
Diabetes Mellitus and Breast Cancer

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Abstract

Over the past decades, type 2 diabetes mellitus has become a major health problem and is now affecting more than 7% of the adult population in developed countries. Diabetes mellitus commonly occurs together with breast cancer and two of the major risk factors for type 2 diabetes, older age and obesity, are also associated with breast cancer. At least four mechanisms may associate diabetes mellitus and breast cancer: activation of the insulin pathway, activation of the insulin-like growth factor pathway, altered regulation of endogenous sex hormones and altered regulation of adipocytokines. Comparative cohort studies and case-control studies suggest that type 2 diabetes mellitus is associated with 10–20% excess risk of breast cancer. Gestational diabetes mellitus, but not type 1 diabetes mellitus, might also be associated with excess risk of breast cancer. Diabetes mellitus and its complications can adversely affect screening utilization and cancer therapy, and clinical studies suggest an association between diabetes and adverse breast cancer characteristics and inferior outcome. Interestingly, several antidiabetic therapies, including the biguanides and the peroxisome proliferator-activated receptor γ ligands may also have activity against breast cancer and are being tested in clinical trials.

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Breast cancer is the most common malignant neoplasm in women, affecting 1 of every 8 women. The estimated new breast cancer cases and deaths among women in the USA in 2007 are 178,000 and 40,000 respectively [1]. Type 2 diabetes is another major health problem in developed countries, and affects about 7% of adults and about 15% of people older than 60 years [2]. The main risk factors for type 2 diabetes are old age, obesity, and genetic predisposition. Similarly to type 2 diabetes, the incidence of breast cancer rises with age, and the cumulative incidence in Western Europe and the USA is about 2.7% by age 55, about 5.0% by age 65, and about 7.7% by age 75. Breast cancer is associated with multiple risk factors, which are commonly divided into modifiable and non-modifiable. Non-modifiable risk factors include family history of breast cancer, germline mutations in breast cancer susceptibility genes including BRCA1, BRCA2,

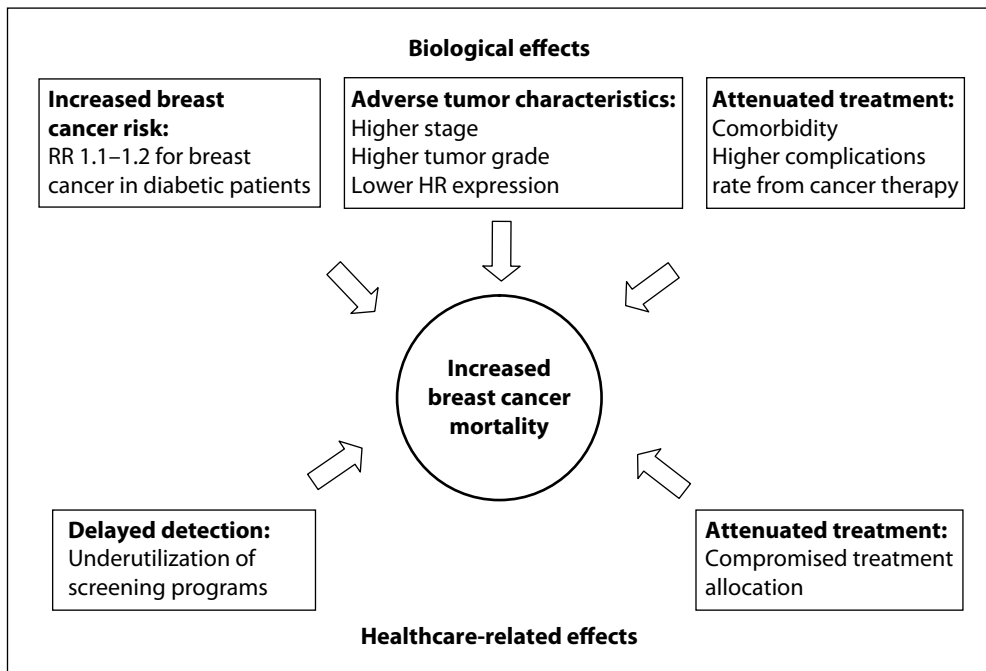


Fig. 1. Schematic representation of biological and health-related factors on breast cancer outcome. RR = Relative risk; HR = hormone receptors.

P53, PTEN, and ATM, hormonal factors such as younger age at menarche and older age menopause, and the presence of benign breast disease [3]. Modifiable risk factors include low parity, use of oral contraceptives and hormone replacement therapy, alcohol consumption, obesity, and lack of physical activity [3].

Breast cancer and diabetes commonly occur together, and up to 16% of older breast cancer patients may suffer from diabetes [4]. An association between diabetes and various types of cancer was first reported more than 100 years ago and diabetes is now recognized as a risk factor for several types of cancer, including endometrial and pancreatic carcinoma [5]. In recent years, a growing number of data, both laboratory and clinical, suggest complex associations between type 2 diabetes mellitus and breast cancer (fig. 1). Diabetes may have direct biologic effects on breast cancer risk, clinical and pathological characteristics, and outcome. Moreover, certain antidiabetic therapies may have direct activity against breast cancer. Diabetes may also affect breast cancer outcome indirectly, and have been shown to influence medical decision-making regarding screening and management of breast cancer.

