

# Insulin in the Adjuvant Breast Cancer Setting: A Novel Therapeutic Target for Lifestyle and Pharmacologic Interventions?

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The use of targeted treatments in breast cancer has led to major important improvements in breast cancer outcomes. Key examples of such therapies include tamoxifen and aromatase inhibitors in estrogen receptor (ER) –positive breast cancer and trastuzumab in human epidermal growth factor receptor 2–positive breast cancer. In general, the introduction of these targeted therapies has paralleled advances in understanding the biology of breast cancer. However, our knowledge is incomplete, and major research efforts continue to focus on identifying additional factors responsible for breast cancer.

Over the last 10 to 15 years, a substantial body of knowledge has developed regarding the role of insulin and other members of the insulin-like growth factor (IGF) family in breast cancer.<sup>1</sup> This family includes three ligands (insulin, IGF-1, and IGF-2), at least four receptors, and six binding proteins. Until recently, much of the research involving this family has focused on IGFs, notably IGF-1. This research has led to the development of antibodies targeting the IGF-1 receptor, which are in the early stages of clinical testing.

In parallel, there has been increasing evidence that insulin, at physiologic concentrations, may play a clinically important role in breast cancer. A modest increased risk of breast cancer has been identified in women with high insulin levels and, to a lesser extent, among women with diabetes.<sup>2,3</sup> Of greater relevance is the growing evidence that insulin increases risk of breast cancer recurrence and death. We identified a significant adverse prognostic effect of fasting insulin levels in locoregional breast cancer.<sup>4</sup> Women with insulin levels in the highest quartile had a doubled risk of recurrence and a tripled risk of death. Similar findings have subsequently been reported by Pasanisi et al,<sup>5</sup> who reported that either high insulin levels or the presence of the insulin resistance syndrome (IRS) was significantly associated with breast cancer mortality. Pollak et al,<sup>6</sup> in a correlative study associated with the National Cancer Institute of Canada MA.14 study (an adjuvant study of octreotide in ER-positive postmenopausal breast cancer), reported that women with high levels of C-peptide (a breakdown product formed when insulin is cleaved from proinsulin) had significantly worse breast cancer outcomes. These studies have also shown that hyperinsulinemia occurring in newly diagnosed breast cancer patients is strongly associated with obesity (an adverse prognostic factor).<sup>7</sup> Furthermore, it seems to reflect the presence of IRS, a condition associated with obesity and physical inactivity that increases risk of diabetes and cardiovascular disease. Thus, insulin may prove to be the elusive link between obesity, other aspects of Western lifestyle, and breast cancer (and possibly colon cancer).<sup>8</sup>

Although the mechanism by which insulin influences breast cancer growth is the subject of intense research, it seems that insulin may signal, at least in part, through its own receptor to activate a cascade of proliferative and antiapoptotic events.<sup>9,10</sup> Recent research has demonstrated that insulin receptors are almost ubiquitously present in human breast cancer and that the presence of these receptors is prognostically important.<sup>11</sup> Furthermore, a fetal form of the insulin receptor (IR- $\alpha$ ), is commonly expressed in breast cancer cells; this receptor seems to play a key role in stimulating growth.<sup>12</sup>

Targeting of insulin as a therapeutic modality in breast cancer is of particular interest because insulin can be modified by lifestyle and pharmacologic interventions. Ligibel et al,<sup>13</sup> in their article in this issue, demonstrate that a lifestyle intervention can lower insulin levels in women with breast cancer. They instituted a mixed strength and endurance exercise intervention to sedentary, obese breast cancer survivors who had completed primary surgery, chemotherapy, and radiation. The intervention resulted in significant reductions in circulating insulin levels (reduced by 28%,  $P = .03$ ), with an associated nonsignificant improvement in insulin sensitivity (calculated empirically using the Homeostasis Model Assessment). The relative reduction in insulin in the intervention arm compared with the control arm attained borderline significance ( $P = .07$ ). These results differ from earlier exercise studies in breast cancer that did not focus on obese, sedentary women and that failed to identify insulin-lowering effects of exercise.<sup>14,15</sup> The demonstration by Ligibel et al<sup>13</sup> that a physical activity program significantly lowers insulin levels raises the intriguing possibility that a lifestyle intervention may act as a targeted therapy in breast cancer.

