

Diabetes mellitus and breast cancer

Ido Wolf, Siegal Sadetzki, Raphael Catane, Avraham Karasik, Bella Kaufman

Type 2 diabetes is a serious health problem that affects more than 7% of adults in developed countries. Up to 16% of patients with breast cancer have diabetes, and two major risk factors for type 2 diabetes—old age and obesity—are also associated with breast cancer. Three mechanisms have been postulated to associate diabetes with breast cancer: activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and regulation of endogenous sex hormones. Comparative cohort studies and case-control studies suggest that type 2 diabetes may be associated with 10–20% excess relative risk of breast cancer. Gestational diabetes mellitus, but not type 1 diabetes, might also be associated with excess risk of breast cancer. Moreover, diabetes and its complications can adversely affect cancer therapy and the use of screening, which will thus affect the outcome of patients with breast cancer.

Diabetes mellitus consists of a group of metabolic diseases characterised by hyperglycaemia. Type 1 diabetes, which accounts for about 5–10% of patients, is a state of absolute deficiency of insulin caused by autoimmune destruction of pancreatic β cells.¹ Type 2 diabetes, which accounts for more than 90% of cases, is a high insulin state caused by insulin resistance in fat and muscle tissues and leads to an inadequate, compensatory increased production of insulin (figure 1). Decompensation of β cells and low absolute insulin concentrations eventually develop in type 2 diabetes, but only in later stages of disease.^{1,2}

Type 2 diabetes is a major health problem in developed countries, and affects about 7% of adults and about 15% of people older than 60 years.³ The main risk factors are old age, obesity, and genetic predisposition.^{1,2}

Breast cancer is the most common malignant neoplasm in women, affecting one in nine women.⁴ Incidence rises with age and is associated with hormonal factors, benign breast disease, family history of breast cancer, and genetic factors.⁴ Obesity, which affects more than 20% of the population in developed countries, is another known risk factor for breast cancer and is associated with increased risk of postmenopausal breast cancer.⁵ Up to 16% of patients with breast cancer who are older than 65 years also have diabetes mellitus.⁶ Thus, the incidence of both breast cancer and type 2 diabetes is high in elderly people and both share a common risk factor—obesity.

Association between diabetes mellitus and various types of cancer was first reported more than 100 years ago, and diabetes is now a recognised risk factor for several types of cancer, including endometrial cancer and pancreatic carcinoma.⁷ Preclinical and clinical data suggest complex associations between diabetes, especially type 2 diabetes, and breast cancer. These associations include the biological effects of diabetes on breast-cancer risk and natural history, and the effects of diabetes on medical-decision making about screening and management of breast cancer. Here, we discuss mainly type 2 diabetes and try to distinguish between the effects of diabetes itself to those of confounding factors such as obesity and age.

Possible associations

Three mechanisms are thought to contribute to the association between type 2 diabetes and breast cancer: activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and impaired regulation of endogenous sex hormones.

The insulin pathway

Insulin is a polypeptide hormone secreted from pancreatic β cells in response to raised glucose concentrations.^{2,8} The first step in activation of the insulin pathway is the binding of insulin to the insulin receptor (IR, figure 2). The main targets for insulin are skeletal muscle, adipose tissue, and the liver; however, many other tissues—including healthy breast tissue and breast-cancer cells—express IR. IR is a tyrosine kinase that consists of two extracellular α subunits and two transmembrane β subunits. The binding of insulin leads to autophosphorylation of tyrosine residues in the intracellular subunits and activation of the tyrosine kinase. Once activated, IR phosphorylates several intracellular proteins, including members of the insulin receptor substrate (IRS) family and the SHC adaptor

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Institutes of Oncology (I Wolf MD, R Catane MD, B Kaufman MD) and Endocrinology (A Karasik MD), Chaim Sheba Medical Center, Cancer and Radiation Epidemiology Unit, Gertner Institute (S Sadetzki MD); and Sackler Faculty of Medicine, Tel Aviv University, Israel

Correspondence to: Dr Ido Wolf, Institute of Oncology, Sheba Medical Center, Tel-Hashomer, 52621 Israel
wolfi@cshs.org

