

Research Paper: The Association Between Diabetes Mellitus With a Five-year Survival Rate of Breast Cancer Patients



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Citation Sharifi Nasab M, Yazdimoghaddam H, Mohaddess ST, Rakhshani MH, Abbaszadeh Goudarzi K. The Association Between Diabetes Mellitus With a Five-year Survival Rate of Breast Cancer Patients. Journal of Research & Health. 2022; 12(1):33-40. <http://dx.doi.org/10.32598/JRH.12.1.1937.1>

doi <http://dx.doi.org/10.32598/JRH.12.1.1937.1>



Article info:

Received: 26 Aug 2021

Accepted: 13 Dec 2021

Publish: 01 Feb 2022

Keywords:

Diabetes Mellitus, Survival, Breast Neoplasms, Neoplasm Metastasis

ABSTRACT

Background: Breast cancer is a highly prevalent malignancy leading to death across the world. However, patient survival is greatly affected by making a diabetes diagnosis. The present assessed the association between diabetes mellitus and the five-year survival rate of breast cancer patients at the cancer treatment centers.

Methods: This retrospective follow-up study was conducted on 534 diabetic women with breast cancer who had been diagnosed during 1999-2013 referring to cancer treatment centers of Mashhad University of Medical Sciences. Demographic and clinical data of patients were collected through questionnaires in these centers searching the patient's available medical files. Notably, the patients were selected via systematic random sampling, and also the five-year survival of the patients was assessed during the follow-up period up to 2018.

Results: In breast cancer patients, the diabetes prevalence was 12.7%. Of note, the mean and median five-year survival were 9.95 and 13, respectively. No significant difference was observed in the survival rate of the diabetic and non-diabetic patients (95% CI: 0.431-1.334; hazard ratio [HR]: 0.758; P=0.34). The survival time increased in the patients receiving metformin as a treatment protocol (95% CI: 0.226-0.950; HR: 0.5; P=0.04).

Conclusion: Based on the results, training diabetic patients regarding risk factors of breast cancer and effective therapies in controlling hyperglycemia that need to screen in the early diagnosis of breast cancer are essential to improve health and increase survival rate in diabetic patients.

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1. Introduction

Cancer is a major public health threat across the world, especially in developing countries [1]. The incidence rate of cancer is increasing due to the prevalence of its risk factors, such as smoking habits, obesity, and immobility [2]. Based on the statistics in 2016, cancer accounted for more than 13% of deaths in Iran [3]. Notably, breast cancer is a more prevalent malignancy among Iranian women as well as the fourth leading cause of cancer deaths in the world [4]. In the United States in 2014, approximately 180,000 cases of invasive breast cancer and 40,000 deaths were reported [5]. The number of new cancer cases is remarkably increased and cancers causing death are also predicted to reach over 11.4 million in 2030 across the world, manifesting cancers to be the major cause of death.

Based on the scientific reports, 40% of cancers could be prevented if the risk factors were decreased [6]. One of the main risk factors that should be reduced is to control disease complications due to the association of some diseases (e.g., diabetes) with cancer. The correlation between type II diabetes and some cancers has been identified, while this diagnostic complexity is remarkably increasing. However, cancers, especially breast cancer, is affected by some risk factors, including diabetes, insulin resistance, obesity, smoking habits, socioeconomic status, age, gender, ethnicity, and hormone receptors (such as estrogen and progesterone) [7]. The global prevalence of diabetes as a risk factor for cancer has a message to take the disease more seriously [8]. In addition, some research has investigated the mechanisms of how diabetes and cancer are associated [9]. According to Fedeli et al. [10] and Pandey et al. [8], various biological conditions, including hyperinsulinemia, hyperglycemia, persistent anti-inflammatory status, and obesity were defined as risk factors in diabetic patients for breast cancer.

Based on the research conducted by Dabrowski et al. [11], breast cancer was the most common malignancy in diabetic patients. Moreover, factors, such as HbA1c level ($\geq 8.5\%$), body mass index ($BMI \geq 30 \text{ kg/m}^2$) and insulin treatment had significant associations with the increased risk of malignancies. Diabetic patients were reported to have a poor prognosis after making a cancer diagnosis as well as an increased risk of cancer [12].

In diabetes patients with breast cancer, evidence shows an increased rate of mortality. Nevertheless, it remains unclear whether or not diabetes is an independent risk factor

for mentioned neoplasms. However, these data have been poorly evaluated and need more investigation [10].