It is likely that other lifestyle interventions (including weight loss interventions) will also lower insulin levels in breast cancer patients. The only lifestyle intervention study in the breast cancer adjuvant setting that has demonstrated a beneficial effect on disease-free survival (the Women's Intervention and Nutrition Study) used an intervention that lowered dietary fat intake and also resulted in significant weight loss (a 2.3-kg relative difference between the two study arms).<sup>16</sup> The beneficial effects of the intervention were greatest in women with the highest baseline body mass index, suggesting that weight loss may have been an important mediator. Although the effect of the intervention on insulin levels has not been reported, it is conceivable that reduction in insulin as a result of weight loss was an important mediating factor. The observation that the beneficial effect of the lifestyle intervention was greatest in ER-negative breast cancer is consistent

with a key role of insulin (as opposed to estrogen) in mediating this prognostic effect. In contrast to the Women's Intervention and Nutrition Study, the Women's Healthy Eating and Living Study, which evaluated a complex dietary intervention (designed to increase intake of fruits, vegetables, and fiber and to reduce fat intake but that did not lead to weight loss), failed to identify any survival effects.<sup>17</sup> The absence of weight loss may have contributed to the absence of a survival effect in that study.

Has the time arrived to target insulin reduction as a therapeutic modality in breast cancer? I believe it has. A variety of lifestyle interventions, including the exercise intervention described by Ligibel et al,<sup>13</sup> can lead to insulin reduction. It is likely that insulin levels in breast cancer patients will be responsive to multimodality weight loss interventions (such as the Diabetes Prevention Program intervention that incorporates both diet and physical activity)<sup>18</sup> that lower insulin in individuals with insulin resistance. Our group is currently addressing this question in a randomized adjuvant trial testing a telephone-based adaptation of the Diabetes Prevention Program to promote weight loss in recently diagnosed postmenopausal breast cancer patients; our primary long-term outcome is event-free survival, and in the short term, we are evaluating the effect of the intervention on insulin levels.

In addition to lifestyle interventions, which can be costly and may not appeal to all breast cancer patients, a number of pharmacologic agents can also lower insulin levels. Recent interest has focused on metformin, a biguanide derivative that has been used to treat diabetes for almost half a century. This agent is inexpensive and generally well tolerated; its use in IRS results in insulin reductions of approximately 25%. We recently found that it reduced insulin levels by 22% in nondiabetic breast cancer patients who had completed primary therapy,<sup>19</sup> which is similar to the reductions with exercise reported by Ligibel et al.<sup>13</sup> Metformin use in diabetics has been associated with reduced cancer incidence and mortality in two population-based observational studies.<sup>20,21</sup> Furthermore, recent evidence suggests that metformin may have direct (ie, insulin independent) effects on cancer cells, acting as a mammalian target of rapamycin (mTOR) inhibitor.<sup>22</sup> This dual action of metformin (insulin reduction and mTOR inhibition) makes it a particularly attractive target for evaluation in breast cancer.

There is sufficient current evidence to justify the evaluation of a variety of interventions that lower insulin levels as targeted treatments in breast cancer. Such interventions will likely focus on the adjuvant setting, at least initially, and may include multimodality weight loss interventions, isolated physical activity interventions, and pharmacologic interventions. Although lifestyle interventions have considerable appeal, their short- and long-term implementation may be challenging for both patients and practitioners. Many will prefer the simplicity and perceived certainty of a drug treatment. Regardless of the approach taken, in addition to investigating the effects of interventions on breast cancer outcomes, studies should also address biologic questions such as the impact of baseline insulin levels on therapeutic benefit, differential effects according to ER and human epidermal growth factor receptor 2 status, the potential for an added contribution of antibodies targeting the IGF-1 receptor, and the molecular mechanisms by which these interventions work. If the interventions lead to insulin reductions in the range of 25% in the adjuvant setting and if those reductions reverse the adverse prognostic effects of insulin

that have been reported, then one might expect to see a 5% to 6% absolute improvement in 5-year disease-free survival. This is a highly clinically significant effect that would be comparable to that of many commonly used adjuvant therapies.

#### AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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