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Research Article

Potential Factors for Affecting the Relationship between Mammary Cancer and Type 2 Diabetes Mellitus

Abdelaziz SI[1]* and Abarsi MA[2]

[1]*Associate Professor of Medicine, Consultant Internal Medicine and Endocrine, Soba University Hospital, University of Khartoum, Khartoum, Sudan*

[2]*Consultant Internal Medicine*

***Corresponding Author:** Abdelaziz SI, Associate Professor of Medicine, Consultant Internal Medicine and Endocrine, Soba University Hospital, University of Khartoum, Khartoum, Sudan.

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Abstract

Introduction: The prevalence type 2 diabetes mellitus (T2DM) in Sudanese women in 2016, was found to be 18.7%, while breast cancer (BC) constitutes 22.9% of all cancers in Sudan. The adult prevalence rate of obesity was 6.6%, which, is a known risk factor for both T2DM and breast cancer. Glucose is an essential element for the growth and maturation of tumor cells.

Aim: We studied the association between breast cancer and T2DM among Sudanese women and determined the common confounding factors.

Results: A total of 203 with breast cancer, who attended Radio Isotope Centre of Khartoum (RICK), represented the study group and a total of 311 patients, without breast cancer represented the control group. We found a significant association (19%) between breast cancer and diabetes [OR = 1.72, (P-value = 0.000), CI (0.704 - 1.871)] in Sudanese women.

Conclusion: Having diabetes mellitus and breast cancer might change the way physicians approach screening and treatment options.

Keywords: *T2DM; Breast Cancer; Sudanese Women*

Introduction

Type 2 diabetes is an increasing health problem in developed countries. It has been known to affect 7% of adults and about 15% of the population over 60 years of age [1]. The main risk factors are obesity, age and some genetic factors that predispose to the cancer [2,3]. In women, breast cancer is one of the most common malignancies, and affects one in nine ladies [4]. This incidence is found to be more as age progresses, changes in hormones, family history or pre-existing breast disease, as well as genetic factors [4]. Obesity is associated with increased risk of breast cancer in postmenopausal women [5]. It has also been noted that 16% of patients above 65 years with breast cancer were also diabetic [6].

Glucose is required for growth and provides energy for the proliferation of tumor cells [7], and hyperglycemia is associated with metastasis. An epidemiology study demonstrated that, in patients with cancer and T2DM, incidence of recurrence, metastasis, or fatal outcome is higher in patients with diabetes [8].

Hyperglycemia is associated with hyperinsulinemia which also promotes cancer progression by enhancing metabolic effect of cancer cells [9]. High levels of glucose and insulin affects the proliferation of the tumor cell lines MCF-7 (human breast adenocarcinoma) and MDA MB468 (human breast adenocarcinoma), [10], so, the addition of oral glucose, insulin injections, or both showed an increase in mammary tumor growth in rats [11].

Apoptosis, is out of control in cancer, hyperglycemia has been found to protect cancer cells from exhibiting apoptosis. On the other hand, Metformin, the first-line drug of choice for the treatment of T2DM, promotes apoptosis on some cancers (e.g., ovarian cancer, breast cancer, and lung cancer) by increasing the apoptotic genes [12-14]. However, cancer cell apoptosis induced by Metformin was prevented under high-glucose homeostasis in a carcinogen-induced rodent model of mammary tumorigenesis [15].

Introduction and literature review

Diabetes mellitus (DM) is an increasing and serious health problem with complications that affect the quality of life of affected patients. As of today, 330 million people have diabetes globally, and this is expected to increase to 380 million in the next coming 20 years. Type 2 diabetes accounts for 90-95% of diabetes cases, therefore, if diabetes is associated with a small risk of cancer, this results in important consequences in the population. A good number of studies, showed that diabetes mellitus (DM) is associated with an increased risk of several types of cancer, including breast cancer.

Cancer risk is increased in diabetic patients

A number of studies confirm that the risk for malignancies such as liver, pancreas, colorectal, kidney, bladder, endometrial and breast cancers, and non-Hodgkin's lymphoma is elevated in patients with diabetes. Type 2 diabetes mellitus has been recognized as a risk factor for liver and pancreatic cancer [16-18]. However, for prostate cancer, the incidence in diabetic patients is reduced.