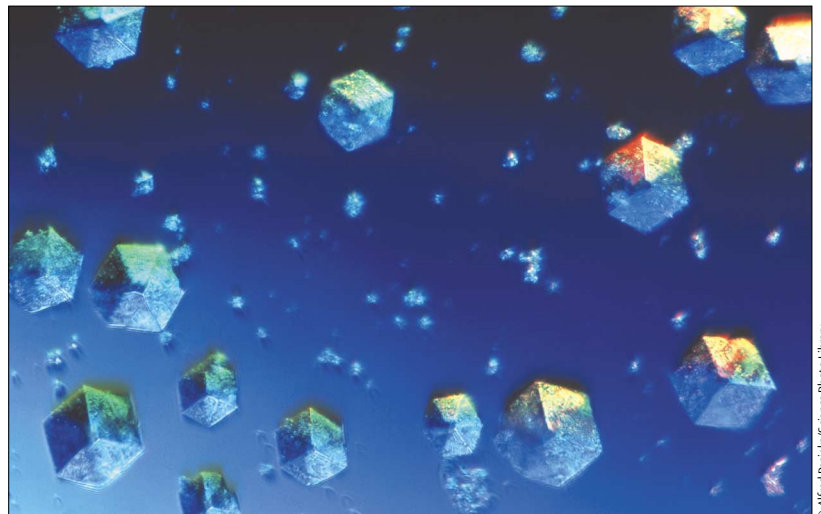


Figure 1: Crystalline structure of insulin

protein 1. Binding of an IRS to IR activates phosphatidylinositol 3-kinase, which in turn activates the AKT pathway. Binding of SHC adaptor protein 1 to IR activates the extracellular-signal-regulated-kinase (ERK) cascade, one of the mitogen-activated protein kinase (MAPK) pathways.^{2,8} Although insulin signalling has a metabolic role, both the AKT and ERK pathways also have important roles in tumorigenesis.^{9,10} Indeed, insulin was found to stimulate cell-cycle progression in MCF-7 breast-cancer cells by itself or synergistically with oestradiol.¹¹

IR has an important role in the activation of the insulin pathway in breast cancer. It is expressed in, and can be stimulated by, insulin in breast-cancer cell lines.¹² Moreover, overexpression of IR can induce malignant transformation in breast epithelial cell lines.¹³ Stimulation by progestins, inactivation of P53, or the activity of oncogenes such as *WNT1*, *ERBB2*, and *RET* can lead to overexpression of IR in breast cancer.^{14–16}

Several clinical studies have investigated the role of the insulin pathway, and mainly the part played by IR, in breast cancer. More than 20 years ago, Benson and Holdaway¹⁷ reported substantial binding of insulin in 22 of 23 samples of breast cancer. The binding of insulin in breast cancer was not reduced, even in the presence of high serum concentrations of insulin. Thus, by contrast with adipose tissue, breast-cancer tissue showed diminished downregulation of IR in response to insulin. Papa and colleagues¹⁸ found that the concentration of IR was six-fold higher in 159 samples of breast cancer than in 33 samples of healthy breast tissue; concentrations of IR were also higher in breast-cancer tissue than in other healthy tissue, including the liver. High IR concentration correlated with tumour size, grade, and oestrogen-receptor concentration. Mathieu and colleagues¹⁹ found detectable concentrations of IR in 444 of 584 (76%) breast-cancer samples and found expression to be a good predictor of disease-free survival. However, disease-free survival was decreased in a small subset of patients with very high IR concentrations. Goodwin and co-workers²⁰ did a prospective study of 512 patients with early-stage breast cancer and found a direct association between fasting insulin concentration, cancer recurrence, and death (hazard ratio 2.0 and 3.1, respectively, for highest vs lowest insulin quartiles). Patients in this study did not have diabetes and probably had lower insulin concentrations than did those with diabetes. However, whether the findings of this study are applicable to patients with diabetes remains to be seen.

