

Association of breast cancer and diabetes mellitus in Korean postmenopausal women

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Abstract

Background: Diabetes mellitus has been associated with an increased risk of breast cancer. This association is, however, controversial, and not elucidated in Asia. This study aimed to determine the association between diabetes mellitus and breast cancer risk in Korean women.

Methods: This retrospective study included subjects who underwent an ultrasound-localized needle-extracted biopsy to investigate questionable breast findings at the Eulji University Hospital breast clinic in Seoul, Korea, between 2000 and 2019. The medical records of the participants were reviewed to determine their age, diabetic status, and breast pathology findings. The participants were categorized into two groups, namely, the control group, that included those with benign breast disease; and, the breast cancer group. Logistic regression analyses were performed to assess the association between diabetes and breast cancer amongst pre- and post-menopausal participants.

Results: A total of 1268 participants were included in this analysis. We found that diabetes was significantly associated with an increased odds of breast cancer (odds ratio [OR] 2.24; 95% confidence interval [CI], 1.76 to 2.84). Additionally, postmenopausal participants (aged ≥ 50 years) showed increased odds for breast cancer (OR 4.32; 95% CI, 3.37 to 5.53). The association between diabetes and breast cancer was significant, after adjusting for age, in the postmenopausal group (adjusted OR [aOR] 1.60; 95% CI, 1.09 to 2.35), but was not significant in the premenopausal group (aOR 1.10; 95% CI, 0.76 to 1.60).

Conclusion: Diabetes was associated with increased odds of breast cancer compared to benign breast disease in postmenopausal women in Korea.

Background

Breast cancer is the most common cancer in women [1] [2]. Diabetes mellitus is a serious and growing health problem worldwide, characterized by insulin resistance and hyperinsulinemia [3]. It has been hypothesized that hyperinsulinemia may increase the risk of breast cancer, either directly through its effects on the breast tissue or indirectly by increasing the concentrations of circulating estrogens, testosterone, and insulin-like growth factors [4] [5]. Thus, diabetes may confer an increased risk of breast cancer.

Previous meta-analyses have shown a significant association between diabetes and breast cancer [6] [7] [8], and higher breast cancer-associated mortality among diabetic women [9] [10] [11]. However, in Asia, this association is not clearly elucidated, with a lack of definitive evidence, and conflicting results. A meta-analysis by Liao et al. [7] showed that the association between diabetes and breast cancer was apparent in Europe and America, but not in Asia. Conversely, a meta-analysis by Larsson et al. [6] showed a significant association among Asians. Cohort studies in Japan [12] [13] and Eastern China [14] did not show significant associations between diabetes and breast cancer. Similarly, a study in Korea showed that pre-existing diabetes was not associated with an increased odds of breast cancer, after adjusting for

other factors [15]. However, a population study conducted by Jee et al. [16] showed a significant association between diabetes and female breast cancer in Korea.

The association between diabetes and breast cancer differs; depending on menopausal status. A meta-analysis by Lio et al. [7] showed a significant association between diabetes and breast cancer among postmenopausal but not among premenopausal women. The results of the Korean population study were not stratified by menopausal status [16]; moreover, the control group in most studies (inadequately) comprised of participants without breast cancer. Only one study included women with benign breast disease (BBD) as the control group [17].

The purposes of this study were to: (1) determine the association between diabetes and breast cancer in Korean women; (2) evaluate the effect of menopausal status on this association and; (3) compare the association between diabetes and breast cancer versus BBD.

Methods

This study included subjects who underwent an ultrasound-localized needle-extracted biopsy for investigating questionable breast findings at the breast clinic of the Eulji University Hospital in Seoul, Korea, between 2000–2019. Ethical approval was obtained for this retrospective study from the Eulji Hospital Institutional Review Board (IRB).

