Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence\textsuperscript{1–4}

Fei Xue and Karin B Michels

ABSTRACT

Incidence of breast cancer, type 2 diabetes, and metabolic syndrome have increased over the past decades with the obesity epidemic, especially in industrialized countries. Insulin resistance, hyperinsulinemia, and changes in the signaling of growth hormones and steroid hormones associated with diabetes may affect the risk of breast cancer. We reviewed epidemiologic studies of the association between type 2 diabetes and risk of breast cancer and the available evidence on the role of hormonal mediators of an association between diabetes and breast cancer. The combined evidence supports a modest association between type 2 diabetes and the risk of breast cancer, which appears to be more consistent among postmenopausal women than among premenopausal women. Despite many proposed potential pathways, the mechanisms underlying an association between diabetes and breast cancer remain unclear, particularly because the 2 diseases share several risk factors, including obesity, a sedentary lifestyle, and possibly intake of saturated fat and refined carbohydrates, that may confound this association. Although the metabolic syndrome is closely related to diabetes and embraces additional components that might influence breast cancer risk, the role of the metabolic syndrome in breast carcinogenesis has not been studied and thus remains unknown. Am J Clin Nutr 2007;86(suppl):823S–35S.

KEY WORDS Breast cancer, type 2 diabetes, metabolic syndrome, insulin resistance, insulin-like growth factor-I, estrogen, meta-analysis

INTRODUCTION

Breast cancer is currently the most common cancer among women in industrialized countries, with \( \approx 213,000 \) projected incident cases in the United States in 2006 (1). The increase in breast cancer incidence has been steady since the 1930s and even more pronounced since the 1980s (2, 3). According to data from the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER), the incidence of breast cancer dropped by 4.8\% annually from 2001 to 2003 (4), possibly as the result of a decrease in hormone replacement therapy use and mammography rates. The last few decades of the 20th century also witnessed an abrupt increase in both type 2 diabetes and metabolic syndrome, especially in industrialized countries (5). From 1980 through 2004, the number of Americans with diabetes increased from 5.8 million to 14.7 million (6).

More than a century ago, hyperglycemia and diabetes were first linked to breast cancer. Hyperglycemia was reported among patients with cancer in 1885 (7). In the 1920s, tumor slices were found to sustain higher rates of glucose utilization than did normal tissues (8). Since the 1950s, incidence reports have described women with breast cancer as having higher rates of diabetes than do healthy women (9, 10).

Type 2 diabetes is characterized by hyperglycemia, hyperinsulinemia, and insulin resistance. Metabolic syndrome refers to a constellation of abnormalities, including abdominal obesity, high blood glucose levels, impaired glucose tolerance, dyslipidemia, and high blood pressure. These risk factors often accompany obesity and are associated with both atherosclerotic cardiovascular disease and type 2 diabetes.

Diabetes mellitus, metabolic syndrome, and breast cancer are all more prevalent in developed than in developing countries, where a sedentary lifestyle and a high intake of refined carbohydrates and saturated fats are more prevalent; however, developing countries are increasingly adopting many of the lifestyle characteristics of more affluent societies. The diabetic condition induces change in several hormonal systems, including insulin, insulin-like growth factors, estrogen and other cytokines, and growth factors, that may affect breast cancer risk (Figure 1). The interaction of these hormonal factors in the diabetic state is complex and is likely involved in cancer promotion, because most of these hormonal factors are known to promote endocrine and other homeostasis.

EPIDEMIOLOGIC EVIDENCE OF THE ASSOCIATION BETWEEN DIABETES AND RISK OF BREAST CANCER

Methods

We conducted a systematic review of epidemiologic studies of diabetes and risk of breast cancer. A previous review by Wolf et al. (11) provided an extensive review of the epidemiologic evidence. We updated this review to include studies published through March 2006. We included only studies of diabetes and breast cancer that reported results on type 2 diabetes or metabolic syndrome. This review was based on studies of type 2 diabetes or metabolic syndrome, as hyperglycemia and hyperinsulinemia are part of the metabolic syndrome definition.

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We included 10 epidemiologic studies (11). We identified 16 additional studies, which thus justified another systematic review of this important topic. We searched PUBMED and MEDLINE (National Library of Medicine, Bethesda, MD) by using the key words diabetes combined with breast cancer restricted to females and humans. We included studies through December 31, 2006, in which original analyses of the association between diabetes and invasive breast cancer were reported. All identified articles were cross-referenced for studies missed with the PUBMED search. We identified a total of 404 articles, of which 26 were eligible for meta-analysis; the other 385 studies were reviews, case reports, or studies on other exposures or outcomes that were therefore excluded from the current meta-analysis. The software REVMAN 4.2 was used to produce forest plots and summary effect estimates (12, 13). We conducted stratified analyses by study design as well as by menopausal status. We used a fixed-effects model weighing each study by the inverse of its variance. If they were available from the published studies, we inputed the relative risk and SE into the REVMAN software on the log scale, the relative risk and 95% CI may differ slightly from the original published paper because of rounding errors. For the summary of each total or subtotal, we provided the chi-square test statistic for heterogeneity across studies with its df and P value, the statistic I² measuring the extent of inconsistency among results, and the test for overall effect (z statistic with P value).