Association between DM and breast cancer risk

Breast cancer is the second leading cause of cancer death among women [19]. The incidence of breast cancer has increased in the past 20 years. Incidence rises with increasing age and is associated with family history of breast cancer, menopause, and hormonal factors [20]. Obesity is another risk factor, which is one main reason for the increase in incidence of breast cancer in past years [17].

Type 2 DM shares some risk factors with breast cancer, such as age and obesity.

Several factors, make it difficult to accurately assess cancer risk in diabetic patients. These factors include diabetes duration, levels of diabetes control, drugs used for treatment, and the presence of complications.

Hyperinsulinemia is a risk for cancer in diabetic patients. Insulin is a growth factor with mitogenic activity, and affects malignant cells by acting at both the receptor and post-receptor level. Obesity, hyperglycemia, and increased resultant oxidative stress all act to increase the risk of cancer. Anti-diabetic drugs have less effect on cancer risk, except, metformin that is associated with less risk. Drugs used to treat cancer may cause diabetes or worsen pre-diabetes or pre-existing diabetes. In addition to the diabetogenic effect of glucocorticoids and anti-androgens, an increasing number of targeted anti-cancer molecules may interfere with glucose metabolism. These act on the signaling substrates in the IGF-I and insulin receptors. Despite all studies and research done so far, the risk of breast cancer in diabetic patients is still controversial.

Objectives

General objective

To determine the association between T2DM and breast cancer in Sudanese patients and discuss the potential factors involved.

Specific objectives

To compare factors such as age, residence, BMI and hormone status between the cases and controls.

Methods

This was a case-control hospital-based study which aimed to investigate the prevalence of diabetes mellitus in the study group and its association with breast cancer. Cases referred to all patients with breast cancer with or without diabetes. While controls were patients without breast cancer but with or without diabetes.

A total of 203 with breast cancer, who attended Radio Isotope Centre of Khartoum (RICK), represented the study group. And total of 311 patients, without breast cancer with the same age range as the study group, who attended Soba University Hospital and other hospitals in Khartoum state, represented the control group.

Study period

This study was conducted between December 2013 to March 2014.

Sample size

Sample was calculated according to the equation:

N= z2pq eff\d2

N==sample size

Z=constant =1.96=2

P= prevalence

Q=1-prevelance

D=10% - 20%.

Since there was no study done in Sudan regarding my topic so I calculate my data according to the equation above, and it is as follow: 4 x0.2 x0.8 x \0.05x0.05 = 200

So, the sample size = 200.

Inclusion criteria

Female adults with breast cancer.

Exclusion criteria

Males with breast cancer.

Data collection

Total number 203 patients with breast cancer, and 311 participants as the control group**.**

Data collected by direct interview using a well-structured questionnaire about awareness of patients to the problem.

Data management

All data obtained was entered in master flow chart then was analyzed using soft word package program for social science (SPSS). The obtained results will be presented in tables and figures.

Ethical clearance

Formal approval was taken from the local ethical committee and administration of the study area. All participants had an informed verbal consent, and the purpose of the study explained. The information collected was kept confidential.

Informed consent

The protocol, aims and benefits of the study were explained for all the participants in the study, and a written voluntary informed consent was obtained from each.

Results

This study included 203 cases of breast cancer and 311 controls. Cases refer to all patients with breast cancer with or without diabetes. While controls were patients without breast cancer but with or without diabetes. Out of the cases, 33 (16.3%) were found to be diabetic while the remaining 170 (83.7%) were not. Out of the control group, 45 (14.4%) had diabetes but 266 (85.6%) were not diabetic (Table 1).

		Cases with BC N (%)	Controls without BC N (%)	Total
T2DM	Yes	33 (16.3%)	45 (14.4%)	78
	No	170 (83.7%)	266 (85.6%)	436
Total		**203**	**311**	**514**

Table 1: *Shows the association of T2DM and breast cancer (BC) in the study (n=514). (P-value =0.000).*

Table 2 compared the age groups of both cases and controls. The majority of cases (39.3%) with both DM and breast cancer were in the 45 - 54 age group, while cases who were not diabetic (35.2%) were in the younger age group (35 - 44 yrs) as shown. However, diabetics in the control group (35.6%) were over the age of 55 years.

