RESEARCH COMMUNICATION

Association between Diabetes Mellitus and Breast Cancer Risk: a Meta-analysis of the Literature

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Abstract

Aim/hypothesis: Diabetes and breast cancer are both serious life-threatening diseases across the world. Some studies shows that diabetes is associated with many kinds of tumor, but links with breast cancer remain controversial. The aim of this study was to assess the association the available evidence. Subjects and methods: A meta-analysis was conducted including 16 studies published between 2000 and 2010 and summary relative risks(RRs) with 95% CIs were calculated using random-effects model. Results: The combined evidence supports that diabetes was associated with a statistically significant 23% increased risk of breast cancer, especially in postmenopausal women (RR=1.25 95%CI 1.20-1.29). The correlation between diabetes and breast cancer was the most obvious in Europe (RR=1.88,95%CI:1.56-2.25), followed by America (RR=1.16, 95%CI:1.12-1.20). In Asia the result was not significant (RR=1.01, 95%CI=0.84-1.21). Diabetes also increased mortality from breast cancer overall (RR=1.44, 95%CI:1.31-1.58). Conclusions/interpretation: This meta-analysis indicated that diabetes can be considered as a risk factor for breast cancer. In addition, menstruation status as well as geographical distribution can affect the relationship.

Keywords: Breast cancer - diabetes - association - systemic review - meta-analysis

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Introduction

Breast cancer is most common disease in women,which is the second leading cause of cancer death among women (Carol et al., 2010). The incidence of breast cancer increased rapidly in past 20 years.Incidence rises with age and is associated with family history of breast cancer, menstruation status,benign breast disease, and hormonal factors (Key et al., 2001).Obesity is another risk factor, which is one main reason for the increase in incidence of breast cancer in past decades (Wolf et al., 2005).

Like breast cancer, diabetes is another worldwide health problem, especially in developed country,which affected more than 9.7% people in America(Centers for Disease Control and Prevention.,2005). Type 2 diabetes account 90-95% diabetes cases, It shares some risk factors with breast cancer, for example: age and obesity.Its character include insulin resistance and hyperinsulinemia in early phase;and lack of insulin which was caused by beta cell decompensation in terminal phase. And type 2 diabetes mellitus has been recognized as a risk factor for several cancers, including liver and pancreatic cancer (Meyerhardt et al., 2005; Wolf et al., 2005; Susanna et al., 2007). In past 20 years, There are a number of studies research the association between breast cancer and diabetes, but the conclusions on the risk of breast cancer in diabetic patients are still controversy. In order to get a more precise estimation of the relationship between the diabetes and breast cancer,we present a meta-analysis from the available evidence which studies the association between breast and diabetes.

Materials and Methods

Data sources and search strategy

We looking for studies carried out between 2000 and March 2010 in MEDLINE database.The key words used were"breast cancer" and "diabetes". We also reviewed the reference lists of retrieved articles to search for more studies,and no language restriction was applied.

Selection criteria

This meta-analysis only included case–control or prospective study design published between 2000 and March 2010.The patients with breast cancer were diagnosed by pathological examination,and the diagnosis of diabetes mellitus was confirmed, according to the definitions of the WHO(WHO,1999), by the presence of fasting glucose levels of above 7.1mmol/L in routine laboratory evaluation or self-reported. The following criteria were required for inclusion:(i)provided original data or the value of relative risk(RR), odds ratio(OR) and 95% confidence interval(95% CI); (ii)diabetes mellitus was the exposure of interest; (iii)the result was the

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incidence or mortality of breast cancer.The literatures of poor quality or lack necessary information and data were excluded.There were 16 studies including in this meta-analysis finally,Among these studies,12 studies research the association between incidence of breast cancer and diabetes, 4 studies were about the mortality.

Data extraction

Data extraction was conducted by LSC and LJX, and discrepancies were solved through discussion. The information focused on study characteristics, which included authors' name,year,design,sample size, RR and 95%CI. The information of patient characteristic were also recorded, which included birthplace, age, menstruation status, diabetes assessment.

Quantitative data synthesis

We divided epidemiological studies of the relationship between diabetes and breast cancer risk into three general types according to design: cohort studies (incidence and/or mortality rate ratio), case-control studies (odds ratio) and cohort studies with an external comparison group (standardised incidence and/or mortality ratio). The data in our study are enumeration data,and the odds ratio in case-control studies and rate ratios,standardised ratios in cohort studies yield similar estimates of RR, so we use relative risk as the analysis of statistics,and indicated by 95%CI.