Description of studies

Of the 26 studies included in this meta-analysis, 10 were case-control studies (10, 14–22), 14 were cohort studies (23–36), and 2 were cross-sectional studies (37, 38). We included the cross-sectional studies in the case-control study category because their study design and statistical analysis were similar to those of the case-control studies. The studies were conducted in 10 countries: the United States (15, 18, 21–24, 29, 30), Italy (16, 17, 19, 20), Japan (25, 33, 36), Sweden (14, 26), Denmark (27, 28), the United Kingdom (34, 37), Canada (31, 38), Germany (10), Netherlands (32), and Korea (35). Because 3 of the publications from Italy (17, 19, 20) were based on the same case-control study, we only included data from the most recent publication in the meta-analysis (20). Although another publication (19) included

FIGURE 1. Potential mechanisms for the influence of type 2 diabetes on the risk of breast cancer. IGF-I, insulin-like growth factor I; IRS, insulin receptor substrate; IGF-1R, IGF-I receptor; SHBC, sex hormone-binding globulin.
slightly more cases, Talamini et al (20) more specifically assessed breast cancer risk, provided effect estimates adjusted for potential confounders, and presented analyses stratified by menopausal status. Most studies included in the meta-analysis did not distinguish type 2 from type 1 diabetes mellitus.

Studies on diabetes and breast cancer

Among all 9 case-control studies in which the association between diabetes and risk of breast cancer was addressed, results from 8 (10, 14–16, 20–22, 31) suggested that breast cancer patients were more likely to have a history of diabetes, with odds ratios ranging from 1.10 to 2.15. In 4 studies, the increase in odds was statistically significant (10, 16, 20, 31; Figure 2). Among all 11 cohort studies, results from 8 indicated that women with a history of breast cancer were more likely to develop breast cancer (23, 25, 26, 28–30, 33, 35), with hazard ratios ranging from 1.10 to 2.06; in 5 studies, the increase in hazard was statistically significant (25, 26, 28, 30, 35; Figure 2). The summary risk ratio and 95% CI for all case-control studies, all cohort studies, and all studies regardless of study design were 1.15 (1.10, 1.20), 1.16 (1.12, 1.20), and 1.15 (1.12, 1.19), respectively (Figure 2). Both the chi-square test and $I^2$ statistic indicated heterogeneity across studies ($P$ for heterogeneity = 0.03, 0.0002, and 0.0001 for case-control studies, cohort studies, and all studies, respectively), probably because of unstable estimates and driven by one study in each category crossing over to indicate an inverse association between diabetes and breast cancer risk (Figure 2). Because the vast majority of the evidence fairly consistently indicated a positive association between diabetes and risk of breast cancer, we present combined estimates despite heterogeneity.

Stratification by menopausal status

For studies in which the association between a history of diabetes and the risk of breast cancer was analyzed separately among postmenopausal women (20, 30) or among women of postmenopausal age (24, 26, 28, 32, 37, 38), a stronger association between diabetes and breast cancer risk was observed in both case-control studies (20, 37) and cohort studies (24, 26, 28, 30, 32, 38), with an overall summary relative risk of 1.19 (95% CI: 1.15, 1.23; Figure 3). Conversely, results from studies in which the analysis was restricted to premenopausal women (20, 21, 30) or women of premenopausal age (26, 28) did not indicate an association between a history of diabetes and the risk of breast cancer, regardless of study design (overall summary OR = 0.94; 95% CI: 0.80, 1.10; Figure 4). Heterogeneity across studies was detected in the analysis among postmenopausal women ($P$ for heterogeneity = 0.02) but not in the analysis among premenopausal women. Pre- and postmenopausal breast cancer may differ in its etiology. A high body mass index is associated inversely with the risk of premenopausal breast cancer (39) but positively with the risk
of postmenopausal breast cancer (40). A high birth weight increases the risk of premenopausal but not of postmenopausal breast cancer (41). Circulating concentrations of insulin-like growth factor-I (IGF-I) appear to be more consistently associated with premenopausal than with postmenopausal breast cancer risk (42, 43). Endogenous estrogen concentrations have been more consistently associated with the risk of postmenopausal than of premenopausal breast cancer, although this difference may be in part due to the fluctuation in endogenous estrogen concentrations throughout the menstrual cycle among premenopausal women, which makes precise measurement difficult (44). Because obesity, birth weight, and alterations in the IGF-I and estrogen signaling system all contribute to the diabetic state, the differential role of these factors in the etiology of premenopausal and postmenopausal breast cancer may partly account for the difference in the association between diabetes and breast cancer risk.