Age group of patients with BC		<35	35-44	45-54	>54	Total
T2DM	Yes	3 (9.1%)	8 (24.2%)	13 (39.4%)	9 (30.2%)	33
	No	24 (14.1%)	60 (35.2%)	45 (26.4%)	41 (18.2%)	170
Age group of patients without BC		**<35**	**35-44**	**45-54**	**>54**	**Total**
T2DM	Yes	4 (8.9%)	7 (15.6%)	6 (13.3%)	28 (62.3%)	45
	No	82 (30.8%)	43 (16.2%)	50 (18.8%)	91 (34.2%)	266

Table 2: *Shows the patients age groups in the cases (n = 203) and controls (n = 311).*

Seventy-three (35.9%) patients with breast cancer resided in Central Sudan. Fifteen (20.5%) had DM, while 58 (79.4%) did not. Fifty-nine (29%) patients were from Western Sudan, but only 7 (11.8%) had DM. Only one case came from Southern Sudan. The majority of controls, 169 patients (54.3.%) also came from Central Sudan and only 27 (81.8.%) had T2DM, while 86 (27.6.%) were from the West and only 7 (21.2%) were diabetic. Ten (3.2.%) patients from the control were from the South. Almost all the study population (97.4%) resided in urban area and (17.6%) were diabetic.

In table 3, the majority of cases with DM (51.5%) and without DM (45.3%) as well as the controls with DM (66.7%) had the same BMI of 25 - 24,9. But controls without DM (59.4%) had a lower BMI at 18 - 24.9. Only a minority of cases (2.4%) and controls (2.3%) were obese.

BMI of cases with BC		18-24.9	25-29.9	30-34.5	35+	Total
T2DM	Yes	15 (45.5%)	17 (51.5%)	1 (3.0%)	0 (0%)	33
	No	75 (44.1%)	77 (45.3%)	14 (8.2%)	4 (2.4%)	170
BMI of controls without BC		**18-24.9**	**25-29.9**	**30-34.5**	**35+**	**Total**
T2DM	Yes	4 (8.9%)	7 (15.6%)	6 (13.3%)	28 (62.3%)	45
		159 (59.4 %)	94 (35.3 %)	7 (2.6 %)	6 (2.3 %)	266

Table 3: *Shows the distribution according to BMI in the cases (n=203) and controls (n = 311).*

Out of the 203, only 108 cases had hormonal analysis. Table 4 showed that 61.1% of cases with diabetes were ER + ve while only 45.6% of the cases, who did not have diabetes, were ER + ve. This denotes a positive correlation between ER positivity and diabetes. However, there is no relation between PR and HER-2 positivity and diabetes. Only 27.8% and 44.5% of cases with diabetes were PR + ve and HER-2 + ve respectively.

		ER + ve	PR + ve	HER-2 + ve
DM	yes	11 (61.1%)	5 (27.8%)	8 (44.4%)
	no	41 (45.6%)	36 (40.0%)	59 (65.5%)
(P-value)		0.002	0.032	0.092

Table 4: *Shows the ER, PR and HER2 receptor status in the patients with breast cancer (n=108).*

Discussion

A total of 203 with breast cancer, who attended Radio Isotope Centre of Khartoum (RICK), represented the study group. And a total of 311 patients without breast cancer with comparable qualities as study group who attended Soba university hospital and other hospitals in Khartoum State, represented the control group. In the study group we found that 16.2% of study group were diabetic while only 14.6% of control group were diabetic (odds ratio 1.7 with confidence interval (0.704 - 1.871), (P-value = 0.000). Theses result are comparable with the study done by Khachatryan et al. {OR = 5.53 CI = 1.34 - 22.82 P = 0.02} in which he found significant association between diabetes and breast cancer in Armenia [38]. Resta., *et al.* found significant association between diabetes and breast cancer [39] as well as Rosato., *et al*. had the same result in a study done in Switzerland [40].

The association was approved also by many meta-analysis studies across the world [41-43], but still some case-control studies failed to show this association. Sanderson et al. in Hispanic women found no association between breast cancer and diabetes [44] Yu., *et al.* In China found no association between diabetes and breast cancer [45]. Baron and colleagues reported an association between diabetes diagnosed after age 35 years and breast cancer [46]. An increased risk of breast cancer in postmenopausal women with diabetes was reported by an Italian group [47]. In this study we found that in 30 cases (93.8%) with diabetes were 35 years and above, the commonest age of presentation is (45 - 54yr) in13 cases (39.4%) p = .056. While in the control group, 41 cases (91.2%) of diabetic patients were 35yrs and above, the commonest age of presentation is (55 – 65 yr) in12 cases (26.7%) p = .005. 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.