Medical records of participants were reviewed and data on their ages, diabetic status, and pathologic findings were extracted. To ensure a level of consistency between pathology reports, comments related to "appearance, resemblance, or possible" were omitted. For the outcome, participants were categorized into two groups: the control group, which included those with BBD, and the breast cancer group. Biopsy results for participants with BBD included fibroadenoma, apocrine metaplasia, fibrocystic disease, atypical hyperplasia, non-atypical hyperplasia, adenosis, duct ectasia, inflammation, papilloma, stromal fibrosis, diabetic mastopathy, and other benign diseases. Biopsy results for participants with breast cancer included ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and defined cancer.

The diabetic status of participants was categorized into two groups, according to the 2019 Clinical Practice Guidelines for Type 2 Diabetes Mellitus in Korea [18]: normal and diabetes. Participants with a fasting glucose level <100 mg/dL or a glycosylated hemoglobin (HbA1C) level < 5.7% or without a history of diabetes constituted the normal (non-diabetes) group, while participants with a fasting glucose level \geq 126 mg/dL or HbA1C level \geq 6.5% or with a history of diabetes constituted the diabetes group. Participants with a fasting glucose level of 100–125 mg/dL or HbA1C level of 5.7–6.4% were considered to have prediabetes and were excluded from further analysis.

The average age of menopause in Korean women is 49.3 years [19]. Therefore, all participants aged less than 50 years or \geq 50 years were categorized into the premenopausal or postmenopausal group, respectively.

Logistic regression analyses were performed to assess the association between diabetes and breast cancer, according to the participant's menopausal status. All analyses were conducted using SPSS 22 (IBM Co., Armonk, NY, USA). A P-value of less than 0.05 was considered statistically significant.

Results

A total of 1630 participants underwent biopsy during the study period. Of these, 362 were classified as prediabetic and, therefore, excluded from further analyses, and 1268 participants were included in the study. The mean age of all participants was 48.3 years: 44.8 years for BBD and 55.3 years for participants with breast cancer. There were 772 participants categorized into the premenopausal group and 496 participants into the postmenopausal group. In addition, 561 participants were found to be diabetic, and 707 participants were non-diabetic (normal) (Fig. 1).

Women in postmenopausal and diabetes groups showed increased odds for breast cancer - (odds ratio [OR] 4.32; 95% CI, 3.37 to 5.53) and (OR 2.24; 95% CI, 1.76 to 2.84), respectively (Table 1).

Table. 1. Characteristics of the study participants

Characteristics	Benign breast disease (n = 847)	Breast cancer (n = 421)	P-value*	OR (95% CI)
Mean age, years (mean \pm SD)	44.8 \pm 10.5	55.3 \pm 12.6	< 0.001	
Age				
Premenopausal (Age < 50 years), n (%)	613 (72.4)	159 (37.8)	<0.001	1
Postmenopausal (Age \geq 50 years), n (%)	234 (27.6)	262 (62.2)		4.32 (3.37–5.53)
Diagnosis of diabetes				
Normal, n (%)	528 (62.3)	179 (42.5)	< 0.001	1
Diabetes, n (%)	319 (37.7)	242 (57.5)		2.24 (1.76–2.84)

Values are presented as mean \pm SD or number (%).

*Obtained by t-test for means \pm SD and χ^2 test for proportions

CI, confidence interval, OR, odds ratio; SD, standard deviation

Table 2 shows the results of the logistic regression analyses after adjusting for age. In the adjusted model, we found that diabetes was associated with increased odds of breast cancer among all participants (adjusted OR [aOR] 1.33; 95% CI, 1.02 to 1.73). Among postmenopausal women, diabetes was also significantly associated with increased odds of breast cancer in the unadjusted (OR 1.95; 95% CI, 1.35 to 2.81) and adjusted (aOR 1.60; 95% CI, 1.09 to 2.35) models. However, the association between diabetes and breast cancer was not significant in the premenopausal women neither before (OR 1.34; 95% CI, 0.94 to 1.93) nor after (OR 1.10; 95% CI, 0.76 to 1.60) adjusting for age (Table 2).