Type 2 diabetes arises mostly after 30 y of age. The apparent effect modification by menopausal status may thus reflect an association between type 2 diabetes and subsequent breast cancer incidence, which would most likely be postmenopausal. Most of the reviewed studies, except 2 (16, 30), did not distinguish type 2 from type 1 diabetes mellitus, probably because of the difficulty in recording the diagnosis. We conducted a separate meta-analysis of all studies that included only diabetes arising at older age, ranging from age older than 30 y (15, 21, 27, 34), older than 35 y (22), to postmenopausal age (20, 24, 38); studies including only type 2 diabetes (30, 37); and a study restricted to women who survived to age 65 y, an age at which most patients with type 1 diabetes are not expected to reach (26). The summary results were slightly strengthened (summary RR = 1.18; 95% CI: 1.13, 1.23), which is consistent with the hypothesis that type 2 diabetes
may promote cancer development through hyperinsulinemia, insulin resistance, and relevant alterations in other hormones.

**Potential confounding factors**

Breast cancer and diabetes share many risk factors, such as obesity and a sedentary lifestyle, and potentially dietary factors such as intake of saturated fat and refined carbohydrates, although their role is less clear for breast cancer etiology than for diabetes (45–48). Hence, the observed association between diabetes and breast cancer risk may be partly due to the clustering of the 2 disorders as a consequence of shared risk factors. Several studies have provided insights into this problem by taking into account the time lag from the diagnosis of diabetes to the diagnosis of breast cancer (26, 28, 30), because if diabetes indeed promotes breast cancer development, one would expect a certain etiologically relevant time window between the occurrence of diabetes and the incidence of breast cancer. In the study by Weiderpass et al (26), diabetes was assessed at baseline, and the relative risk for breast cancer diagnosed after 5–9 y (standardized incidence ratio (SIR) = 1.9; 95% CI: 1.6, 2.2) or 10–24 y (SIR = 1.6; 95% CI: 1.2, 2.1) of follow-up did not differ appreciably from the relative risk after 1–4 y of follow-up (SIR = 1.9; 95% CI: 1.6, 2.2). Similarly, in the study by Wideroff et al., the relative risk for breast cancer diagnosed 5–9 y (SIR = 1.8; 95% CI: 1.2, 2.7) or ≥10 y (SIR = 2.4; 95% CI: 1.2, 4.1) after the assessment of diabetes at baseline did not differ much from the relative risk after 1–4 y of follow-up (SIR = 2.3; 95% CI: 1.2, 4.1) (28). In the study by Michels et al (30), a significant positive association between diabetes and breast cancer was restricted to breast cancer diagnosed ≤5 y and 10.1–15 y after the diagnosis of diabetes; however, the data were sparse for the analysis restricted to cases diagnosed >15 y after the diagnosis of diabetes. Because circulating insulin concentrations may decrease in later stages of type 2 diabetes as the result of the decomposition of β-cells, any weakening of the association between diabetes and breast cancer over time may also reflect lower insulin concentrations as type 2 diabetes progresses.

Because obesity is a risk factor shared between type 2 diabetes and postmenopausal breast cancer, this potential confounding factor has been controlled for by matching on weight and height (10) or by adjusting for body mass index (BMI) in the analysis (20–22, 29, 30, 33, 36, 37). A statistically significant positive association between diabetes mellitus and the risk of breast cancer remained in 3 of the studies (10, 20, 30). Despite the possibility of residual confounding, the results from these studies suggest that, although part of the observed association may be accounted for by obesity, diabetes affects the risk of breast cancer through mechanisms independent of obesity, such as hyperinsulinemia, and alterations in IGF-I signaling. Dietary intake of fat and carbohydrates and physical activity are difficult to assess in observational studies with sufficient accuracy. To our knowledge, in no previous study of the association between diabetes and breast cancer risk was dietary intake of saturated fat and refined carbohydrates adjusted for. Michels et al (30) controlled for physical activity, and this adjustment did not alter the positive association between diabetes and breast cancer risk. These data collectively suggest that the association between diabetes and breast cancer risk cannot be entirely explained by the clustering of the 2 diseases as the result of shared risk factors.

**DIABETES AND BREAST CANCER MORTALITY**

Although the overall mortality rate for breast cancer has decreased in the past 15 y (1), diabetes has also been related to increased mortality from breast cancer. In a prospective cohort study, Coughlin et al (49) followed 1.2 million US men and women (588,321 women) in all states, the District of Columbia, and Puerto Rico biannually from 1982 to 1988 and found that, after adjustment for potential confounding variables, women with diabetes at baseline were more likely to die from breast cancer than were women not diagnosed with diabetes (HR = 1.27; 95% CI: 1.11, 1.45). Similarly, Verlato et al (50) followed a cohort of 3782 diabetic women in northern Italy from 1987 to 1996 and observed a higher risk of dying from breast cancer in that cohort than among the general population (HR = 1.40; 95% CI: 1.06, 1.81). On the basis of data from the SEER cancer registry, Yancik et al (51) found that breast cancer patients with diabetes were more likely to die prematurely from breast cancer than were patients without diabetes (RR = 1.76; 95% CI: 1.23, 2.52), which suggests that, besides affecting the incidence rate, diabetes also promotes breast cancer mortality, possibly by accelerating cancer growth through altering growth hormones, such as IGF-I and insulin.

