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Insulin Breast Cancer Connection: Confirmatory Data Set the Stage for Better Care

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A growing body of evidence indicates a strong association between type 2 diabetes and cancer.[1] These two common diseases, increasing in incidence as a consequence of Western lifestyle, frequently occur in the same patient. The biologic nature of this association, however, is not completely clear. Epidemiologic data suggest that patients with diabetes have a higher risk of developing several types of cancer, including liver, pancreatic, colorectal, gynecologic, and breast cancer. Cancer prognosis has also been suggested to be adversely affected by diabetes. In recent years, extensive research has attempted to evaluate and clarify the possible links between type 2 diabetes and breast cancer. In particular, the role of insulin in breast cancer etiology and prognosis has received growing attention.[2]

The association between insulin and cancer is biologically plausible: hyperinsulinemia induces proliferative tissue abnormalities because of the strong anabolic effect of insulin, which results in stimulated DNA synthesis and cell proliferation.[3] This effect may also be explained by the cross-activation of the insulin-like growth factor (IGF) receptor family.[4] IGFs are endocrine mediators of growth hormone and also act in a paracrine and autocrine fashion to regulate cell growth, differentiation, apoptosis, and transformation in different tissues, including breast tissue. The pathways downstream of the insulin/IGF system are well defined: insulin-like growth factor-I (IGF-I) and insulin activate the tyrosine kinase growth receptor pathway, that is, insulin, IGF-I, and hybrid IGF-I/insulin receptors, all of which are frequently overexpressed in breast cancer cells. Activation of these receptors results in upregulation of the insulin receptor substrate 2, which leads to downstream activation of the mitogen-activated protein kinase and phosphatidylinositol 3-kinase-Akt pathways.[5]

In this issue of *Journal of Clinical Oncology*, four articles[6-9] shed additional light on the prognosis of breast cancer in women with diabetes or insulin resistance. All of the studies provide additional proof of an unfavorable breast cancer prognosis in patients with either overt or undiagnosed type 2 diabetes or patients with different forms of glucose intolerance as defined by high C-peptide, high homeostasis model assessment (HOMA) index (ie, the ratio of fasting blood glucose to insulin), and low adiponectin levels. In the first article, a meta-analysis by Peairs et al,[6] the investigators were able to detect, using standard meta-analytic procedures, a 49% increased risk of death as a result of nonspecific breast cancer in women with breast cancer and diabetes compared with women with breast cancer who did not have diabetes. Adverse prognostic features, such as delayed diagnosis and suboptimal treatments, were more likely to occur in the population with diabetes. Breast cancer-specific mortality analysis yielded inconsistent results, possibly because of the small number of available studies with specific mortality data (two out of six) and the short follow-up (one study had a follow-up of only 1 year). This meta-analysis does not come without some limitations; the most important limitation is that it is based on published data. Although it is unlikely that mortality results would differ in an analysis conducted on individual patient data, quality control and analyses of the original records were not possible, and the only feasible subgroup analyses were those for which information was available in the original reports. Despite these constraints, this pragmatic analysis provides quantitative evidence of a significantly increased risk of death in patients with breast cancer who also have a clinical diagnosis of type 2 diabetes. Moreover, given the indirect method of diabetes ascertainment, it is possible the risk of death was underestimated. Indeed, undiagnosed or delayed-diagnosed diabetes in patients who are asymptomatic has been reported to occur in approximately 30% of patients with breast cancer.[10]

The clinical importance and prognostic relevance of undiagnosed and unreported type 2 diabetes in patients with breast cancer is particularly evident in the article by Erikson et al.[7] In this study, archived baseline blood samples from the Women's Healthy Eating and Living study, a dietary intervention trial, were retrieved to measure baseline hemoglobin A1c to evaluate the prognostic effect of chronic hyperglycemia among 3003 survivors of early breast cancer who were observed for a median of 7.3 years for additional breast cancer events and 10.3 years for all-cause mortality. In this retrospective analysis, 6% of the patients had chronic hyperglycemia as defined by A1c levels of 6.5% or greater. A1c level was significantly associated with an increased risk of all-cause mortality (hazard ratio [HR], 2.35; 95% CI, 1.56 to 3.54, for A1c $>$ 7.0% $v <$ 6.5%) after adjustment for stage, grade, age, ethnicity, education, and physical activity. When adjusting for the same factors, the breast cancer–specific event rate (disease-free survival) did not differ significantly by A1c levels. However, women with A1c levels of greater than 7.0% had a clinically meaningful, albeit not significant, 26% increased risk of breast cancer recurrence. Given the retrospective nature of the study and the inconsistent association between hyperglycemia and breast cancer recurrence found in some studies,[11] these results should be regarded as