Estimates of the summary relative risk with a 95% confidence interval (CI) were obtained using a DerSimonian and Laird random effects model, which provides a more conservative estimate of the overall response by taking into account between- and within-study variance. We use chi-square test and I2 statistic to check the statistical heterogeneity in results.P<0.01 means the sub-groups included in this meta-analysis have significant heterogeneity. Publication bias was assessed by constructing a funnel plot (Egger et al.,1997) and by Egger's regression asymmetry test (Egger et al.,2001). The incidence and mortality are analyzed separately.

Statistics

Statistical analysis was performed using Review Manager 4.2(Cochrane Collaboration) and Microsoft Excel 2010.

Results

Breast cancer incidence

Study characteristics: A total of 12 articles (Baron et al., 2001; Resta et al., 2004; Lipscombe et al., 2006; Susan et al., 2009; Mink et al., 2002; Michels et al., 2003; Lawlor et al., 2004; Inoue et al., 2006; Khan et al., 2006; Maria et al., 2007;Wu et al., 2007; Beji et al.,2007) were retrieved. A total of 730,069 patients were in this study, with a sample size ranging from 43 to 478,560.Of the 12, there are 5 case-control and 7 cohort studies. Study populations came from Asia(3 studies), America(6 studies) and Europe(3 studies) respectively.

Association between breast cancer incidence and diabetes: The results are presented in Figure 1a. There were 10 studies shows a increasing incidence of breast cancer in diabetic patients. Of the 10 studies,8 studies have significant difference.The result suggested that breast cancer patients were more likely to have a history of diabetes(summary RR=1.23 95%CI, 1.18-1.27; test for heterogeneity p<0.001, chi=35.20, I2=68.7%,12 studies). Stratifying study result by study design, case-control studies showed that diabetes was associated with