**METABOLIC SYNDROME AND BREAST CANCER**

Metabolic syndrome, which is characterized by abdominal obesity, high blood glucose, impaired glucose tolerance, dyslipidemia, and high blood pressure, is associated with both arteriosclerotic cardiovascular disease and type 2 diabetes (52, 53). The development of metabolic syndrome has been related to obesity and a lack of physical activity. The prevalence of metabolic syndrome has increased with the increasing incidences of breast cancer, diabetes, and obesity worldwide (54, 55). Factors that may account for the association between diabetes and breast cancer, such as hyperinsulinemia and insulin resistance, may also link metabolic syndrome to the risk breast cancer.

A higher risk of postmenopausal breast cancer has been related to higher waist-to-hip ratio or waist circumference in some (56–60) but not all prospective studies (61–64). In some studies, the positive association between abdominal obesity and breast cancer was also found to be independent of BMI (56–58). Although BMI is inversely related with premenopausal breast cancer, a high waist-hip ratio or waist circumference has been linked to an increased risk of premenopausal breast cancer in some studies (61, 62) but not in others (57, 65–67). Despite these inconsistencies, abdominal obesity as a marker of metabolic consequences of obesity appears to influence breast cancer risk. In at least 3 studies, hypertension was associated with a higher risk of breast cancer (68–70), especially among women 50 y or older (69, 70), whereas no association was found in other studies (71–73). However, measurement error in blood pressure or self-reported hypertension may compromise the interpretation of the results. The mechanisms underlying the hypertension–breast cancer association remain unclear, but breast cancer and hypertension may share common pathophysiologic pathways including those involved in inflammation and hormone synthesis and metabolism (74–76).

Dyslipidemia refers to a reduction in serum concentrations of HDL cholesterol and an elevation in serum concentrations of total cholesterol, LDL cholesterol, and triacylglycerols. Cholesterol has been hypothesized to increase the risk of breast cancer...
because cholesterol is a precursor of steroid hormones (77, 78), and endogenous sex steroid hormones are positively related to breast cancer risk (79). High HDL-cholesterol concentrations have been related to a reduced risk of breast cancer, especially among postmenopausal women, because lower serum HDL-cholesterol concentrations may be a marker of relative androgen excess. Androgens are key modulators of serum lipids (80), and after menopause, the bioavailable estrogens formed in adipose tissue by the aromatization of androgens are major stimuli for breast carcinogenesis (81). The relation between serum cholesterol concentration and breast cancer risk has been examined in several retrospective case-control (82–90) and prospective (68, 77, 91–100) studies. Results from most of these studies indicated elevated total cholesterol (82, 84–87, 90) and LDL cholesterol (85, 87) and decreased HDL cholesterol (84, 87, 89) among breast cancer patients, although the variation of the association according to menopausal status remains conflicting. A stronger association among postmenopausal women in some studies (87, 90) and among premenopausal women in others (84). Results from prospective studies are more conflicting and mostly fail to support an association between serum cholesterol concentrations and breast cancer (92–97, 98, 100), but both positive (91) and negative (68, 77) associations between breast cancer risk and total serum cholesterol concentration have been reported. A higher risk of breast cancer associated with lower HDL-cholesterol concentrations was reported in at least 2 prospective studies (96, 99). Although in prospective studies blood samples are obtained before the diagnosis of breast cancer, most available prospective studies are restricted by their small sample size and limited covariate information.

Remarkably, the relation between metabolic syndrome and breast cancer risk has not been considered in any observational study. Metabolic syndrome embraces several components potentially related to breast cancer etiology. We identified one small case-control study conducted in Italy with an increased prevalence of type 2 diabetes mellitus, hypertension, and dyslipidemia among breast cancer cases compared with women with benign breast pathology or women with no breast pathology (101). Epidemiologic studies of the association between metabolic syndrome and breast cancer risk are warranted.

MARKERS OF INSULIN RESISTANCE AND BREAST CANCER

Fasting glucose

Hyperglycemia and potential influence on cancer development

Chronic hyperglycemia in patients with type 2 diabetes develops as a result of resistance to the action of insulin. Insulin resistance in muscle tissue reduces glucose uptake, whereas insulin resistance in the liver reduces glucose storage, both of which lead to an elevated blood glucose concentration. Neoplastic cells use glucose for proliferation (102), and one of the central characteristics of malignant tissues is increased metabolism of glucose toward the pentose phosphate pathway (103). Therefore, a higher circulating glucose concentration may foster cancer development by providing an amiable environment for the growth of malignant cell clones (102).

Epidemiologic evidence on fasting glucose concentrations and risk of breast cancer

Higher fasting glucose concentrations were related to an elevated risk of breast cancer in 3 (29, 104, 105) of 5 studies (29, 35, 71, 104, 105), and the association was statistically significant in 2 of them (104, 105; Table 1). These studies provided conflicting evidence regarding breast cancer risk according to menopausal status: the positive association between high fasting glucose concentrations and breast cancer risk was found to be restricted to premenopausal women in one study (104), restricted to postmenopausal women in another (105), and not different according to menopausal status in the other 2 (29, 71). The inconsistency may be partly due to variations in assessment of fasting glucose or the study population with respect to the profile of circulating glucose. For instance, results from 2 studies suggested that a fasting glucose concentration ≥126 mg/dL, which is the cutoff for defining type 2 diabetes, was related an increased risk of breast cancer (29, 105), whereas the glucose concentration was considerably lower in the other 2 studies (71, 104).