hypothesis-generating findings that require additional confirmation before A1c screening is introduced into routine clinical practice. Moreover, the cost effectiveness of A1c screening may be challenged by the low prevalence (only 6%) of altered A1c levels in the study population.

Two additional works derived from the Health, Eating, Activity, and Lifestyle Study[8,9] analyzed the prognostic significance of markers of glucose intolerance and obesity on all-cause and breast cancer–related death among approximately 600 women with stage I to IIIa breast cancer, most of whom did not have diabetes, who were observed for a median of approximately 6 years. In the study by Irwin et al,[8] a 1 ng/mL increase in serum C-peptide level, a reliable and stable marker of insulin secretion, was associated with a 31% increased risk of any death (HR, 1.31; 95% CI, 1.06 to 1.63) and a 35% increased risk of death as a result of breast cancer (HR, 1.35; 95% CI, 1.02 to 1.87). Associations were stronger for women with a body mass index of less than 25 kg/m^2, women with higher-stage disease, and whose with estrogen receptor–positive disease. The results are in line with those previously reported by Goodwin et al,[12] who showed a three-fold increased risk of death in women with higher fasting insulin levels collected 3 months after diagnosis of breast cancer. A limitation of the study by Irwin et al[8] is the lack of C-peptide measurement after breast cancer diagnosis and before adjuvant treatment (measurements were performed on blood drawn an average of 3 years after diagnosis). Moreover, both the study by Irwin et al[8] and that by and Goodwin et al[12] refer to the adjuvant treatment era before aromatase inhibitors became the standard of care, so additional data are necessary to confirm these findings in light of current treatment guidelines. In the study by Duggan et al,[9] increasing insulin resistance levels as measured by the HOMA index[13] were associated with reduced breast cancer survival (HR, 1.12; 95% CI, 1.05 to 1.20) and reduced all-cause survival (HR, 1.09; 95% CI, 1.02 to 1.15) after adjustment for covariates. Moreover, higher levels (above the median of 15.5 ug/mL) of adiponectin were associated with longer breast cancer survival (HR, 0.39; 95% CI, 0.15 to 0.95). Interestingly, low levels of adiponectin, a parameter that is inversely related to obesity and insulin resistance,[14] have recently been shown to be a risk biomarker for both diabetes[15] and breast cancer.[16] Admittedly, both studies[8,9] were hampered by limited statistical power, so that the associations between study biomarkers and mortality were not always consistent and were of borderline significance. Nevertheless, the results of all four works[6-9] published in this issue of *JCO* harbor important clinical implications, given the growing body of evidence that shows that treatment of diabetes and insulin resistance with dietary interventions, increased physical activity, and insulin-lowering drugs, such as metformin, may improve prognosis and responsiveness to anticancer treatments in patients with diabetes and breast cancer.[17]

In particular, the renewed interest in metformin in cancer prevention and treatment is the consequence of the recent convergence of several areas of research. Exciting preclinical studies have demonstrated that metformin can inhibit the growth of cancer cells in vitro and in vivo.[18] Moreover, recent data indicate that the abnormally high proliferative activity of premalignant and malignant cells requires high levels of nutrients to meet the increased demands for energy consumption and protein biosynthesis.[19] Aberrations of genes involved in the metabolic pathways, such as the AMP-activated protein kinase/LKB1 pathway, thus represent an emerging hallmark of carcinogenesis that is increasingly recognized as a plausible preventive and therapeutic target.[20]