Table. 2 Odds ratios (ORs) and 95% confidence interval (CI) for association between diabetes and breast cancer risk

		Benign breast disease (n = 847)	Breast cancer (n = 421)	OR (95% CI)	aOR (95% CI)^a
Total, N (%)	Normal	528 (62.3)	179 (42.5)	1	1
	Diabetes	319 (37.7)	242 (57.5)	2.24 (1.76–2.84)	1.33 (1.02–1.73)
Premenopausal (Age <50 years), n (%)	Normal	419 (68.4)	98 (61.6)	1	1
	Diabetes	194 (31.6)	61 (38.4)	1.34 (0.94–1.93)	1.10 (0.76–1.60)
Postmenopausal (Age ≥50 years), n (%)	Normal	109 (46.6)	81 (30.9)	1	1
	Diabetes	125 (53.4)	181 (69.1)	1.95 (1.35–2.81)	1.60 (1.09–2.35)

Values are presented as number (%)

^aaOR adjusted for age

CI, confidence interval; OR, odds ratio; aOR, adjusted odds ratio

Discussion

Results from this study support a positive association between diabetes and breast cancer. We found that diabetic women had 1.3-fold increased odds of suffering from breast cancer. This association was also influenced by advancing age, with postmenopausal diabetic women having 1.6-fold increased odds of suffering from breast cancer, as compared to premenopausal diabetic women.

Previous meta-analyses have shown a significant association between diabetes and breast cancer [6] [7] [8], and results from the Nurses' Health Study showed that women with diabetes had a 1.17 fold increased odds of breast cancer [20]. While a previous study demonstrated that diabetes is associated with breast cancer in Europe and America [7], there are discrepancies in studies reported from Asia. It remains unclear if diabetes is associated with breast cancer in Korea [12] [13] [14] [15] [16] [21]. In addition, a meta-analysis of population-based cohort studies on the risk of breast cancer and diabetes in Asian women showed that the history of diabetes mellitus was not associated with the risk of breast cancer in Asian women [22]. However, this study did not conduct a subgroup analysis by menopausal status at diagnosis of breast cancer in Asian women.

Hyperinsulinemia increases the risk of breast cancer [4]. Insulin resistance is common in diabetes, in which the circulating insulin level frequently increases. The insulin/insulin-like growth factor (IGF) axis plays an essential role in diabetes-associated increased odds and progression of cancer. Insulin has been demonstrated to have mitogenic effects on breast tissue as cancer cells overexpress insulin and IGF-1 receptors [23]. Hyperinsulinemia also results in decreased levels of IGF binding protein-1, and thus increases levels of bioactive IGF-1 [24, 25]. Hyperinsulinemia could increase the levels of bioactive estrogens by reducing the concentration of circulating sex hormone-binding protein in diabetic women. It is well-known that bioactive estrogens are risk factors for malignancies of female reproductive organs [26]. Increased bioactive estrogen stimulates the proliferation of breast and endometrial cells and inhibits apoptosis, increasing cancer risk [3]. Women with diabetes reportedly have higher concentrations of circulating estrogens and androgens than their healthy counterparts [27] [28]. Although epidemiologic studies have generally indicated positive relationships between estrogen and testosterone concentrations and risk of breast cancer in postmenopausal women [29] [30], some studies have found that such associations are also present in premenopausal women [31] [32], but these associations seem weaker than in postmenopausal women [6]. This may explain why the association between diabetes and breast cancer risk was seen only in postmenopausal women in the current study.