Fasting insulin

Biology of insulin and potential influence on breast cancer

Insulin, a polypeptide hormone secreted from pancreatic β-cells, mediates a wide spectrum of biological responses from stimulation of glucose uptake; glycogen, lipid, and protein synthesis; and antilipolysis to activation of transcription of specific genes and modulation of cellular growth and differentiation (116). The function of insulin is mediated through activation of the insulin receptor (IR), an α2β2 tetramer that is expressed in many human tissues. Insulin receptor substrate-1 (IRS-1) and IRS-2 are widely expressed in different mammalian tissues (116) and breast cancer cell lines (117). In normal cells, IRS-1 is the main docking protein for the binding and activation of the insulin signaling system, but evidence exists that, in patients with type 2 diabetes, the concentration of IRS-1 is decreased whereas that of IRS-2 is unaffected and able to replace IRS-1 as the main docking protein in adipocytes and muscle fibers (118, 119). Insulin exerts a significant mitogenic action in normal mammary tissue as well as in breast cancer cells (120, 121). IR concentrations are higher in breast cancer tissues than in normal breast tissues (122), and IR relates directly to tumor size (122), grade (122), and mortality (123). It is therefore plausible that the interaction between insulin and IR influences breast cancer development through modification of growth and differentiation of breast cell lines.

Epidemiologic evidence for fasting insulin in relation to breast cancer

It has been suggested that insulin resistance resulting from high intakes of saturated fat and weight gain after the age of 30 y contributes to an increased risk of postmenopausal breast cancer (124). In most prospective studies, an increased risk of breast cancer among postmenopausal women was related to upper abdominal obesity (56–58, 125), which is commonly associated with hyperinsulinemic insulin resistance, which suggests that aberrant insulin signaling may be involved in breast cancer etiology. Goodwin et al (126) also reported a direct association between serum insulin concentrations and recurrence and death in breast cancer cases. Among 5 studies (29, 37, 104, 106, 107) in which the role of fasting insulin was explored in relation to subsequent breast
cancer risk, an increased risk associated with higher insulin concentrations was found in 3 (37, 104, 106), and the association was statistically significant in 2 (37, 106; Table 1). A stronger association of fasting insulin with premenopausal breast cancer risk was suggested in 2 studies (104, 106), whereas Lawlor et al (37) reported a positive association among postmenopausal women. In the only prospective cohort study identified, the fasting insulin concentration assessed at baseline was not found to be related to the incidence of breast cancer on the basis of 7 y of follow-up among 7894 women (29).

Overall, the results of these studies provide suggestive yet inconsistent evidence of the role of fasting insulin in breast carcinogenesis. The American Heart Association (127) has suggested that a practical measure of hyperinsulinemia is the fasting insulin concentration (<15 mU/L [104 pmol/L], normal; 15–20 mU/L [104–139 pmol/L], borderline; >20 mU/L [139 pmol/L], high). In only one study, however, was the risk of breast cancer assessed among women with borderline insulin concentrations (29), and hyperinsulinemia defined as >139 pmol/L was not reported in any of the studies, probably because overall insulin