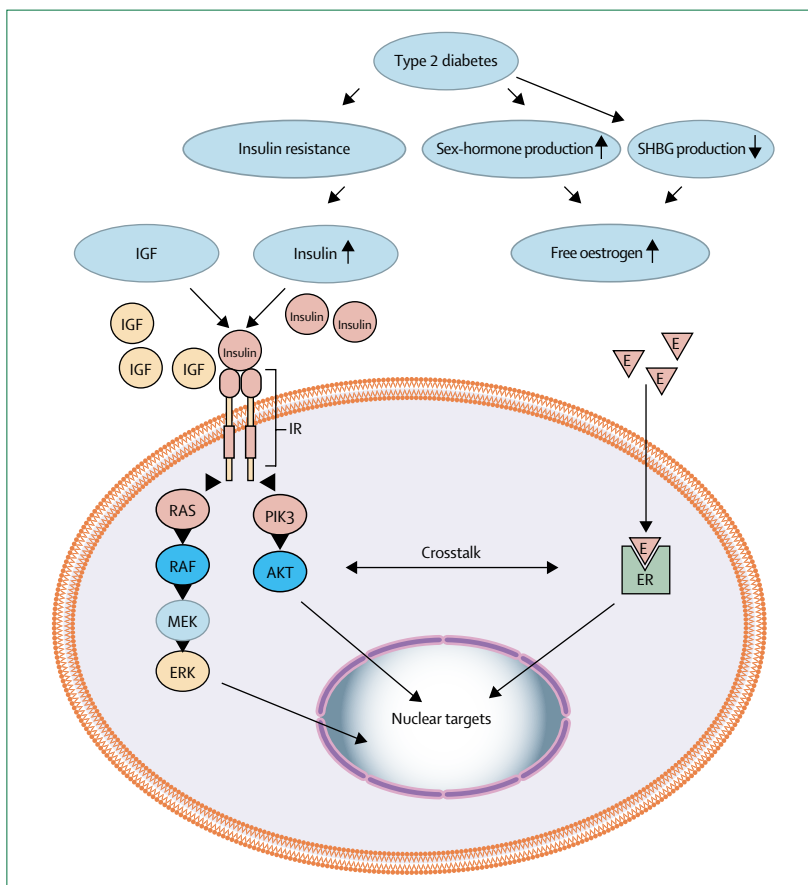


Figure 2: Activated signal transduction pathways in type 2 diabetes also involved in breast cancer
Insulin resistance leads to high plasma insulin concentrations, which activate the extracellular-related-kinase cascade and the AKT pathway through activation of the insulin receptor or the insulin-like-growth-factor (IGF) receptor. High expression of the insulin receptor in breast cancer augments activation of these pathways. Diabetes mellitus increases production of sex hormones and decreases sex hormone binding globulin (SHBG) production, leading to high plasma-free oestrogen concentrations, which in turn activate the oestrogen receptor (ER). Activation of these pathways can lead to cell-cycle progression and decreased apoptosis.

Insulin-like growth factors (IGF) pathway

This pathway consists of a network of ligands (IGF1 and IGF2), insulin-like growth factor binding proteins (IGF-BP), and the IGF1 receptor (IGF1R).^{21,22} IGF1 and IGF2 are highly homologous to insulin and IGF1R shares 55% homology with IR.^{21,22} IGF1R and IR can form hybrid receptors, which, like IGF1R, have high affinity with IGF1 and low affinity with insulin.²² Activation of IGF1R by IGF1 activates the same proteins and pathways that are activated by insulin and IR—ie, the IRS family, SHC adaptor protein 1, phosphatidylinositol 3-kinase, and ERK (figure 2). Therefore, the specificity of the IGF pathway depends mainly on the ligand and its receptor and not on the downstream parts of the cascade.²² The insulin-like-growth-factor system is thought to be a key regulatory pathway in breast cancer.²¹ High circulating concentrations of IGF1 and IGF-BP3 are associated with increased risk of premenopausal breast cancer,²³ and increased IGF1 is thought to be an important link between obesity and increased risk of breast cancer.²⁴ However, type 2 diabetes usually affects postmenopausal women and, controlled for obesity, blood concentrations of IGF1, IGF2, and their binding proteins are usually not raised in patients with diabetes,^{25,26} suggesting that these