Despite receiving multiple treatments, the survival rate of these patients declines due to the metastatic nature of cancer. However, the diagnosis of cancer patients with diabetes increases the complications in the treatment process, which in turn reduces the survival rate. With this background, the present study assessed the association between diabetes mellitus and the five-year survival rate of breast cancer patients at the cancer treatment centers.

2. Methods

This retrospective follow-up study was conducted to analyze the patients' data diagnosed with breast cancer receiving treatment at the cancer treatment centers. The sample population included the women patients diagnosed with breast cancer during 1999-2013, who were referred to the oncology chemotherapy and hematology of Imam Reza (A. S.), Ghaem (AJ), and Isar Chemotherapy Center, Mashhad, Iran. The aims of the investigation were explained to the patient or the patient's legal representative by telephone. These patients were followed-up to evaluate survival time up to five years since diagnosis time (2018).

The inclusion criteria of the study were the female patients with the pathological diagnosis of breast carcinoma and age of more than 18 years. Notably, the exclusion criteria were the family history of breast cancer, incomplete cancer therapy due to leaving the hospital with personal consent, and failure to complete the treatment. After receiving the required permission from the Ethics Committee of the university, the medical records dating back to 1999-2013 were selected via systematic random sampling, and the related variables were systematically extracted. According to the sample size, after dividing the number of samples between five years, the sample size for breast cancer was obtained each year. Then, in each year, the research samples were selected by systematic sampling method and the relevant variables were extracted, and then, the 5-year survival of patients was followed.

In addition, required clinical and demographic data were retrospectively collected for 534 eligible patients from their medical records. Then, the patients were divided into two groups based on their history of diabetes and its absence. The patients diagnosed with breast cancer were followed up to evaluate survival time up to five years since the diagnosis time to investigate the relationship between diabetes and risk factors with survival rate.

Informed consent

In order to obtain informed consent through telephone contact with the patient's family, the objectives of the research were explained to the patient or the patient's legal representative, and then the patient or the patient's legal representative was asked to refer to the medical center if able and after obtaining informed consent research variables were questioned.

The breast cancer diagnosis was confirmed based on the criteria of the International Classification of Diseases (ICD), the American Commission on Cancer, and pathology reports. To make a diabetes diagnosis, fasting blood sugar (FBS) and HbA1c tests were precisely carried out. More importantly, diabetes diagnosis was recorded based on FBS ≥ 126 mg/dl.

Statistical analysis

Data analysis was performed by SPSS software, v. 17 nonparametric equation, Mann-Whitney U test, Chi-square test, and Cox proportional hazards model to evaluate risk factors and Hazard Ratio (HR) in the diabetic and non-diabetic breast cancer patients. In all the statistical analyses, the $P < 0.05$ was considered significant.

3. Results

The mean age of the diabetic and non-diabetic breast cancer patients was 56.75 and 49.28 years, respectively. The demographic characteristics of the participants are presented in Table 1.

In diabetic and non-diabetic patients, cancer risk factors indicated that 100% of diabetic and 99.4% of non-diabetic patients had no smoking habits. Regarding using Oral Contraceptive Pill (OCP), the results of the Chi-square test indicated no significant difference between diabetic and non-diabetic patients ($P=0.80$). Moreover, all diabetic patients (100%) and the majority of non-diabetic patients (99.8%) had no history of hormone replacement therapy. The results of Fisher's exact test demonstrated no significant differences between diabetic and non-diabetic patients ($P=1.000$). In addition, other risk factors, such as the BMI and age at menarche, menopause, and first full-term pregnancy in breast cancer patients is presented in Table 2.

In this study, the stage of cancer was considered based on the patient's history recorded by the doctor, whether the cancer is in the non-metastatic stage, there is lymph node involvement or metastasis to distant areas. In non-metastatic stage breast cancer, metastasis to distant areas is considered as stage 0 and I, lymph node involvement

Table 1. Basic demographic characteristics of the subjects

Characteristic	Variables	Patient	No.(%)
Marital status	Single	Diabetic	0(0)
	Married	Diabetic	60(88.2)
	Other (divorced-Widow)	Diabetic	8(11.8)
	Single	Non-diabetic	21(4.5)
	Married	Non-diabetic	437(93.8)
Residence	Other (divorced-Widow)	Non-diabetic	8(1.7)
	City	Diabetic	61(7.89)
	Village	Non-diabetic	70(0.15)
	City	Diabetic	396(0.85)
Job status	Village	Non-diabetic	7(3.2)
	Homemaker	Diabetic	63(6.92)
	Employed	Non-diabetic	5(3.7)
	Homemaker	Diabetic	383(2.82)
	Employed	Non-diabetic	83(9.17)