### Table 1

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Study design</th>
<th>Age at diagnosis of breast cancer</th>
<th>Comparison[^1^]</th>
<th>No. of breast cancer cases</th>
<th>No. of controls or person-years</th>
<th>Relative risk estimate (95% CI)^[^2^]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
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<tr>
<td>Manjer, 2001 (71)</td>
<td>Prospective cohort</td>
<td>45–64 y at baseline</td>
<td>≥140 mg/dL vs &lt;90 mg/dL</td>
<td>NA</td>
<td>468 615</td>
<td>HR = 0.82 (0.61, 1.21)</td>
</tr>
<tr>
<td>Munt, 2002 (104)</td>
<td>Case-control</td>
<td>Premenopausal</td>
<td>&gt;86 mg/dL vs ≥71 mg/dL</td>
<td>64</td>
<td>238</td>
<td>OR = 1.63 (0.59, 4.46)</td>
</tr>
<tr>
<td>Mink, 2002 (29)</td>
<td>Prospective cohort</td>
<td>45–64 y at baseline</td>
<td>&gt;125 mg/dL vs &lt;100 mg/dL</td>
<td>187</td>
<td>56 184 person-years</td>
<td>HR = 1.39 (0.86, 2.23)</td>
</tr>
<tr>
<td>Jee, 2005 (35)</td>
<td>Prospective cohort</td>
<td>30–65 y at baseline</td>
<td>≥140 mg/dL vs &lt;90 mg/dL</td>
<td>NA</td>
<td>468 615</td>
<td>HR = 0.82 (0.61, 1.21)</td>
</tr>
<tr>
<td>Rapp, 2006 (105)</td>
<td>Prospective cohort</td>
<td>Overall</td>
<td>≥126 mg/dL vs &lt;40 mg/dL</td>
<td>872</td>
<td>77 228</td>
<td>HR = 1.38 (1.02, 1.86)</td>
</tr>
<tr>
<td>Del Giudice, 1998 (106)</td>
<td>Case-control</td>
<td>Premenopausal</td>
<td>&gt;58 to ≥180 pmol/L vs ≤35 pmol/L</td>
<td>99</td>
<td>99</td>
<td>OR = 3.72 (1.32, 10.47)</td>
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<tr>
<td>Jernstrom, 1999 (107)</td>
<td>Case-control</td>
<td>Continuous rank</td>
<td>&gt;1.07 mU/L vs ≥0.7 mU/L</td>
<td>143</td>
<td>143</td>
<td>HR = 2.7 (1.2, 5.9)</td>
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<tr>
<td>Munt, 2002 (104)</td>
<td>Case-control</td>
<td>Premenopausal</td>
<td>&gt;76 pmol/L vs ≤38 pmol/L</td>
<td>69</td>
<td>265</td>
<td>OR = 1.72 (0.71, 4.15)</td>
</tr>
<tr>
<td>Mink, 2002 (29)</td>
<td>Prospective cohort</td>
<td>45–64 y at baseline</td>
<td>&gt;108 pmol/L vs ≤43 pmol/L</td>
<td>165</td>
<td>50 654 person-years</td>
<td>OR = 1.01 (0.55, 1.86)</td>
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<tr>
<td>Lawlor, 2004 (37)</td>
<td>Cross-sectional</td>
<td>60–79 y</td>
<td>Each unit [log(6.945 pmol/L)] of increase</td>
<td>147</td>
<td>2985</td>
<td>OR = 1.35 (1.00, 1.81)</td>
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<tr>
<td>Fasting C-peptide</td>
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<tr>
<td>Jernstrom 1999 (107)</td>
<td>Case-control</td>
<td>53–90 y</td>
<td>Continuous rank</td>
<td>45</td>
<td>393</td>
<td>OR = 1.00 (0.97, 1.03)</td>
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<td>Yang 2001 (108)</td>
<td>Case-control</td>
<td>Overal 1</td>
<td>&gt;1.07 mU/L vs ≤0.7 mU/L</td>
<td>143</td>
<td>143</td>
<td>OR = 2.7 (1.2, 5.9)</td>
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<tr>
<td>Malin 2004 (109)</td>
<td>Case-control</td>
<td>25–64 y</td>
<td>Highest vs lowest quartile</td>
<td>397</td>
<td>397</td>
<td>OR = 2.64 (1.47, 4.74)</td>
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<tr>
<td>Verheus 2006 (110)</td>
<td>Nested case-control</td>
<td>50–60 y</td>
<td>≥3.38 ng/mL vs &lt;1.98 ng/mL</td>
<td>192</td>
<td>251</td>
<td>OR = 0.77 (0.36, 1.64)</td>
</tr>
<tr>
<td>Verheus 2006 (110)</td>
<td>Nested case-control</td>
<td>&gt;60 y</td>
<td>≥3.38 mg/mL vs &lt;1.98 ng/mL</td>
<td>136</td>
<td>262</td>
<td>OR = 1.27 (0.64, 2.52)</td>
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<td>Nonfasting C-peptide</td>
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<tr>
<td>Bruning 1992 (111)</td>
<td>Case-control</td>
<td>Overall</td>
<td>≥3.5 ng/mL vs &lt;1.5 ng/mL</td>
<td>223</td>
<td>441</td>
<td>OR = 0.80 (0.28, 2.29)</td>
</tr>
<tr>
<td>Tontiolo 2000 (43)</td>
<td>Nested case-control</td>
<td>Premenopausal</td>
<td>&gt;3.9 ng/mL vs &lt;1.8 ng/mL</td>
<td>172</td>
<td>486</td>
<td>OR = 0.76 (0.44, 1.31)</td>
</tr>
<tr>
<td>Keinan-Boker 2003 (112)</td>
<td>Nested case-control</td>
<td>Postmenopausal</td>
<td>≥5.2 ng/mL vs &lt;2.4 ng/mL</td>
<td>115</td>
<td>220</td>
<td>OR = 1.24 (0.66, 2.34)</td>
</tr>
<tr>
<td>Hirose 2003 (113)</td>
<td>Case-control</td>
<td>Overall</td>
<td>≥0.68 mg/mL vs ≥0.36 mg/mL</td>
<td>187</td>
<td>190</td>
<td>OR = 0.97 (0.53, 1.77)</td>
</tr>
<tr>
<td>Schauzer 2004 (114)</td>
<td>Case-control</td>
<td>Postmenopausal</td>
<td>≥2.5 ng/mL vs ≥1 ng/mL</td>
<td>185</td>
<td>159</td>
<td>OR = 1.5 (0.7, 3.0)</td>
</tr>
<tr>
<td>Verheus 2006 (110)</td>
<td>Nested case-control</td>
<td>Overall</td>
<td>≥5.72 mg/mL vs ≥2.43 mg/mL</td>
<td>546</td>
<td>1038</td>
<td>OR = 1.20 (0.83, 1.73)</td>
</tr>
<tr>
<td>Falk 2006 (115)</td>
<td>Case-control</td>
<td>Overall</td>
<td>≥5.93 mg/mL vs ≥2.68 mg/mL</td>
<td>251</td>
<td>232</td>
<td>OR = 0.79</td>
</tr>
</tbody>
</table>