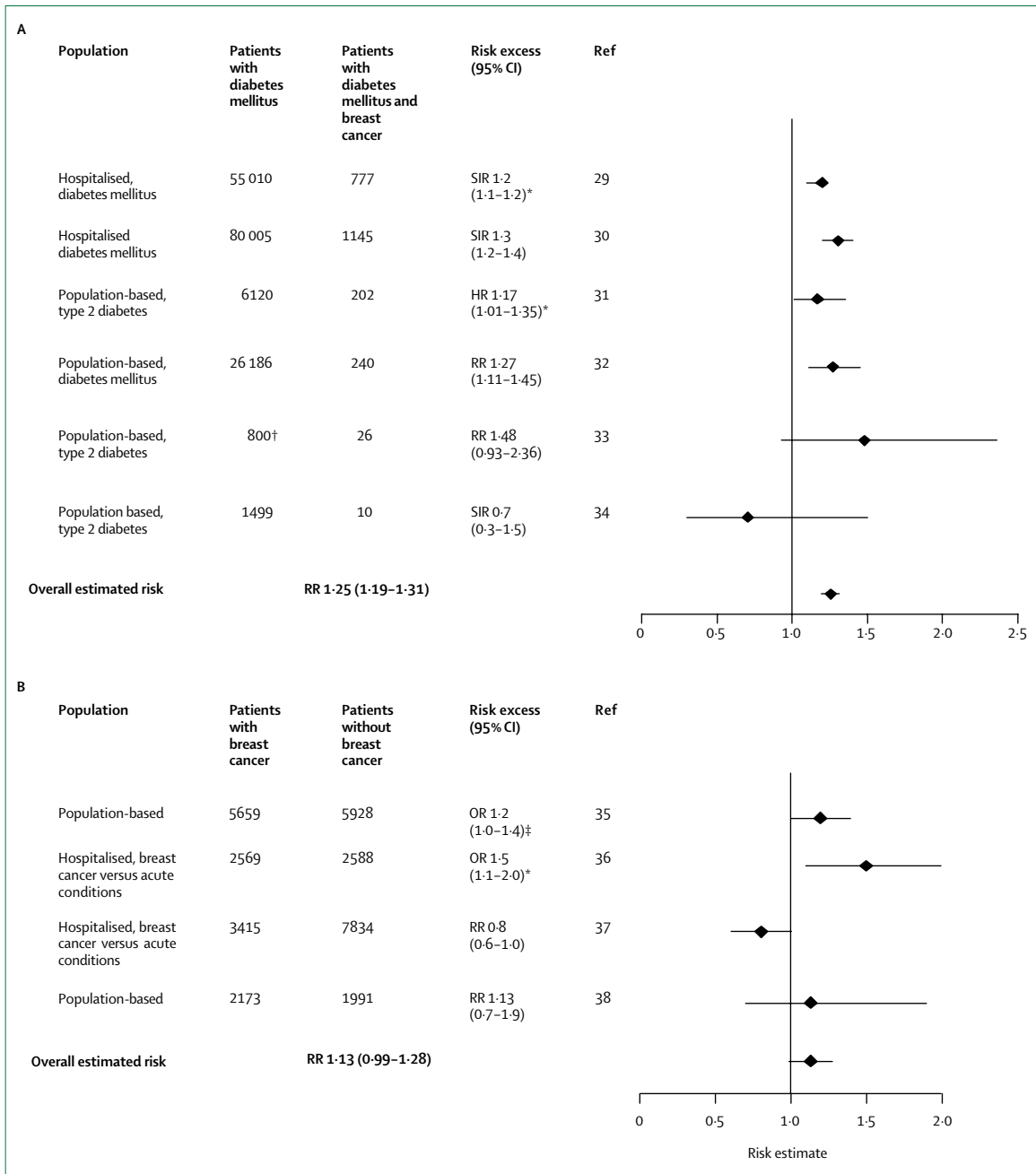


Figure 3: Diabetes and risk of breast cancer

(A) Cohort studies. (B) Case-control studies. SIR=standardised incidence ratio. HR=hazard ratio. RR=relative risk. OR=odds ratio. *Significant only for postmenopausal women. †6463 years at risk. ‡Significant only for women older than 35 years.

growth factors might not have a direct 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 IGF1R and the IGF1R/IR hybrid receptor.^{21,22} However, the importance of this mechanism in the pathogenesis of breast cancer remains to be defined.

Sex-hormone regulation

High endogenous plasma concentrations of oestrogens and androgens, as well as low plasma concentrations of sex hormone binding globulin (SHBG) are strongly associated with breast-cancer risk in postmenopausal women.²⁷ Deregulation of plasma concentrations of sex hormones, caused by increased production of oestradiol and androgens combined with decreased liver

production of SHBG, has been suggested as the main mechanism that connects postmenopausal obesity and breast-cancer risk.²⁴ Similar changes in concentrations of sex hormones and SHBG are found in women with diabetes, and these changes remain significant even after adjustment for obesity.²⁸

Diabetes mellitus and risk of breast cancer

Different strategies have been used to define the possible association between diabetes mellitus and breast-cancer risk. We divided these studies into three categories: cohort and case-control studies that type 2 diabetes; those that assessed blood concentrations of insulin-resistance markers (eg, glucose or insulin); and those that assessed other conditions, such as type 1 diabetes and gestational diabetes mellitus.

Cohort studies

Six cohort studies that measured the incidence of breast cancer in patients who had diabetes met our selection criteria (figure 3A). These studies vary substantially in sample size (from 800 to more than 80 000 patients with diabetes), inclusion criteria (all diabetics or only type 2), population (hospitalised or ambulatory, population-based or sample) and years of the study (1965–96). Four studies^{29–32} reported a modest but significant enhanced breast-cancer risk in patients with diabetes. Two studies included all hospitalised patients diagnosed with diabetes: in Denmark in 1977–89²⁹ and in Sweden in 1965–83.³⁰ Both reported a greater risk of breast cancer in patients who had diabetes compared with the general population (standardised incidence ratios 1.2 [95% CI 1.1–1.2] and 1.3 [1.2–1.4], respectively). However, the results of these studies should be interpreted with caution: use of hospitalisation records and of former definitions of diabetes meant that both studies included patients with severe type 2 diabetes that would not be included with current definitions and did not exclude patients with type 1 diabetes. Moreover, neither study adjusted properly for obesity or for other risk factors for breast cancer such as menopausal status, parity, family history of breast cancer, and use of screening.