Obesity, is a well-known risk factor for breast cancer and is associated with increased risk of postmenopausal breast cancer [48]. In this study, the BMI in the case group, 17 cases (51.5%) of diabetics were over-weight, one case (3%) obese and 15 cases (45%) had normal weight (p = .005) suggesting a common risk factor, obesity, as an association. In the control group 30 cases (66.7%) of diabetic were overweight, one case (2.2%) obese, 14 cases (31.1%) of normal weight (p = .003).

Michels., *et al.* [49] found type 2 diabetes to be a risk factor in ER-positive postmenopausal ladies with breast cancer, bearing in mind the interaction between insulin and estrogens in the stimulation of breast cancer progression, Goodwin., *et al.* [29], when demonstrating an association between the fasting serum insulin, insulin resistance, and breast cancer prognosis, did not observe any modifying influence of ER status.

Gillespie., *et al.* [48] found that diabetes was associated with an increased risk for a tumor type that is negative for ER, PR, and HER2 receptors, possesses an aggressive metastatic phenotype, and has a poor prognosis. In this study, 108 out of 203 of patients with breast cancer had hormonal status evaluation, and 11 cases (61.1%) with diabetes were ER + ve, 5 cases (27.8%) PR + ve, and 8 cases (44.4%) were HER2 + ve. Adverse interactions between hormone therapy and diabetes are uncommon. Tamoxifen use is associated with four-times increased risk of endometrial cancer, and several studies have also reported a 1.5 times increased risk of endometrial cancer in patients with diabetes[46]. However, no evidence was found to link endometrial cancer in patients with diabetes who were treated by tamoxifen compared with those without diabetes.

There are three mechanisms that are thought to contribute to the association between type 2 diabetes and breast cancer

1. Activation of the insulin pathway.
2. Activation of the insulin-like-growth-factor pathway.
3. Impaired regulation of endogenous sex hormones.

The insulin pathway

Insulin is secreted from pancreatic cells in response to hyperglycemia [3,21]. Activation of the insulin pathway causes binding of insulin to the insulin receptor (IR) in the skeletal muscle, adipose tissue, and the liver. Other tissues including healthy breast tissue and breast-cancer cells also express IR. IR is a tyrosine kinase that consists of two extracellular subunits and two transmembrane subunits. The binding of insulin leads to a cascade of events including 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 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 [3,21]. Insulin signaling has a metabolic role and both the AKT and ERK pathways have important roles in tumorigenesis [17,22,]. IR has an important role in the activation of the insulin pathway in breast cancer as well. It is expressed in, and can be stimulated by, insulin in breast-cancer cell lines [23,24]. Overexpression of IR can induce malignant transformation in breast epithelial cell lines [25]. 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 Holdaway reported substantial binding of insulin in 22 of 23 samples of breast cancer. Thus, by contrast with adipose tissue, breast-cancer tissue showed diminished downregulation of IR in response to insulin [26]. Papa and colleagues 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 concentrations of IR correlated with tumor size, grade, and estrogen-receptor concentration [27]. Mathieu and colleagues 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. Goodwin and co-workers 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.

Insulin-like growth factors (IGF) pathway

This pathway consists of two ligands (IGF1 and IGF2), insulin-like growth factor binding proteins (IGFBP), and the IGF1 receptor (IGF1R). IGF1 and IGF2 are similar to insulin and IGF1R shares 55% homology with IR [30,31]. IGF1R and IR can form hybrid receptors, which, like IGF1R, have high affinity with IGF1 and low affinity with insulin [31]. Activation of IGF1R by IGF1 activates the same proteins and pathways that are activated by insulin and IR, the IRS family, SHC adaptor protein 1, phosphatidylinositol 3-kinase, and ERK [31]. High circulating concentrations of IGF1 and IGF-BP3 are associated with increased risk of premenopausal breast cancer [32], and increased IGF1 is thought to be an important link between obesity and increased risk of breast cancer [33]. 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 [34,35], suggesting that these growth factors might not have a direct role in the association between diabetes and breast cancer.

Sex-hormone regulation

High plasma concentrations of endogenous estrogens and androgens, and low plasma concentrations of sex hormone binding globulin (SHBG) are strongly associated with breast-cancer risk in postmenopausal women [36]. Deregulation of plasma concentrations of sex hormones, caused by increased production of estradiol and androgens combined with decreased liver production of SHBG, has been suggested as the main mechanism that connects postmenopausal obesity and breast-cancer risk [33,37].