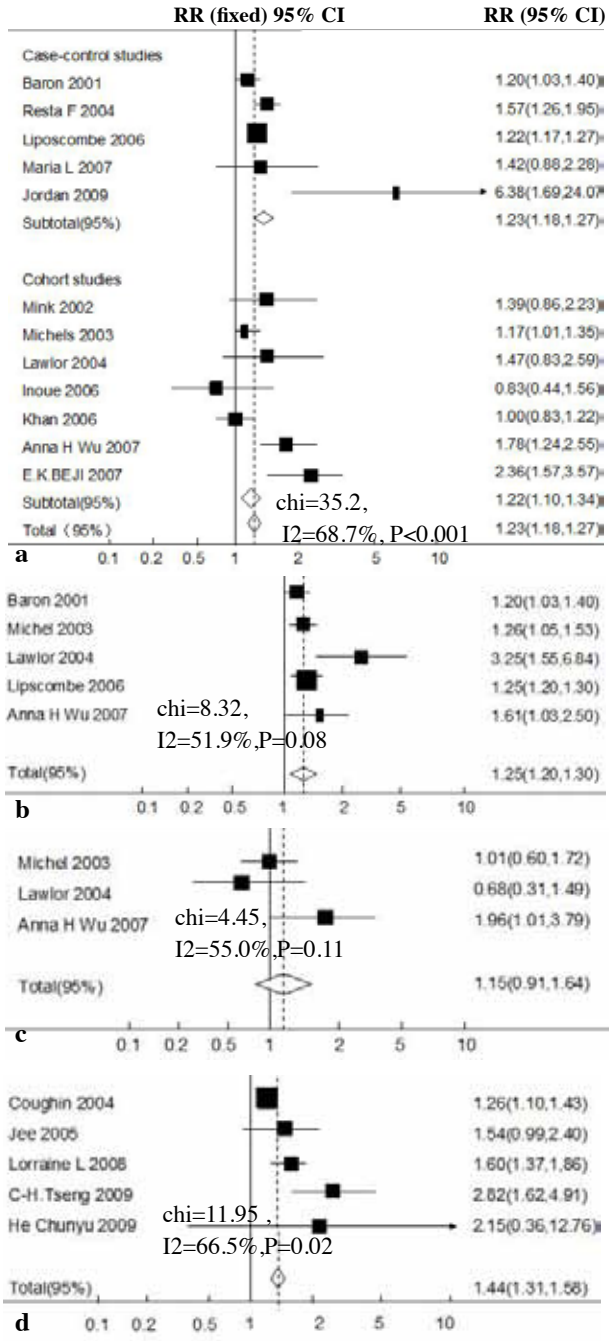

Figure 1. Relative Risks for the Association between Diabetes and Breast Cancer. a) Incidence Case-contol and cohort studies; b) Incidence Postmenopausal; c) Incidence Premenopausal; d) Mortality. Squares, study-specific RR estimate (size of the square reflects the study-specific statistical weight); horizontal lines, 95% CI; diamond, summary RR estimate and its corresponding 95% CI.All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with chi-square test and I2 statistic.Test for heterogeneity among studies:chi, I2 and P value

Table 1. Regional Differences in the Association between Diabetes and Breast Cancer

		Number of studies	RR	95%CI
Incidence	America	6	1.16	1.12-1.20
	Europe	3	1.88	1.56-2.25
	Asia	3	1.01	0.84-1.21
Mortality	Asia	3	2.05	1.48-2.85
	America	2	1.40	1.27-1.54

a statistically significant 23% increased risk of breast cancer. In addition, cohort studies also showed a similar association (RR=1.22; 95%CI, 1.10-1.34). Both the chi-square test and I2 statistic indicated heterogeneity across studies.Instable estimates and some studies in each category have an inverse association between diabetes and breast cancer risk were probably reasons. We used a DerSimonian and Laird random effects model to decrease the heterogeneity.The summary RR is increased (RR=1.72,95%CI,1.47-2.00)And test for heterogeneity:p=0.11, 0.16, and 0.13 for case-control studies, cohort studies and all studies, respectively.

Stratification by menstruation status: Five studies (Baron et al., 2001; Lipscombe et al., 2006; Michels et al., 2003; Lawlor et al., 2004; Wu et al., 2007) were analyzed among postmenopausal women or among women of postmenopausal age (Figure 1b). We observed a strong relationship between both diseases,with an summary relative risk of 1.25 (95%CI 1.20-1.29). Diabetes can increase the breast cancer incidence in 3 studies (Michels et al., 2003; Lawlor et al.,2004; Wu et al., 2007),which study population were restricted to premenopausal or patients of premenopausal age (Figure 1c), but it didn't have significant difference (RR=1.15; 95%CI, 0.81-1.64). They didn't have statistically significant heterogeneity among these studies (Chi=4.45, P=0.11,I2=55.0% in premenopausal studies; Chi=8.32, P=0.08, I2=51.9% in postmenopausal studies).

Stratification by area: If we stratified by area (Table 1), we found that the incidence of diabetes with breast cancer in the America, Europe, rose by 16% and 88% respectively,and the difference was statistically significant(95%CI 1.12-1.20 in America;95%CI 1.56-1.25 in Europe). But this phenomenon didn't appear in Asia(RR=1.01 95%CI 0.84-1.21). This result shows that the incidence of breast cancer may be related with ethnic and regional differences.

Breast cancer mortality

A total of 5 studies (Coughlin et al., 2004; Jee et al., 2005; Lorraine et al., 2008; Tseng et al., 2009; Chunyu and Qing Ling, 2009) were selected for the meta-analysis. Study population of 3 articles came from Asia, 2 other data from North America.

The association between breast cancer mortality and diabetes were showed in Figure 1d. All results from 5 studies suggested that breast cancer patients were more likely to die with a history of diabetes, with relative risk ranging from 1.31 to 1.58(RR=1.44). There was heterogeneity among studies (Chi=11.95, P=0.02, I2=66.5%) but funnel plots did not reveal signs of publication bias.

Stratification by area: Diabetes had higher mortality than non-diabetic patients (Table 1) among both Asia and America breast cancer patients. The difference of breast cancer mortality between diabetic and non-diabetic patients in Asia is larger than America (RR=2.05 in Asia;RR=1.40 in America). This phenomenon may be related with medical conditions, lifestyle, economic and educational situation, especially related with popularity of mammography.

Discussion

In this meta-analysis,we investigated the association between incidence and mortality of breast cancer and type2 diabetes mellitus. The data from meta-analysis indicate that women with type 2 diabetes have a 23% higher risk of developing breast cancer compared with non-diabetic women. The increased incidence of breast cancer was apparent among postmenopausal women.Although diabetes can increase the incidence of premenopausal women, but they were not significant different.The correlation between diabetes and breast cancer was the most obvious in Europe (RR=1.88, 95% CI: 1.56-2.25), followed by the America (RR=1.16, 95% CI: 1.12-1.20). The correlation in Asia didn't have significant different (RR=1.01, 95% CI: 0.84-1.21). The result of this study also suggest that the mortality of breast cancer increased, if the breast cancer patients suffer from diabetes.