The significance of our study lies in the investigation of the association between diabetes and breast cancer by menopausal status. We found that the association between diabetes and breast cancer was significant only in postmenopausal women. These findings are consistent with several previous studies. The Nurses' Health Study showed a borderline elevated breast cancer risk among postmenopausal, but not premenopausal women [20]. Moreover, a meta-analysis by Lio et al. [7] identified a significant association between diabetes and breast cancer among postmenopausal, but not premenopausal women in Western countries. Additionally, a report from Korea showed that pre-existing diabetes significantly increased the odds of breast cancer only in the postmenopausal group, with no significant association in the premenopausal group [15]. However, this previous study in Korea, which showed an

insignificant association in the combined analyses, had small number of participants. In contrast, our study had a larger number of participants and showed a consistent positive association between diabetes and breast cancer, as shown previously in other meta-analyses [6] [7]. Furthermore, the results of the previous population study conducted by Jee et al. in Korea were not stratified by menopausal status [16]. Our study is the first to analyze the association between diabetes and breast cancer in a large cohort of Korean women, stratified by menopausal status, showing results that are consistent with Western studies [7]. This study is also the first to examine the association between diabetes and breast cancer compared to BBD in Korea, Asia. In most studies, the control group consisted of participants without breast cancer, with only one other study involving women with BBD as controls [17].

There are some limitations to our study. Firstly, this study only confirmed the presence of diabetes and did not investigate the duration of diabetes. Secondly, the pathology reports of breast cancer were read by several physicians over the course of the 20-year study period. This may have generated discrepancies in the diagnoses. We tried to eliminate some of this bias by not including any reports with conflicting or subjective findings. Thirdly, we did not have data specifying if the patients with diabetes were administered insulin or other medications to treat diabetes. In epidemiologic studies, both insulin glargine and human insulin use is shown to adversely affect breast cancer incidence [33] [34]. Additionally, insulin users may also concomitantly be consuming an oral anti-diabetic drug (metformin) that may be related to favorable breast cancer outcomes [34] [35] [36] [37]. Therefore, administration of insulin and medication would not change the results of this study. Finally, as a retrospective study, body mass index, smoking, alcohol history, and family history of breast cancer, which may increase the risk of cancer, were not investigated and, therefore, not statistically adjusted in this study. As there may also be a selection bias, a long-term prospective nation-wide study will be necessary in the future to confirm our results.

Despite these limitations, this study is significant in that it is the first large scale study to show a consistent positive association between diabetes and breast cancer among Korean women, stratified by menopausal status, both in all participants and in postmenopausal women. It is also the first study to examine the association between diabetes and breast cancer compared to BBD in Korea, Asia. We found a positive correlation between diabetes and breast cancer in postmenopausal Korean women, which could lead to targeted breast exams for postmenopausal women with diabetes to increase early diagnosis of breast cancer. However the breast cancer screening rate in people with diabetes in the Korean population, resulted from the Korea National Health and Nutrition Examination Survey, was lower than in people without diabetes [38][39]. Therefore, efforts to increase the screening rate in diabetic postmenopausal diabetic women should be implemented.

Conclusions

In summary, diabetes is strongly associated with an increased odds of breast cancer compared to BBD in postmenopausal women in Korean

List Of Abbreviations

OR: odds ratio

aOR: adjusted odds ratio

BBD: benign breast disease

DCIS: ductal carcinoma in situ

LCIS: Lobular carcinoma in situ

IGF: insulin-like growth factor

CI: confidence interval

Declarations

Acknowledgments

None

Declarations

Conflicts of Interest

The authors declare that they have no conflict of interest

Ethical Approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration (1964) and its later amendments, or comparable ethical standards. The study was approved by the Eulji Hospital Institutional Review Board (No:2020-03-006).

Consent to participate

Since this was a retrospective study, formal consent was not required.

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Boram Kim selected the thesis topic, designed the study, analyzed the data, interpreted the results, and wrote the first draft of the manuscript. Hee Yong Kwak, Kil Young Kwon, and Junghwan Kim provided data and academic advice. Jee Hye Han suggested questions that could arise regarding the thesis and presented the logical flow of the thesis and is responsible for the research results and supporting data. All authors have read and approved the final manuscript.