Obesity, which affects more than 20% of the population in developed countries, is a major risk factor for the development of type 2 diabetes. It is also a well-established risk factor for breast cancer and is associated with increased risk for the development

of postmenopausal breast cancer, but with reduced breast cancer risk among premenopausal women [6]. Obesity is also a poor prognostic factor and is associated with adverse outcomes in both pre- and postmenopausal women with breast cancer. Mechanisms connecting obesity to postmenopausal breast cancer include altered regulation of estrogen and adipocytokines levels, and increased insulin synthesis. Thus, obesity is a major confounding factor in many studies regarding the association between diabetes and breast cancer.

Diabetes Mellitus and Breast Cancer: Possible Associating Mechanisms

Four major mechanisms may contribute to the association between type 2 diabetes mellitus and breast cancer (fig. 2): activation of the insulin pathway, activation of the insulin-like growth factor (IGF)-1 pathway, altered regulation of endogenous sex hormones, altered regulation of adipocytokines.

The Insulin Pathway and Breast Cancer

Insulin is a polypeptide hormone secreted from pancreatic β -cells in response to elevation in glucose levels [7]. The first step in activation of the insulin pathway is binding of insulin to the insulin receptor (IR). The primary targets for insulin are skeletal muscle, adipose tissue and the liver, however many other tissues, including normal breast tissue and breast cancer, express the IR. The IR is a tyrosine kinase receptor, composed of two extracellular α -subunits and two transmembrane β -subunits. Insulin binding leads to autophosphorylation of tyrosine residues in the intracellular subunits and thus activates the tyrosine kinase. Once activated, the IR phosphorylates a number of intracellular proteins, including members of the insulin receptor substrate family (IRS) and SHC adaptor protein. Binding of IRS to the IR leads to activation the phosphatidylinositol 3-kinase (PI3K), which turns on the Akt pathway. Binding of Shc to the IR leads to activation of the extracellular signal-regulated kinase (ERK) cascade, one of the mitogen-activating protein kinase (MAPK) pathways [8]. Although the major role of insulin is metabolic, both the Akt and the MAPK pathways also have important roles in tumorigenesis. Indeed, insulin was found to stimulate cell cycle progression in MCF-7 breast cancer cells either by itself or synergistically with estradiol [9]. IRS-1 may also interact directly and activate the estrogen receptor (ER). Thus, activation of the insulin pathway may also affect the ER pathway [10].

The IR has a major role in the activation of the insulin pathway in breast cancer. The IR is expressed and can be stimulated by insulin in breast cancer cell lines, and overexpression of it can induce malignant transformation in breast epithelial cell lines. Stimulation by progestins, inactivation of p53 or activity of oncogenes such as Wnt-1, Neu and Ret can lead to overexpression of the IR in breast cancer [11].

Several clinical studies have investigated the role of the insulin pathway, and mainly the part played by the IR, in breast cancer. Papa et al. [12] measured IR content