Michels and co-workers³¹ found an association between type 2 diabetes and breast cancer in the Nurses' Health Study, a prospective population based study. Use of a prospective database allowed the researchers to control for several confounding factors, including age, obesity, reproductive factors, and benign breast disease, and to find a modest but significant risk of breast cancer in postmenopausal women with diabetes (hazard ratio 1.17 [95% CI 1.01–1.35]). Coughlin and colleagues³² analysed cancer mortality from another large prospective cohort, the Cancer Prevention Study II, which consisted of about 590 000 women. 16 years after enrolment, patients with diabetes had significantly higher breast-cancer mortality (relative risk 1.27, 95% CI 1.11–1.45). The risk was adjusted for several confounding factors

such as age, obesity, and reproductive factors but not for others such as benign breast disease or use of screening. Mortality is representative not only of incidence, but also of differences in natural history, diagnosis, and treatment between patients with breast cancer who had diabetes and those who did not have diabetes, and thus may not give accurate measurements of incidence. Other limitations of this study include the use of self-reported information about history of diabetes and the inclusion of both type 1 and type 2 diabetes.

Mink and colleagues³³ also analysed data from a prospective, population-based study, the Atherosclerosis Risk in Communities Study, and found higher incidence of breast cancer in patients with diabetes (relative risk 1.48, 95% CI 0.93–2.36) compared with those who did not have the disease. The association was attenuated by adjustment for obesity and other factors for risk of breast cancer, but the sample size (26 patients with breast cancer) was too small to detect small differences in cancer risk. No association between diabetes and breast cancer was found in another study,³⁴ but the number of patients with breast cancer was also very small—only ten. We did a pooled analysis of the six studies and found an estimated relative risk of 1.25 (95% CI 1.19–1.3). Thus, the results of the cohort studies might suggest that breast-cancer risk is increased in patients with type 2 diabetes. However, this excess risk is fairly small and some of the studies did not properly adjust for various confounding factors—including obesity. Therefore, the possibility that diabetes mellitus is an innocent bystander and not a mutually exclusive risk factor for breast cancer cannot be ruled out.

Case-control studies

The association between diabetes and breast cancer has also been assessed in several case control studies (figure 3B), which controlled for a range of confounding factors. Baron and colleagues³⁵ reported an association between diabetes diagnosed after age 35 years and breast cancer (odds ratio 1.2, 95% CI 1.0–1.4). An increased risk of breast cancer in postmenopausal women with diabetes (1.5, 1.1–2.0) was reported by an Italian group.³⁶ An earlier study³⁷ by the same group did not find an association between diabetes and breast cancer, although the frequency of diabetes was very low (4.1%), probably because of underdiagnosis of diabetes.³⁹ Weiss and co-workers,³⁸ who studied breast-cancer risk in young women who had other medical conditions, did not find any association between diabetes and breast cancer. However, only 33 of the 2200 patients with breast cancer who participated in the study had diabetes. Pooled analysis of these studies shows an odds ratio of 1.13 (0.99–1.28). Thus, the results of the case-control studies might also suggest a modest association between diabetes mellitus and risk of breast cancer.

Insulin-resistance markers and breast cancer

Eight studies^{33,39–45} have investigated the association between breast-cancer risk and fasting plasma concentrations of glucose, insulin, and C-peptide—all indirect markers of insulin resistance (table 1). Three studies were large cohort studies^{33,40,41} and five were case-control studies.^{39,42–45} Of the three studies^{33,40,42} that measured fasting glucose, only one case-control study⁴² reported an association between fasting glucose concentrations and breast-cancer risk, whereas two large cohort studies^{33,40} did not show an association. The study reporting an association found it was significant only in premenopausal women and the confidence interval was very wide.⁴² Only one⁴³ of the five studies^{33,41–44} that measured insulin reported a significant association with breast-cancer risk. However, in this case-control study of premenopausal women, the results were adjusted only for age and weight and the confidence interval was very wide. A cohort study⁴¹ reported a linear association between insulin concentrations and breast-cancer risk but reached only borderline significance after adjustment for several risk factors.

Two studies^{39,45} found an association between concentrations of C-peptide and high risk of breast cancer. However, these studies did not properly control for other confounding factors and had very wide confidence intervals. Thus, although four of five case-control studies reported significant associations between different variables and breast-cancer risk, none of the three cohort studies reported a significant association. Differences between cohort studies and case-control studies could have resulted from a bias in the selection of patients and from no adjustment for several risk factors in the case-control studies. Furthermore, the lack of more case-control studies that reported negative results raises the possibility of publication bias. In our opinion, the available data is insufficient to suggest an association between blood concentrations of insulin-resistance markers and breast-cancer risk.

Risk in subgroups

Despite study of only small numbers of patients, a significant association between breast cancer in men and type 2 diabetes was reported in a cohort study³⁰ and in a large case-control study (table 2).⁴⁶ This association seems to be stronger compared with breast cancer in women and suggests a particular importance for the insulin pathway in the pathogenesis of breast cancer in men.