[^1^]: The comparison included here is only the comparison between the highest and the lowest level of the respective biomarker. The number of cases and participants or controls includes persons involved in all comparisons. Concentrations of each biomarker have been converted to the same unit for convenient comparison across studies.

[^2^]: HR, hazard ratio; OR, odds ratio.

[^3^]: The number of cases and participants of this study does not include the reference group (fasting glucose <2.2 mmol/L), among whom data were not available.
concentrations in the study populations were low. Therefore, if there is an effect at a high insulin concentration, these studies may fail to detect it. Conversely, insulin concentrations may decrease in later stages of type 2 diabetes with decomposition of \( \beta \)-cells. A single assessment of fasting insulin may not be sufficient to determine the insulin profile of type 2 diabetes, especially for patients at later stages of diabetes.

**C-peptide**

**Biology of C-peptide**

C-peptide and insulin are both synthesized in the \( \beta \)-cells of the islet of Langerhans by enzymatic cleavage of proinsulin and are both released into the circulation in equimolar amounts (128). Compared with insulin, the function of C-peptide is largely unknown. Because C-peptide has a longer half-life in plasma than does insulin, it is generally used as a marker to reflect insulin secretion (129).

**Epidemiologic evidence**

In at least 10 studies, serum concentrations of C-peptide have been related to the risk of breast cancer (Table 1). Whereas insulin secretion is largely influenced by diet, fasting C-peptide concentrations are less affected by within-person variation. Fasting C-peptide concentrations were assessed in 4 studies (107–110). The studies by Yang et al and Malin et al were based on the Shanghai Breast Cancer Study, a population-based case-control study. In both studies, women in the highest category of fasting C-peptide had a significantly higher risk of breast cancer than did women in the lowest category of C-peptide by a factor of more than 2.5. Results from the other 2 studies (107, 110), including a nested case-control study (110), did not suggest an effect of C-peptide of the same magnitude. No consistent pattern according to menopausal status was apparent in these studies.

Nonfasting C-peptide was assessed in 7 studies; a positive association between C-peptide and breast cancer risk was observed in 6 (43, 110–114), and the association was statistically significant in 1 (111). Three studies were prospective (43, 110, 112), thus avoiding reverse causality. In some studies, the association was most consistent among postmenopausal women (43, 112, 113) or women at older age (110), but C-peptide concentrations are generally higher among older women. Differences in study population, storage of blood samples, and methods of biomarker assessment may have contributed to the inconsistent results.

**DIABETES, INSULIN-LIKE GROWTH FACTOR-I, AND BREAST CANCER**

**IGF-1 and breast cancer**

IGFs are 7-kDa polypeptides with structural homology to proinsulin and are synthesized by almost all tissues, but in humans primarily by the liver (130, 131). They play an important role in mediating cell growth, differentiation, and transformation (130). IGF-I and IGF-II are structurally similar to insulin (132, 133). IGF-II is primarily responsible for regulating fetal growth (134–136), and IGF-I becomes predominant after birth as a result of the onset of growth hormone–stimulated IGF-I production by the liver. Similar to insulin, IGF-I initiates its biological effects by binding to the cell surface receptor IGF-1R (137), which shares structural and functional homology with IR (132). At high concentrations, the ligands of IGF-I and insulin can cross-react with each others’ receptors (138, 139). Results from previous studies of IGF-I suggested a positive although inconsistent association with premenopausal breast cancer and largely no association with postmenopausal breast cancer (140). More recent studies based on large amounts of prospective data did not support an association between IGF-I and breast cancer incidence among premenopausal women (141–143).

**Possible role of IGF-I in the association between diabetes and breast cancer**

The influence of diabetes on circulating concentrations of IGF-I has remained unclear: IGF-I concentrations were found to be either not changed (144, 145), decreased (146–148), or increased in diabetic patients (149). Furthermore, the expression of IGF-1R in breast tissue was similar among diabetic patients and healthy control subjects (145). Thus, there is not sufficient evidence that the interaction of circulating IGF-I and IGF-1R is directly involved in the association between diabetes mellitus and breast cancer risk.