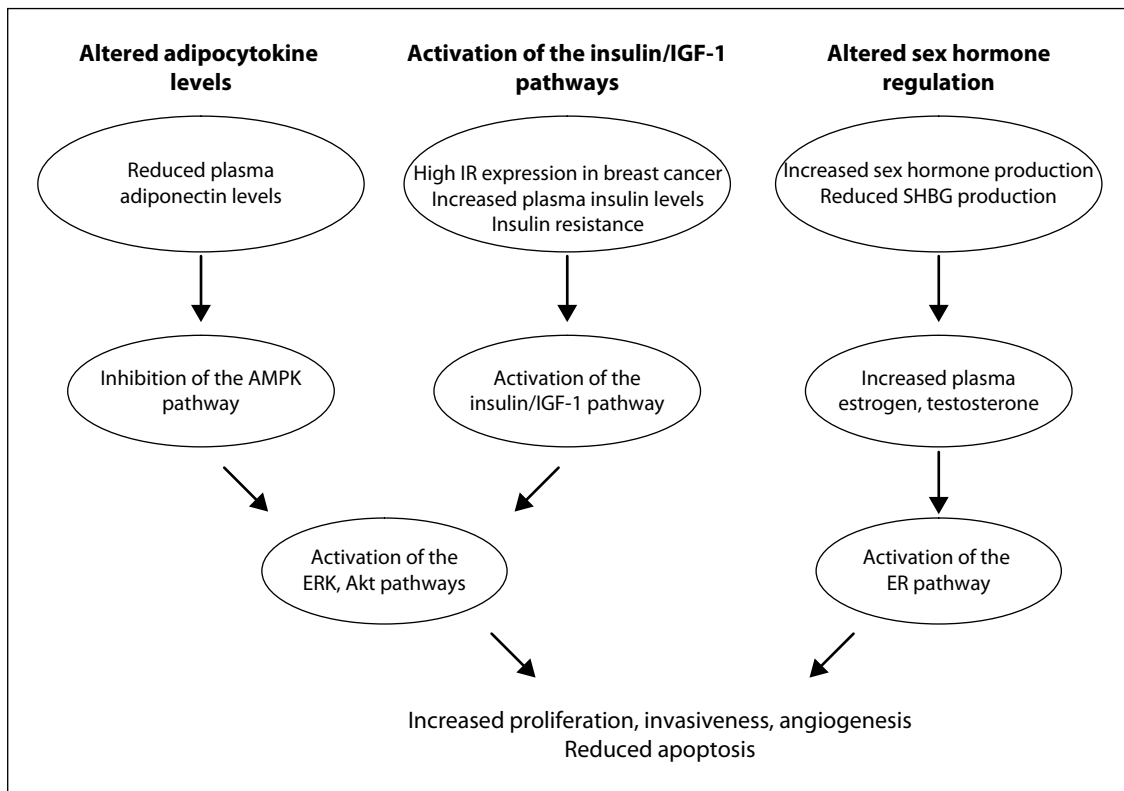


Fig. 2. Mechanisms associating type 2 diabetes and breast cancer. Insulin resistance leads to high plasma insulin concentrations, which activate the extracellular-related-kinase (ERK) and the AKT pathways through activation of the insulin receptor (IR) or the insulin-like-growth-factor-1 (IGF-1) receptor. High expression of the insulin receptor in breast cancer augments activation of these pathways. Diabetes is associated with reduced adiponectin plasma levels, which inhibits the AMP kinase (AMPK) and activates the ERK and Akt pathways in breast cancer cells. Diabetes increases production of sex hormones and decreases sex hormone binding globulin (SHBG) production, leading to high plasma-free estrogen concentrations, which in turn activate the estrogen receptor (ER). Activation of these pathways can lead to proliferation, invasiveness, angiogenesis and decreased apoptosis.

in 159 breast cancer specimens and found it to be sixfold higher than in 33 samples of normal breast tissues, and also higher than in other normal tissues, including the liver. High IR content correlated positively with tumor size, grade and ER content. Mathieu et al. [13] found detectable IR levels in 444 of 584 (76%) breast cancer specimens and found it to be a strong predictor of disease-free survival. Similarly, analysis of IR expression in a cohort of 191 early breast cancer patients revealed an association between high IR expression and favorable prognostic factors and improved disease-free and overall survival [14].

An important evidence for the adverse role of insulin on breast cancer comes from a recent report by Goodwin et al. [15] who found, in a prospective study of 512 early stage breast cancer patients, a direct association between fasting insulin levels and cancer recurrence and death (hazard ratio (HR) of 2.0 and 3.1 respectively for highest vs. lowest insulin quartile). The patients in the study were all non-diabetic and probably had lower insulin levels than diabetic patients. Whether the findings of this study are applicable to diabetic patients remains to be seen.

The IGF Pathway as a Possible Link between Diabetes and Breast Cancer

The IGF system comprises a network of ligands (IGF-1 and IGF-2), which are highly homologous to insulin; IGF-1 receptor (IGF-1R), which shares 55% homology with the IR; and IGF-binding proteins (IGF-BPs) [16]. The IR and the IGF-1R are capable of forming a hybrid receptor, which, like the IGF-1R, show high affinity to IGF-1 and lower affinity to insulin. Activation of the IGF-1R by its ligand results in activation of the same proteins and pathways activated by the insulin and IR, i.e. the IRS, SHC adaptor proteins, PI3K and MAPK. Thus, the specificity of the IGF pathway depends mainly on the ligand and its receptor, and not on the downstream parts of the cascade. The IGF system is considered to be a key regulatory pathway in breast cancer and is an attractive target for the development of novel breast cancer therapies. High circulating levels of IGF-1 and IGF-BP3 are associated with increased risk of premenopausal breast cancer, and increased IGF-1 is considered to be a link between obesity to increased risk of breast cancer [17]. However, type 2 diabetes usually affects postmenopausal women and, controlled for obesity, blood concentrations of IGF-1, IGF-2, and their binding proteins are usually not raised and may actually be reduced in both type 2 diabetes mellitus and the metabolic syndrome [18]. These findings suggest that the IGFs and the IGF-BPs may not play a major role in the association between diabetes and breast cancer. A high concentration of insulin could stimulate the IGF pathway in type 2 diabetes through the non-specific activation of the IGF-1R and the IGF-1R/IR hybrid receptor. However, the importance of this mechanism in the pathogenesis of breast cancer remains to be defined.

Altered Sex Hormone Regulation as a Possible Link between Diabetes and Breast Cancer

High endogenous plasma levels of estrogens and androgens and low plasma levels of sex hormone binding globulin (SHBG) are strongly associated with breast cancer risk in postmenopausal women. Obesity, a breast cancer risk factor, is characterized by increased production of sex hormones in the adipose tissue and decreased liver production of SHBG levels [6]. A meta-analysis of 43 prospective and cross-sectional studies, comprising 6,974 women, indicated lower levels of SHBG and higher levels of estrogen and testosterone among patients with type 2 diabetes, compared to controls, even after adjustment for obesity [19]. Thus, deregulation of sex hormones may be an important link between diabetes and breast cancer.