Gestational diabetes mellitus is the state of insulin resistance closely related to type 2 diabetes mellitus and women with this disorder are at high risk of developing type 2 diabetes. A cohort study⁴⁷ of patients with gestational diabetes mellitus found that high plasma glucose concentrations during pregnancy were associated with up to a 10.7 increase in relative risk of breast cancer 18 years later.

Type of study	Patients with breast cancer/ patients without breast cancer	Risk excess (95% CI)	Ref
Fasting glucose			
Cohort	187/7894	RR 1.23 (0.88–1.71)	33
Cohort	369/9738	RR 1.05 (0.67–1.63)	40
Case-control	144/503	RR 2.8 (1.18–6.46)*	42
Insulin			
Cohort	187/7894	RR 1.01 (0.55–1.86)	33
Cohort	147/3690	OR 1.35 (1.0–1.81)	41
Case-control	144/503	RR 1.7 (0.7–4.1)	42
Case-control†	99/99	OR 3.72 (1.32–10.47)	43
Case-control	45/393	RR 1.0 (0.97–1.03)	44
C-peptide			
Case-control	223/441	RR 2.9 (1.7–5.1)	39
Case-control	143/143	OR 2.9 (1.1–8.0)*	45

RR=relative risk. OR=odds ratio. *Significant only for premenopausal women. †Included only premenopausal women.

Table 1: Association between insulin-resistance markers and breast-cancer risk

Sellers and colleagues⁴⁸ found no association between breast cancer and family history of diabetes. However, in view of the modest increased risk for patients with diabetes, this finding is not surprising.

Two studies^{34,49} found no association between breast cancer and type 1 diabetes, one of which³⁴ included more than 29 000 patients with type 1 diabetes.

Effects of diabetes mellitus on outcome, diagnosis, and treatment

Diabetes can change the outcome of cancer either directly, through biological mechanisms, or indirectly, by affecting the use of screening and treatment allocation. Direct biological effects probably account for the inadequate outcome for patients with diabetes who have pancreatic cancer⁵⁰ and hepatocellular carcinoma.⁵¹ Meyerhardt and co-workers⁵² analysed data from a large randomised controlled trial of adjuvant chemotherapy in colon cancer and showed that diabetes had direct adverse effects on recurrence and mortality for patients. These findings remained significant even after control for disease manifestations and treatment allocation.

The direct biological effects of diabetes for patients with breast cancer are difficult to define, mainly because of the presence of confounding factors such as obesity, old age, comorbidity, and differences in screening use or treatment allocation. These factors are associated with undertreatment and a worse outcome for patients with breast cancer.^{53,54} However, most studies on the effects of diabetes on breast-cancer outcome did not control for these factors. In a cohort of 936 patients with breast cancer, 112 (12%) of whom had diabetes, higher comorbidity was associated with higher mortality, even after control for variables such as age, stage, and grade.⁵⁵ Yancik and co-workers⁶ investigated the role of age and comorbidity in 1800 postmenopausal women with breast cancer and reported an enhanced all-cause mortality in patients with diabetes. However, about half the reported causes

Study type	Patients with breast cancer/patients without breast cancer	Risk excess (95% CI)	Ref
Male breast cancer			
Cohort	13/63 988	SIR 2.0 (1.0–3.4)	30
Case-control	156/468	OR 2.6 (1.3–5.3)	46
Type 1 diabetes mellitus			
Cohort	3/1659	SIR 0.8 (0.2–2.1)	34
Cohort	69/29 187	SIR 1.0 (0.8–1.3)	49
Gestational diabetes mellitus			
Cohort	18/753	RR 10.7 (1.34–85.0)	47
Family history of diabetes mellitus			
Cohort	1013/41 837	RR 0.9 (0.77–1.05)	48

SIR=standardised incidence ratio. OR=odds ratio. RR=relative risk.

Table 2: Association between diabetes mellitus and breast-cancer risk in subgroups

of death were not cancer related but could be affected by diabetes (eg, heart disease or cerebrovascular disease).

Fleming and colleagues,⁵⁶ who did similar analyses in a cohort of 848 elderly patients with breast cancer, did not find increased mortality in patients with diabetes. In a retrospective analysis of 176 patients with diabetes, Unterburger and colleagues⁵⁷ reported a correlation between diabetes and development of metastatic disease, but no adjustment for other prognostic factors or treatment methods was done. Guastamacchia and co-workers⁵⁸ found no association between diabetes and breast-cancer stage or hormone-receptor status; however, there was no adjustment for major confounding factors. We investigated the effects of type 2 diabetes on breast cancer at presentation in 79 consecutive patients with diabetes and breast cancer by comparison with 158 age-matched patients who did not have diabetes. We found that patients with diabetes present with breast cancer at a more advanced stage, a finding that could not be attributed to parity, family history of breast cancer, obesity, or other risk factors for breast cancer (Wolf I, unpublished data). However, more studies are needed to define further the effects of diabetes on breast cancer.