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Figures

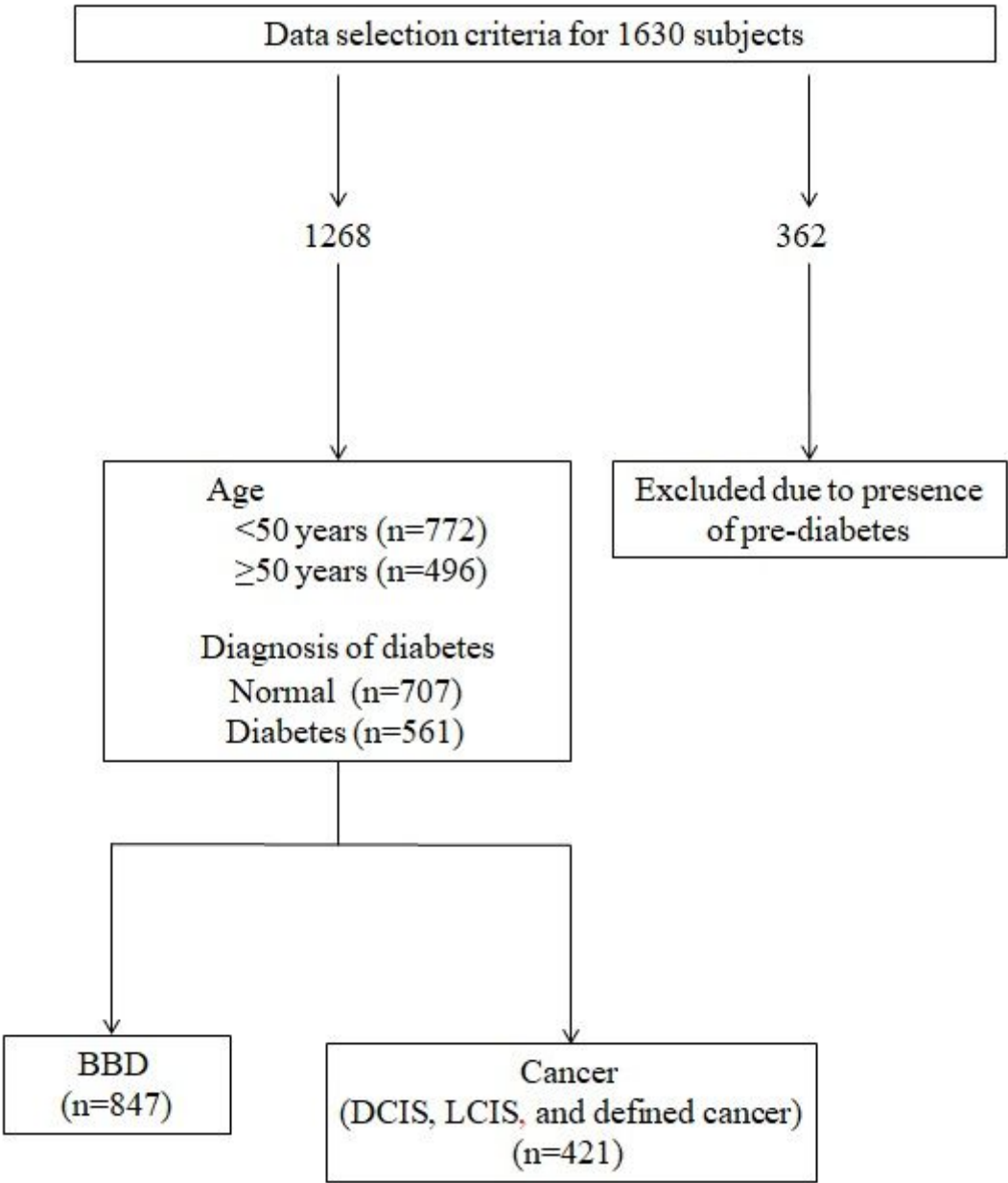


Figure 1

Flow diagram of the study showing the number of participants in each group. The pathway on the right shows the number of subjects excluded from the study. BBD, benign breast disease; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