Inexpensive and well tolerated, metformin is a widely prescribed antidiabetic drug for the treatment of hyperglycemia, hyperinsulinemia, and polycystic ovarian syndrome.[21] Preliminary data also show an increase in adiponectin levels with metformin treatment.[22] Metformin effects on cancer outcome have been retrospectively evaluated in population studies that show a lower cancer-specific mortality rate in patients with diabetes who were treated with metformin compared with other treatments,[23] as well as an improved responsiveness to preoperative chemotherapy in patients with breast cancer and diabetes compared with patients with breast cancer who do not have diabetes.[24] A phase III adjuvant trial has recently been initiated (Metformin Hydrochloride in Treating Patients With Early-Stage Breast Cancer [NCIC MA.32]) to assess the efficacy of adding metformin to standard adjuvant treatment to reduce breast cancer recurrence in more than 3,500 women with stage I and II breast cancer.[17] Metformin has also been associated with decreased cancer risk in observational studies in patients with diabetes,[25] with an overall, statistically significant 31% decrease in global cancer risk and a nonsignificant 30% decrease (summarized risk ratio, 0.70; 95% CI, 0.28 to 1.77) in breast cancer incidence compared with other antidiabetic treatments (Table 1).

Whereas the routine use of metformin in any patient with breast cancer for the purpose of reducing breast cancer recurrence is still premature and requires convincing evidence from dedicated clinical trials, a few simple procedures are ready to be introduced into clinical practice. First, the measurement of waist circumference should be

Table 1. Observational Studies That Assessed Metformin Use and Breast Cancer Risk in Patients With Diabetes

Source	Country	Design	Population	Risk Estimates	95% CI	Adjusting Variables*
Libby et al, 2009	Scotland, United Kingdom	Population-based, historical cohort study	N = 8,170	0.6	0.32 to 1.10†	Smoking, BMI, HbA1c, material deprivation, other drug use (sulfonylureas or insulin)
Currie et al, 2009	United Kingdom	General practices, retrospective cohort study	N = 7,897	1.02	0.71 to 1.45‡	Smoking, comorbidity, HbA1c, diabetes duration, weight
Bodmer et al, 2010	United Kingdom	Nested case-control study	17 cases, 120 controls	0.44	0.24 to 0.82†	General practice and calendar time, other use of prandial glucose regulators, acarbose, estrogen, smoking, BMI, diabetes duration, and HbA1c
Summary risk ratio				0.70	0.28 to 1.77	

NOTE. Data are modified from study by DeCensi et al.[25]
Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.
*Adjusting variables listed do not include age or sex.
†As compared with nonmetformin users.
‡As compared with sulfonylureas monotherapy.

mandatory in all patients with breast cancer to detect visceral obesity (males ≥ 94 cm; females ≥ 80 cm). Visceral obesity was the main feature of the metabolic syndrome[26] that is associated with the chronic hyperglycemia, hyperinsulinemia, and type 2 diabetes studied in the four articles discussed.[6-9] The metabolic syndrome also includes any two of the following four features: a fasting plasma glucose level of 100 mg/dL or greater, raised blood pressure (systolic: ≥ 130 mmHg, or diastolic: ≥ 85 mmHg), a high-density lipoprotein cholesterol level of less than 40 mg/dL in men and less than 50 mg/dL in women, and triglyceride levels of 150 mg/dL or greater. Patients with these characteristics are at higher risk for cardiovascular disease[27] and may also have a greater risk of tumor-related events.[27,28] Second, measurement of the HOMA index, a reliable indicator of insulin resistance[13] that involves assays for glucose and insulin performed on a single fasting blood specimen, should become part of the routine clinical practice of the treating physician. These simple measures would enable us to tailor interventions on the basis of lifestyle, such as dietary modifications and physical activity programs that have already been associated with improved survival in selected patients,[29-33] and they will assist in identification of patients with undiagnosed diabetes. Third, in patients with breast cancer who have overt diabetes or glucose intolerance, metformin should be regarded as the antidiabetic drug of choice given its potential lower association with cancer development compared with insulin or sulfonylureas.[25]

In summary, the findings provided in this issue of *JCO* highlight the influence of insulin resistance on breast cancer progression. In the era of treatment selectivity and molecular-targeted anticancer drugs, the accumulating evidence of common pathways linking breast cancer and impaired glucose intolerance or diabetes is increasingly pointing the way forward. The time has come to overcome the conventional tunnel vision that results in two diseases being treated by separate clinicians, and to move towards a comprehensive approach that ideally integrates oncologists, internists, nutritionists, and other health care professionals in an attempt to improve breast cancer prognosis in a significant proportion of patients.

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