Treatment of diabetes mellitus and risk of breast cancer

Insulin treatment

Insulin treatment often results in very high plasma concentrations of insulin. However, despite the adverse effects in vitro and in vivo of insulin on breast cancer,^{11,20} no association between insulin treatment and breast-cancer risk has been reported. In a study⁵⁹ of 2720 patients with diabetes (most patients had type 2 diabetes) given insulin, no association between insulin treatment and cancer risk was found, irrespective of treatment duration or insulin dose. Furthermore, type 1 diabetes, which needs life-long use of insulin treatment, is not associated with increased incidence of breast cancer.^{34,49} The non-physiological, pulsating plasma

insulin concentrations after exogenous administration, and a possible need for other factors such as insulin-like growth factors, to operate in concert with insulin could explain the lack of clinically important effects of exogenous insulin on breast-cancer risk

Oral hypoglycaemic agents

Biguanide oral hypoglycaemic agents such as metformin and phenformin lower insulin concentrations by increasing insulin sensitivity and thus might have favourable effects on the treatment and prevention of breast cancer. This hypothesis was tested in a study⁶⁰ on the effects of long-term use of phenformin to female C3H/Sn mice, which are susceptible to breast cancer. The incidence of mammary carcinoma was 80% in treated mice, compared with 21% in the control group. The effectiveness of metformin as adjuvant treatment for early breast cancer is now being tested in a phase II trial. To date, no data support an association between the sulfonylurea oral hypoglycaemic agents and breast-cancer risk.

Peroxisome proliferator-activated receptor γ (PPAR γ)

PPAR γ is a member of the nuclear-hormone-receptor family.⁶¹ On binding to its ligand, it forms a heterodimer with the retinoid X receptor (RXR), and the activated heterodimer then acts as a transcription factor. PPAR γ is highly expressed in adipocyte tissue and most of its known target genes belong to lipid-metabolism pathways. However, many other tissues, including the breast, also express PPAR γ . Endogenous ligands for PPAR γ include polyunsaturated fatty acids and prostaglandin J₂; synthetic PPAR γ ligands include members of the thiazolidinedione family rosiglitazone, pioglitazone, and troglitazone. These synthetic ligands decrease insulin resistance and thus serve as antidiabetic drugs, although the use of troglitazone has been discontinued because of liver toxicity. The role of PPAR γ in cancer has been reviewed⁶¹ and most current data suggests a tumour-suppressor role for PPAR γ in breast cancer. Breast-cancer cells commonly express PPAR γ , and use of various PPAR γ ligands can inhibit proliferation and induce differentiation and apoptosis in in-vitro and in-vivo studies of breast cancer. These ligands also prevent carcinogen-induced transformation of breast tissue in mice.

Measurement of PPAR γ concentrations in 120 samples of breast-cancer tissue showed a lower expression than did samples of healthy breast tissue.⁶² Moreover, low expression of PPAR γ has been associated with advanced disease, high tumour grade, and more aggressive histology. Interestingly, forced overexpression of PPAR γ in the breasts of transgenic mice who are prone to mammary-gland cancer accelerates the development of breast tumours compared with wildtype mice, suggesting a possible role for PPAR γ in breast-cancer tumorigenesis.⁶³

Use of troglitazone as treatment for breast cancer has been tested in a phase II study⁶⁴ of 22 patients with refractory breast cancer; however none of these patients showed a response. Whether PPAR γ agonists have a role in the prevention or treatment of early-stage breast cancer remains unknown.

Screening of breast cancer in patients with diabetes

With current antidiabetic treatment, many patients with diabetes do not have additional comorbidity and thus may benefit from screening.⁶⁵ However, a study⁶⁶ in the USA reported that women with diabetes were significantly less likely to undergo screening mammography than were controls. The researchers suggested that both physicians and patients had a compromised attitude to preventive care in the setting of diabetes, and that the high costs of screening might also be a deterrent. Different results were reported by a study from the UK,⁶⁷ in which diabetes had no effect on the attendance to a cancer-screening programme. Importantly, this screening programme was free of charge and women were invited irrespective of coexisting comorbidity. Thus, implementation of an affordable, invitation-based screening programme for breast cancer has the potential to improve substantially the screening of patients with diabetes.

Breast-cancer treatment in patients with diabetes

Several well-known complications of diabetes, including nephropathy, neuropathy, heart disease, impaired wound healing, and susceptibility to infection, can adversely affect all forms of cancer therapy: surgical, radiation, chemotherapy, and hormonal therapy.