Conclusion

Data suggest that type 2 diabetes might be associated with increased risk for breast cancer and that it could negatively affect the natural history, diagnosis, and treatment of breast cancer and several confounding factors, such as obesity, might account for these observa-

tions. Diabetes mellitus might adversely affect decisions on breast-cancer screening and treatment. However, patients with diabetes might benefit from breast cancer screening and should be encouraged to participate in these programs.

Authors Contribution

The main author, Dr. Sulaf, drafted the main idea and proposal. Also, supervised the original work, revised the manuscript writing and final editing. The second author collected the data, drafted the literature review, analysis, results and data presentation. Both first and second authors reviewed the manuscript and approved the final version.

Conflict of Interest

None of the authors have any conflict of interest.

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Bibliography

1. The DECODE Study Group. "Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 13 European cohorts". *Diabetes Care* 26 (2003): 61-69.
2. American Diabetes Association. "Diagnosis and classification of diabetes mellitus". *Diabetes Care* 27 (2004): S5-S10.
3. Saltiel AR. "New perspectives into the molecular pathogenesis and treatment of type 2 diabetes". *Cell* 104 (2001): 517-529.
4. Key TJ., *et al*. "Epidemiology of breast cancer". *The Lancet Oncology* 2 (2001): 133-140.
5. Van den Brandt PA., *et al*. "Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk". *American Journal of Epidemiology* 152 (2000): 514-527.
6. Yancik R., *et al*. "Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older". *The Journal of the American Medical Association* 285 (2001): 885-892.
7. ME Beckner., *et al*. "Glycolysis as primary energy source in tumor cell chemotaxis". *Journal of the National Cancer Institute* 82.23 (1990): 1836-1840.
8. T Krechler., *et al*. "Pancreatic cancer and diabetes mellitus". *Casopis Lekaru Ceskych* 143.2 (2004): 97-100.
9. MA Iqbal., *et al*. "Insulin enhances metabolic capacities of cancer cells by dual regulation of glycolytic enzyme pyruvate kinase M2". *Molecular Cancer* 12.72 (2013).
10. K Masur., *et al*. "Diabetogenic glucose and insulin concentrations modulate transcriptom and protein levels involved in tumour cell migration, adhesion and proliferation". *British Journal of Cancer* 104.2 (2011): 345-352.
11. P Vigneri., *et al*. "Diabetes and cancer". *Endocrine-Related Cancer* 16.4 (2009): 1103-1123.
12. A Yasmeen., *et al*. "Induction of apoptosis by metformin in epithelial ovarian cancer: involvement of the Bcl-2 family proteins". *Gynecologic Oncology* 121.3 (2011): 492-498.

13. A Malki and A Youssef. "Antidiabetic drug metformin induces apoptosis in human MCF breast cancer via targeting ERK signaling". *Oncology Research* 19.6 (2011): 275-285.

14. N Wu., *et al*. "Metformin induces apoptosis of lung cancer cells through activating JNK/p38 MAPK pathway and GADD153". *Neoplasma* 58.6 (2011): 482-490.

15. R Wahdan-Alaswad Z Fan., *et al*. "Glucose promotes breast cancer aggression and reduces metformin efficacy". *Cell Cycle* 12 (2013): 3759-3769.

16. Meyerhardt JA., *et al*. "Impact of diabetes mellitus on outcomes in patients with colon cancer". *Journal of Clinical Oncology* 21 (2003): 433-440.

17. Wolf I and Seger R. "The mitogen-activated protein kinase signalling cascade: from bench to bedside". *The Israel Medical Association Journal (IMAJ)* 4 (2002): 641-647.

18. Sussanne 2007.

19. Carol 2010.

20. Key 2001.

21. Taha C and Klip A. "The insulin signaling pathway". *The Journal of Membrane Biology* 169 (1999): 1-12.

22. Fresno Vara JA., *et al*. "PI3K/Akt signalling pathway and cancer". *Cancer Treatment Reviews* 30 (2004): 193-204.

23. Lai A., *et al*. "Insulin/insulin-like growth factor-I and estrogen cooperate to stimulate cyclin E-Cdk2 activation and cell cycle progression in MCF-7 breast cancer cells through differential regulation of cyclin E and p21(WAF1/Cip1)". *Journal of Biological Chemistry* 276 (2001): 25823-25833.