Instead, if the IGF-I system plays a role in enhanced breast carcinogenesis among diabetic patients, its effect is more likely mediated through the activation of the IGF-I signaling pathway via a high concentration of insulin through cross-activation of IGF-1R and therefore modified cell growth, differentiation and transformation, and cancer development. Insulin/IGF-I hybrid receptors, which are composed of an IR \( \alpha \beta \)-dimer and an IGF-I receptor \( \alpha \beta \)-dimer, are also expressed in tissues where cells co-express IRs and IGF-I receptors, including mammalian tissues (150). Results from functional studies with purified insulin/IGF-I hybrid receptors indicate that they behave like IGF-I receptors rather than IRs, because they bind IGF-I with an affinity similar to that of the IGF-I receptor, whereas they bind insulin with a much lower affinity (151). The insulin/IGF-I hybrid is overexpressed in breast cancer tissues (151) as well as in adipose tissues and skeletal muscle of patients with type 2 diabetes (152, 153). Thus, IGF-I may influence breast cancer development among diabetic patients by activating overexpressed insulin/IGF-I hybrid receptors. Despite the biological plausibility, the influence of diabetes on breast cancer through the IGF-I pathway is likely limited, given the uncertain effect of the IGF-I system on breast cancer risk, especially for postmenopausal women, among whom type 2 diabetes is most prevalent.

**DIABETES, ENDOGENOUS ESTROGEN, AND BREAST CANCER**

**Endogenous estrogen and breast cancer**

Estrogen is essential for the growth and development of the mammary gland and has been associated with the promotion and growth of breast cancer (154). Estrogen function is mediated through the intracellular estrogen receptor, which acts as a hormone-dependent transcriptional regulator (154, 155). The relation between endogenous steroid hormones and breast cancer risk among postmenopausal women has been assessed in ≥14 prospective studies (156–169) from 9 study groups, all but a few of which (157, 162, 165, 169) have provided supportive evidence of a positive association between endogenous estrogen and breast cancer risk. In a recent pooled analysis of prospective
studies, the highest quintile of estradiol was associated with a relative risk for breast cancer among postmenopausal women of 2.58 (95% CI: 1.76, 3.78) compared with the lowest quintile; the magnitude of risk associated with other estrogens was similar (79). The association of endogenous estrogen and premeno-
pausal breast cancer has been assessed in fewer studies because of the difficulty of assessing endogenous estrogen concentra-
tions, which highly fluctuate throughout the menstrual cycle. Results from previous studies have collectively suggested some-
what higher prediagnostic circulating estrogen concentrations among breast cancer cases than among women free of breast
cancer, but the differences were not statistically significant and were inconsistent among the follicular and luteal phases (44, 165, 166, 170–172).

Possible role of estrogen in the association between
diabetes and breast cancer

The influence of insulin resistance on estrogen is complex. In
patients with type 2 diabetes, hyperinsulinemia and hyperglyce-
mia have generally been related to an inhibition of aromatase
activity, which down-regulates estrogen (173). Nonetheless, in-
sulin is also an important regulator of sex hormone–binding
globulin (SHBG) in the liver. In the hyperinsulinemic state,
SHBG is suppressed, and free available estrogen concentrations
may be elevated (174). Furthermore, IGF-I stimulates the pro-
duction of androgens in the ovarian stroma, and testosterone may
competitively displace estrogens from SHBG (175).

Cross-talk between the IGF-I signaling system and estrogen
activity has also been found on many levels: estradiol alters the
expression of almost all components of the IGF-I system; the
ligand-bound estrogen receptor binds to and activates IGF-1R
directly; IGF-I signaling enhances estrogen receptor activation
by inducing phosphorylation of the estrogen receptor; and IGF-I
and estrogen have synergistic effects on the cell cycle signaling
cascade and proliferation (176). Because the IGF-I system can be
cross-activated by insulin, the synergetic effects of IGF-I and
estrogen may also play a role in the etiology of breast cancer in
the hyperinsulinemic state of type 2 diabetes (177, 178).

If alterations of endogenous estrogen concentrations indeed
play an important role in the association of type 2 diabetes with
the risk of breast cancer, this association is expected to be stronger
for tumors that are estrogen receptor positive. Future studies are
warranted to further assess breast cancer according to hormone
receptor status to better understand the influence of insulin
resistance on endogenous estrogen activity and on the etiology of
breast cancer.

CONCLUSION

The combined evidence from epidemiologic studies suggests
a modest link between type 2 diabetes and breast cancer inci-
dence. A meta-analysis of all available studies indicates that
women with a history of diabetes have an ≈16% higher risk of
developing breast cancer than do nondiabetic women, and this
risk was most pronounced among postmenopausal women and
those with type 2 diabetes. Diabetes may affect the risk of breast
cancer by altering hormones, such as the signaling of insulin, the
insulin-like growth factor system, and steroid sex hormones. An
alternative explanation may be residual confounding by obesity
or a sedentary lifestyle. Current evidence supports a healthy
lifestyle, including maintaining a healthful body weight, regular
physical activity, and a healthy diet, to counter the growing
epidemic of obesity, type 2 diabetes, and possibly breast cancer.
Future studies are warranted to clarify the underlying mechanism
of the association between type 2 diabetes and breast cancer,
to explore the association between metabolic syndrome and breast
cancer, and to develop effective intervention programs to prevent
diabetes and breast cancer by promoting a healthy lifestyle.

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