Surgery

Diabetes is associated with increased risk of complications after surgery for breast cancer. Analysis of 326 patients showed a strong association between diabetes and wound infection after breast surgery.⁶⁸ Diabetes is associated not only with immediate complications but also with ipsilateral upper arm dysfunction 5 years after mastectomy.⁶⁹

Radiotherapy

To our knowledge, there have been no studies on the association between diabetes and radiotherapy for breast cancer. However, diabetes is associated with increased risk of early and late complications of radiation.⁷⁰ In patients treated for cervical cancer, diabetes was associated with formation of rectovaginal fistula and bowel obstruction and, in elderly patients with prostate cancer given radiotherapy, with early and late gastrointestinal and genitourinary complications.⁷⁰ Diabetes might also be associated with radiation

morbidity in elderly patients with breast cancer, but this association remains to be proven.

Chemotherapy

To our knowledge, no study has reported on specific complications of chemotherapy in patients with breast cancer and diabetes. In a study⁷¹ of 33 patients with ovarian cancer and diabetes who were given cisplatin or paclitaxel, 21 (64%) had neurological symptoms and exacerbation of hyperglycaemia; treatment changes were needed in five patients. Another study⁷² has been reported on the toxic effects of fluorouracil in seven patients with diabetes that was poorly controlled; however, neither of these studies included a control group. Diabetes may accentuate other side-effects and complications of cancer chemotherapy. For example, patients with diabetes who have peripheral neuropathy are more prone to complications of vinca alkaloids or taxanes,⁷³ and those who have nephropathy or diabetic cardiomyopathy are probably more susceptible to complications from nephrotoxic or cardiotoxic medications. The possibility of severe complications from infection should also be considered.

The common use of high-dose glucocorticoids as part of antiemetic regimens can cause severe hyperglycaemia in patients with diabetes, who thus need close monitoring of their blood-glucose concentrations.⁷¹

Search strategy, selection criteria, and statistical analysis

Data for this review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms "diabetes mellitus and breast cancer", "diabetes mellitus and chemotherapy", "diabetes mellitus and radiation therapy", "diabetes mellitus and estrogen", "breast cancer and insulin", "breast cancer and IGF", "breast cancer and obesity", "breast cancer and comorbidity", "MCF7 and insulin", "breast cancer and PPAR γ ", "breast cancer and biguanides", and "breast cancer and sulphonylureas". Only papers published between 1980 and June, 2004, were included. For association of analysis we searched and identified studies published in English between 1992 and June, 2004. We included all studies that expressed their findings as either standardised incidence ratio, hazard ratio, odds ratio, or relative risk, with 95% CI. For calculation of overall estimates we used a fixed-effect model with precision (inverse-variance) weights. The overall point estimate was obtained as exponential of the point estimate of the overall log estimate. The overall log estimate was the weighted mean of the log of separate relative risks (or odds ratios for case-control studies). The weights were proportional to the reciprocal of the variance of the separate log estimates. This variance was taken to be a square of the length of 95% CI, divided by 3.92. The 95% CI for the overall estimate was obtained as the exponential of 95% CI for the overall log estimate.

Hormone therapy

Adverse interactions between hormone therapy and diabetes are probably uncommon. Tamoxifen use is associated with up to four-times increased risk of endometrial cancer, and several studies have also reported an up to 1.5 times increased risk of endometrial cancer in patients with diabetes.⁷⁴ However, no evidence suggests an enhanced risk of endometrial cancer in patients with diabetes who were treated by tamoxifen compared with those without diabetes. Acute pancreatitis due to severe hypertriglyceridaemia after tamoxifen treatment in patients with diabetes has been described,⁷⁵ but the frequency of this side-effect is not known and is probably very low. At present, there is no evidence for an interaction between aromatase inhibitors and diabetes.

Conclusion

Data suggest that type 2 diabetes might be associated with up to 10–20% excess risk for breast cancer and that it could also have detrimental effects on the natural history, diagnosis, and treatment of breast cancer. However, because most epidemiological studies have not properly adjusted for several confounding factors, including obesity, other factors, not diabetes, might account for these observations. Diabetes mellitus might adversely affect decisions regarding breast-cancer screening and treatment allocation. However, patients with diabetes can benefit from breast-cancer screening and should therefore participate in these programmes. Furthermore, patients with breast cancer and diabetes should be treated according to existing guidelines, although special care should be taken to keep to a minimum the risk of treatment complications in this unique subgroup. In the future, better understanding of the mechanisms involved in the association between type 2 diabetes mellitus and breast cancer could lead to the identification of new therapeutic targets for the prevention and treatment of breast cancer.

Conflict of interest

We declare no conflicts of interest.

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