Table 2. Frequency of risk factors in breast cancer patients

Variables	Patient	Mean±SD
BMI	Diabetic	35.5±60.29
	Non-diabetic	60.5±85.27
Menarche age	Diabetic	33.1±17.13
	Non-diabetic	12.93±1.11
Age at menopause	Diabetic	49.68±2.61
	Non-diabetic	49.02±3.62
Age at first full-term pregnancy	Diabetic	3.49±98.18
	Non-diabetic	3.47±93.19

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occurs in stage II and III, the metastatic stage is considered as stage IV. According to the histopathological diagnosis, 52.9% of diabetic patients and 45.3% of non-diabetic patients were in the stage of lymph node metastasis. The Chi-square test ($P=0.18$) did not show a significant difference between the diabetic and non-diabetic groups in terms of tumor stage. In addition, 70.5% of patients had estrogen receptor-positive cancer, while 70.5% had progesterone receptor-positive cancer. However, Chi-square results indicated no significant difference between diabetic and non-diabetic patients ($P=0.88$). Notably, about 54.9% of patients had HER2-negative receptors. Based on the HER2 receptor subtype, 40.5% of patients were in the luminal-A subgroup. However, in terms of the HER2 receptor and its subgroup, Chi-square results showed no significant difference between diabetic and non-diabetic patients. The Mean±SD CA15-3 tumor marker was estimated at 27.74±26.93 and 74.17±397.41 in diabetic and non-diabetic patients, respectively. However, the Mann-Whitney U test demonstrated no significant differences between the groups ($P=0.63$).

Based on the results, the prevalence of diabetes was 12.7% in breast cancer patients and the Mean±SD duration of diabetes was 8.27±4.71 years. With respect

to controlling risk factors, such as diabetes controlling drugs, 47.1% of patients were using metformin and glibenclamide, and 36.8% and 13.2% of the patients were using metformin and NPH/regular insulin, respectively.

The mean survival rate of non-diabetic and diabetic patients with breast cancer was 10.021 and 7.420 years, respectively. To investigate the impacts of diabetes on the survival rate of breast cancer patients in the presence of effective factors, such as age (at menarche, menopause, and the first full-term pregnancy), smoking habits, history of OCP use, BMI, the related data were fitted in the Cox regression model. However, findings indicated no significant differences between survival time of diabetic and non-diabetic patients (95%CI: 0.431-1.334; HR: 0.758; $P=0.34$).

Concerning diabetes-controlling drugs, the Cox regression model indicated that mortality risk significantly decreased in the patients receiving metformin, as their survival rate increased (95%CI: 0.226-0.950; HR: 0.5; $P=0.04$). However, insulin injection had no effect on the survival rate of breast cancer patients. In breast cancer cases, the effects of using drugs on the survival rate of diabetic and non-diabetic patients are presented in Table 3.

Table 3. Effects of diabetes and drugs on survival of breast cancer patients

Variables	HR	95%CI	P
Diabetes	0.758	0.431-1.334	0.34
Metformin	0.5	0.266-0.950	0.04
Insulin	1.310	0.172-9.977	0.80

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4. Discussion

According to the World Health Organization (WHO), breast cancer is the most prevalent cancer among women across the world as well as a leading cause of death among Iranian women [1]. Recent evidence suggests that more than half a million women in Iran die due to breast cancer, and the mortality rate has been on the rise [13]. In the current research, no significant difference was observed between diabetic and non-diabetic groups in terms of the survival rate, which is consistent with the results of Villarreal-Garza et al. [14] and Behrouzi et al. [15]. Therefore, it seems that diabetes does not affect the survival rate independently. In another study, De Bruijn et al. [16] considered diabetes as a risk factor for breast cancer and cancer death. In similar research, Currie et al. [17] reported the increased mortality rate associated with cancer, especially breast cancer in diabetic patients compared to non-diabetic ones. Furthermore, Erickson et al. [18] showed a significant reduction in the overall survival rate of the survivors of primary breast cancer by chronic hyperglycemia. This discrepancy between our findings and the aforementioned studies might be due to metformin use in diabetic patients with breast cancer, which was observed to increase the survival rate of our subjects. In summary, further investigation is recommended to confirm our findings.

