskarinec G, Pagano I, Lurie G, Wilkens LR, Kolonel LN. Mammographic density and breast cancer risk: the multiethnic cohort study. Am J Epidemiol 2005;162:743–52.

Insulin-Like Growth Factor-I and Mammographic Breast Density

Rudolf Kaaks

Cancer Epidemiol Biomarkers Prev 2005;14:3019.