The phenomenon that diabetes can change breast cancer incidence and mortality may be caused by potential biological mechanism which was unclear now. An explanation is offered by the following hypotheses: 1) Activation of the insulin pathway (Taha and Klip, 1999; Lai et al., 2001; Saltiel, 2001; Wolf and Seger, 2002; Fresno Vara et al., 2004) -ncreased insulin can bind with its receptors ,then it can activates phosphatydylinositol 3-kinase, which in turn activates the AKT pathway, and the AKT pathways have important roles in tumorigenesis; 2) activation of the insulin-like-growth-factor pathway (Kaaks et al., 2002; Hankinson and Schernhammer, 2003; Nardon et al., 2003; Dominguez et al., 2004; Schernhammer et al., 2005; Schernhammer et al., 2007) - IGF can bind with both insulin receptor and IGF receptor,which will initiate cascade of mechanisms, and finally stimulate the development of breast cancer. However, as IGF-1 is mainly associated with pre-menopausal breast cancer and as IGF-1 is not increased in type 2 diabetes, the contribution of the IGF pathway to the effects of diabetes on breast cancer isn't probably important; 3) Regulation of endogenous sex hormones (Hankinson et al., 1998; Gustafsson and Warner., 2000; Kabuto et al., 2000; Missmer et al., 2004). Hyperinsulemia is also associated with high concentration of estrogen and low levels of sex hormone binding globulin (SHBG), which leads to an increase in the bioavailability of estradiol. Moreover, hyperglycemia which was caused by diabetes also promote tumor cell's growth and proliferation (Warburg, 1956;

Dang and Semenza, 1999). Recent years, Increased leptin and decreased adiponectin levels have been observed in individuals with obesity, type 2 diabetes ,which may also contribute to the increasing risk of breast cancer, especially the more aggressive ones (Papa et al.,1990; Mathieu et al., 1997; Fischer et al., 2002; Wauters et al., 2003;Franks et al., 2005; Chu et al., 2006; Sieminska et al., 2006; Vona-Davis and Rose, 2007).

A number of potential limitation should be mentioned in this meta-analysis. First, diagnosis of diabetes In some studies which was included in this meta-analysis was based on patients self-report or history, it is possible that some diabetic patients were misclassified as non-diabetes. Several studies didn't distinguished the type of diabetes. Some type 1 diabetes maybe include in this meta-analysis. If this happened, it will affect the accuracy of this study. Larsson and colleague (Susanna et al., 2007) do a similar study,and the result showed that if diagnosis of diabetes is based on discharge diagnosis, the relative risk will decrease a little. Second, the treatment for diabetes is unknown in most studies in this meta-analysis. Because some oral antidiabetic drug can prevent breast cancer 's development, such as metformin.but the effect of reduction in cancer risk does not occur with all oral diabetic agents. Glibenclamide was associated with increased cancer risk (Goodwin and Jennifer, 2009; Monami et al., 2008). Thus, the effect of diabetes treatment can not be sufficient estimated, and it also can change the incidence and mortality of breast cancer. Third, Some studies didn't adjust the confounding factor, like obesity, age and the postmenopausal hormone use. If adjust this risk factor,the result maybe change at some degree. Larsson and college (Susanna et al., 2007) adjust this confounding factors in his study. After adjust these confounding factor, there is a 20%-26% increased in breast cancer incidence. Forth,the number of diabetic patients in some article was small,which may result in lager error. Moreover, inherent in meta-analysis of published studies is the possibility of publication bias.

From our result, we suggest that elderly diabetic patients should do regular breast examination every year, such as mammography, B ultrasound; and breast cancer patients with diabetes should treat diabetes actively,while close observation and treatment of breast cancer.

The result indicate that diabetes not only increase the risk of breast cancer, but also affect the prognosis of breast cancer. Diabetes can be considered as a risk factor for breast cancer independent of obesity and age.But the biological mechanisms are still unclear, and studies are still have limitations. Future studies are needed to clarify the phenomenal and develop a safe and effective intervention programs to prevent diabetes and breast cancer.

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