History evaluation based on oral antidiabetic drugs revealed a significant decrease in the mortality rate in patients receiving metformin treatment, which in turn increased their survival rate. In a study by Sonnenblick et al. [19], the patients without metformin treatment were reported to have a lower survival rate compared to the other subjects ($P=0.004$). Moreover, Lega et al. [20] reported an association between the improved survival rate of diabetic patients with breast cancer and the increased duration of diabetes treatment with metformin. In another research, Currie et al. [17] denoted the decreased survival rate of the patients receiving metformin treatment. Similarly, Pandey et al. [8] stated that metformin could decrease the risk of cancer, while Bayraktar et al. observed that metformin use during chemotherapy had a significant effect on the survival rate of diabetic patients with triple-negative breast cancer [21]. Therefore, it could be concluded that metformin is an effective drug to reduce blood glucose and is widely recognized as the primary treatment for patients with type II diabetes [22]. In the present study, metformin could increase the survival rate of diabetic patients, which highlighted the importance of hyperglycemia treatment in breast cancer patients.

In a study by Collins et al. [9], hyperglycemia was reported to increase the production of free radicals causing DNA damage, leading to mutations in the tumor suppressor/oncogenes. In addition, it could induce the proliferation of cancer cells. Therefore, the improper control of hyperglycemia may decrease the survival time in diabetic patients with breast cancer.

In the current research, insulin injection had no impact on the survival rate of diabetic patients with breast cancer. However, Sonnenblick et al. [19] reported that insulin injection adversely affected diabetic patients with breast cancer having positive HER2. In another study, Ferroni et al. [23] observed a significant correlation between insulin and disease stage as a negative prognosis indicator that could reduce the survival rate. Moreover, Tseng et al. [24] claimed that insulin use (mostly human insulin) for more than three years might be associated with the potential risk of death due to breast cancer. Insulin may also increase the risk of breast cancer through alterations in the circulating estrogen levels. Therefore, it could be inferred that insulin may accelerate breast cancer progression, leading to disease recurrence and death due to breast cancer after long-term consumption. In contrast, some studies have indicated that insulin treatment could not predict poor prognosis in breast cancer patients [25]. The discrepancy with our findings might be due to the proper control of hyperglycemia and the prevention of diabetes complications in breast cancer patients.

To evaluate risk factors, the BMI of diabetic patients with breast cancer was higher compared to non-diabetic patients. Erickson et al. concluded that the overall risk of mortality was twice higher in the women with the HbA1C level of ≥ 7.0 after modifying the confounding factors compared to the subjects with HbA1C level less than 6.5% [18], which might be due to the reduced susceptibility to anti-angiogenic regimens [26]. In addition, in the study by Behrouzi et al. [15], the BMI of diabetic patients with breast cancer was also reported to be higher. However, a significant difference in BMI was observed between diabetic and non-diabetic groups ($P<0.001$). Considering the importance of metabolic syndrome and insulin resistance, our findings demonstrated the effects of factors, such as high BMI on the prognosis of breast cancer [27]. BMI was recognized as a risk factor in the diagnosis of diabetic patients with breast cancer.

5. Conclusion

The high prevalence of breast cancer is an important public health issue. According to the study results, diabetic patients are at risk of developing types of cancer,

especially breast cancer due to drug treatments and the presence of risk factors; therefore, screening is important. Given the increased survival in metformin-treated patients, the importance of treating hyperglycemia in diabetic patients with breast cancer is important. Therefore, early screening of diabetic women by physicians, for faster diagnosis of breast cancer in early stages and timely treatment and prevention of metastasis can improve their survival.

According to the results, in the follow-up survival of patients with breast cancer and diabetes, given the increased risk of death in patients with metastasis to distant sites, identifying risk factors and early diagnosis could be effective in increasing the survival of patients with breast cancer. Despite different results, training diabetic female patients regarding risk factors of breast cancer, effective therapies in controlling hyperglycemia, such as metformin, and also screening in the early stages of breast cancer are essential to improve health and increase survival rate in diabetic patients.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Medical Sciences Faculty at Sabzevar University of Medical Sciences (Code: IR.MEDSAB.REC.1397.020).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization and supervision: Marjan Sharifi Nasab, Hamideh Yazdimoghaddam, Seyedeh Tahereh Mohaddess; Methodology: Marjan Sharifi Nasab, Hamideh Yazdimoghaddam, Mohammad Hasan Rakhshani; Writing, original draft: Hamideh Yazdimoghaddam; Review & editing: Kazem Abbaszadeh Goudarzi; Data collection: Marjan Sharifi Nasab; Data analysis: Mohammad Hasan Rakhshani.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

We extend our gratitude to the authorities of the hospitals affiliated with Mashhad University of Medical Sciences for assisting us in this research project.

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