24. Milazzo G., *et al*. "Insulin receptor expression and function in human breast cancer cell lines". *Cancer Research* 52 (1992): 3924-3930.

25. Frittitta L., *et al*. "Insulin receptor overexpression in 184B5 human mammary epithelial cells induces a ligand-dependent transformed phenotype". *Journal of Cellular Biochemistry* 57 (1995): 666-669.

26. Benson EA and Holdaway IM. "Regulation of insulin binding to human mammary carcinoma". *Cancer Research* (1982).

27. Papa V., *et al*. "Elevated insulin receptor content in human breast cancer". *Journal of Clinical Investigation* 86 (1990): 1503-1510.

28. Mathieu MC., *et al*. "Insulin receptor expression and clinical outcome in node-negative breast cancer". *Proceedings of the Association of American Physicians* 109 (1997): 565-571.

29. Goodwin PJ., *et al*. "Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study". *Journal of Clinical Oncology* 20 (2002): 42-51.

30. Sachdev D and Yee D. "The IGF system and breast cancer". *Endocrine-Related Cancer* 8 (2001): 197-209.

31. Siddle K., *et al*. "Specificity in ligand binding and intracellular signalling by insulin and insulin-like growth factor receptors". *Biochemical Society Transactions* 29 (2001): 513-525.

32. Renehan AG., *et al*. "Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis". *Lancet* 363 (2004): 1346-1353.

33. Friedenreich CM. "Review of anthropometric factors and breast cancer risk". *European Journal of Cancer Prevention* 10 (2001): 15-32.

34. Frystyk J., *et al*. "Circulating levels of free insulin-like growth factors in obese subjects: the impact of type 2 diabetes". *Diabetes/Metabolism Research and Reviews* 15 (1999): 314-322.

35. Nardon E., *et al*. "Insulin-like growth factor system gene expression in women with type 2 diabetes and breast cancer". *Journal of Clinical Pathology* 56 (2003): 599-604.

36. The Endogenous Hormones and Breast Cancer Collaborative Group. "Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies". *Journal of the National Cancer Institute* 94 (2002): 606-616.

37. Nyholm H., *et al*. "Androgens and estrogens in postmenopausal insulin-treated diabetic women". *The Journal of Clinical Endocrinology and Metabolism* 69 (1989): 946-949.

38. Khachatryan L., *et al*. "Influence of diabetes mellitus type 2 and prolonged estrogen exposure on risk of breast cancer among women in Armenia". *Health Care for Women International* 32 (2011): 953-971.

39. Resta F., *et al*. "The impact of body mass index and type 2 diabetes on breast cancer: current therapeutic measures of prevention. Current Drug Targets". *Immune, Endocrine and Metabolic Disorders* 4 (2004): 327-333.

40. Rosato V., *et al*. "Metabolic syndrome and the risk of breast cancer in postmenopausal women". *Annals of Oncology* 112 (2011): 630-634.

41. Prue J Hardefeldt., *et al*. "Diabetes increases the risk of breast cancer: a meta-analysis". *Endocrine-Related Cancer* 19 (2012): 793-803.

42. Shichong Liao., *et al*. "Association between Diabetes Mellitus and Breast Cancer Risk: a Meta-analysis of the Literature". *Asian Pacific Journal of Cancer Prevention* 12 (2011): 1061.

43. Sanderson M., *et al*. "Diabetes, physical activity and breast cancer among Hispanic women". *Cancer Epidemiology* 34 (2010): 556-561.

44. Yu ZG., *et al*. "Risk factors related to female breast cancer in regions of Northeast China: a 1:3 matched case-control population-based study". *Chinese Medical Journal* 125 (2012): 733-740.

45. Baron JA., *et al*. "Metabolic disorders and breast cancer risk (United States)". *Cancer Causes Control* 12 (2001): 875-880.

46. Talamini R., *et al*. "Selected medical conditions and risk of breast cancer". *British Journal of Cancer* 75 (1997): 1699-1703.

47. Michels KB., *et al*. "Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study". *Diabetes Care* 26 (2003): 1752-1758.

48. Gillespie EF., *et al*. "Obesity and angiolymphatic invasion in primary breast cancer". *Annals of Surgical Oncology* 17 (2010): 752-759.

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