RISK FACTORS

Does insulin resistance influence breast cancer outcomes?

Three articles published in the same issue of the *Journal of Clinical Oncology* have shed new light on the potential association between metabolic dysfunction and breast cancer prognosis. The findings of these studies implicate insulin resistance as a key player.

Certain cancers, including breast cancer, seem to occur more frequently in people with diabetes mellitus. Conversely, hyperglycemia and hyperinsulinemia might be associated with poor outcomes in women with breast cancer. "The role of these factors in breast cancer outcomes is not completely clear," explains Kimberly Peairs, an Assistant Professor of Medicine at Johns Hopkins University School of Medicine, Baltimore, MD, USA. "However, the hypothesis suggests that they may influence tumor-cell proliferation and metastasis." Peairs and her colleagues, therefore, decided to review the available published evidence of a correlation between pre-existing diabetes mellitus and breast-cancer-related outcomes.

Peairs *et al.* performed a systematic review of the literature to identify studies that evaluated a population with cancer and reported on prognostic outcome by diabetes status. Prognostic outcomes included breast-cancer-related mortality; stage of breast cancer at diagnosis; cancer treatment regimens; treatment-related adverse effects; and disease-free survival. In all, eight articles were included in the systematic review of breast cancer outcomes; of these eight studies, six met the investigators' criteria for inclusion in a meta-analysis of all-cause mortality. Sample sizes ranged from 588 to 70,781 individuals; the proportion of patients with diabetes mellitus also varied by study (range 8–31%).

The researchers made a number of important findings. First, women with pre-existing diabetes mellitus who were diagnosed with breast cancer had a 49% increased risk of death from any cause when compared with their nondiabetic peers. Furthermore, women with diabetes mellitus were also more likely to be diagnosed at a late stage of breast cancer, undergo different cancer treatment regimens than nondiabetic women, and experience increased toxicity or adverse effects in response to chemotherapy.

Peairs points out that her team's findings "do not necessarily suggest a causal relationship". Nonetheless, data reported from the Health, Eating, Activity, and Lifestyle (HEAL) study could provide clues as to the biological mechanism/s underlying the observed association. HEAL is a multicenter, multiethnic, prospective cohort study of 1,183 women with early-stage breast cancer. The aim of this study is to investigate how lifestyle factors and hormone exposure affect breast cancer outcomes.

Irwin and colleagues evaluated fasting C-peptide levels (a marker of insulin secretion) and mortality 3 years after breast cancer diagnosis in 604 of the HEAL participants, 58 of whom also had type 2 diabetes mellitus. The researchers found a positive correlation between high levels of C-peptide and mortality: as little as a 0.333 nmol/l increase in C-peptide level was associated with a 31% increased risk of death from any cause and a 35% increased risk of breast-cancer-related death. The association of C-peptide with mortality was particularly marked among women with type 2 diabetes mellitus.

In a second analysis, Duggan *et al.* measured levels of fasting glucose, insulin and adiponectin in 527 of the women enrolled in HEAL (none of whom were diagnosed with type 2 diabetes mellitus). The investigators also assessed insulin resistance using the Homeostatic Model Assessment (HOMA) score. Elevated HOMA scores—indicative of insulin resistance—correlated with increased mortality (all-cause and breast-cancer-specific) in this cohort. By contrast, high

levels of adiponectin were associated with improved breast cancer prognosis.

Taken together, these three studies demonstrate a potential relationship between hyperglycemia or hyperinsulinemia and inferior breast cancer outcomes. A targeted strategy to improve the overall prognosis for women with breast cancer could, therefore, include aggressive treatment of pre-existing diabetes mellitus. "Preclinical data exist to suggest that metformin, a commonly used antidiabetic medication that reduces hyperinsulinemia, may improve prognostic outcomes," Peairs remarks. A large study is already underway to determine the benefits of this approach.

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Original articles Peairs, K. S. *et al.* Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J. Clin. Oncol.* **29**, 40–46 (2011) | Irwin, M. L. *et al.* Fasting C-peptide levels and death resulting from all causes and breast cancer: the Health, Eating, Activity, and Lifestyle Study. *J. Clin. Oncol.* **29**, 47–53 (2011) | Duggan, C. *et al.* Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J. Clin. Oncol.* **29**, 32–39 (2011)