



ORIGINAL RESEARCH PAPER

General Surgery

THE DIFFERENCE OF INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR EXPRESSION IN BREAST CANCER PATIENTS WHO ARE SUFFERING AND NOT DIABETES MELLITUS TYPE 2 IN ADAM MALIK HOSPITAL

KEY WORDS: Breast Cancer, Type 2 Diabetes Mellitus, Insulin Growth Factor 1 Receptor

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ABSTRACT

Background: Breast cancer is a global problem and a prominent international health issue, including the most common malignancies in women in developed countries. Like breast cancer, diabetes mellitus (DM) is still a global problem, especially in developed countries. This study would like to see the difference of insulin-like growth factor 1 receptor expression in diabetic breast cancer patients and non-diabetic breast cancer patients.

Methods: The design of this study is case-control, with the patients included in this study are the breast cancer patients with or without a history of type 2 DM who already had an examination of insulin growth factor (IGF) histopathology. The statistical analysis was done with chi-square analysis to determine the relationship between the overexpression of the IGF1 receptor (IGF1R) and the history of type 2 diabetes mellitus (DM).

Result: There was a statistically significant difference between the overexpression of the IGF1R incident and a history of type 2 DM in a patient with breast cancer (p = 0.001, OR: 4.9; 95% CI 1.898 – 12.697). Further analysis of the sample characteristics also showed a significant difference between the overexpression of IGF1R incident and the incident of distant metastasis (p = 0.049).

Conclusion: In this study, it was found that there was a significant difference in the expression of IGF1R in breast cancer patients suffering from and not type 2 diabetes mellitus; and could be a predictor of breast cancer, especially in patients with diabetes mellitus.

INTRODUCTION

Breast cancer is a global problem and an important international health issue, including the most common malignancies in women in developed countries. According to the World Health Organization (WHO), 8-9% of women will experience breast cancer in their lives. Based on the 2012 International Agency for Research on Cancer (IARC), new cases of breast cancer were 43.1 per 100,000 women, with a mortality rate of 12.9 per 100,000 women (Sobri et al., 2017). Based on data from the Jakarta Breast Cancer Foundation, 10 out of 10,000 Indonesians have breast cancer, 70% of patients come to the doctor or hospital at an advanced stage. The low level of public awareness causes high levels of stadium of breast cancer patients in Indonesia (YKPJ, 2005). Based on data from the Hospital Information System (SIRS) in 2009, breast cancer ranked first among inpatients throughout Indonesia, namely 21.69% of all cancer patients. In the oncology surgery subdivision, H. Adam Malik General Hospital alone, the number of cases of breast malignancy recorded from 2012 through 2014 was 1,427 cases (RSUP. H. Adam Malik, 2015).

Like breast cancer, diabetes mellitus (DM) is still a global problem, especially in developed countries, attacking more than 9.7% of people in America (Centers for Disease Control and Prevention, 2005). In 2004, an estimated 3.4 million people died due to high fasting blood sugar. In a 2011 study, the DM incidence reached 71,400,000 (Mohan et al., 2013).

Interestingly, people with type 2 diabetes mellitus are at high risk for breast cancer (Giovannucci et al., 2010) Collecting data shows that diabetes has an impact on the prevalence, development, and prognosis of breast cancer (Cohen DH, 2012). Both diseases share the same risk factors and the use of anti-diabetes drugs has an effect on cancer patients with diabetes. Increased evidence suggests that insulin such as growth factor/insulin receptors (IGF/IR) signaling can play an essential role in the pathogenesis of diabetes and cancer (Shimizu et al., 2004). In this study, we assessed the expression of Insulin-like growth factor 1 receptor protein in breast

cancer tissue of patients with or without type 2 DM in H. Adam Malik General Hospital Medan.

METHODS

Study design and data collection

The design for this study is case-control, in which the data was obtained from medical records of the breast cancer patients with and without a history of type 2 diabetes and already had an examination of insulin growth factor histopathology who came to H. Adam Malik Hospital, Medan, North Sumatera between January 2015 and December 2017. The data collection method for this study is by using simple random sampling. The inclusion criterion in this study was all the breast cancer patients with or without a history of type 2 diabetes who already had insulin growth factors histopathology examination. The exclusion criteria in this study were incomplete data, the patients who did not want to be included in the study, the patients had a history of other malignancies, and the patients who had a history of having breast implants.

Cases and Controls

The case in this study is the breast cancer patients with type 2 DM who already had an examination of insulin growth factor histopathology, while the control of this study is the breast cancer patients without a history of type 2 DM who already had an examination of insulin growth factor histopathology.

Outcome variables

The outcome variable of this study is the result of the insulin growth factor histopathology. The results of this examination are expressed as the overexpression of insulin growth factor 1 receptor (IGF1R), determined by an immunoreactive score of 0-1, and normal expression of IGF1R, determined by an immunoreactive score of 2-3 in histopathology examination.

Statistical Analysis

The results of this study were analyzed with statistics software SPSS version 22 (SPSS software, SPSS Inc., Chicago, US). The data were analyzed as a descriptive study with the results

were expressed in frequency, mean and median with standard deviation. The relationship between case and control group was analyzed with chi-square, in which the value $p < 0.05$ was considered as significant. All the results will be expressed in the text, tables, or figures.

Ethics statement

This study has already been approved by the ethics committee of the faculty of medicine, Universitas Sumatera Utara (USU).

RESULTS

Demographic characteristics

A total of 80 patients were included in this study. The patients were divided into two groups, in which 39 patients were included in the type 2 DM group, and 41 patients were included in the group without type 2 DM. Among all the type 2 DM group, the mean age of the patients was 52.33 ± 8.32 years old, while in the group of breast cancer without the type 2 DM, and the mean age was 55.32 ± 11.32 years old. There was no significant difference in the age between the two groups. The prevalence of the breast cancer incidence was observed as highest in the patients with age of 50-59 years old, with a total of 16 patients (20.0%) in the type 2 DM group, and 13 (16.3%) in the group without type 2 DM.

We also observed the type of breast cancer in the patients, the TNM staging of the patients, and the overall staging of the patients. The result of this observation is shown in Table 1.

Table 1. Demographic Characteristics

Characteristics	n (%)		Mean \pm SD	
	Type 2 DM	Without Type 2 DM	Type 2 DM	Without Type 2 DM
Age interval (year old)			52.33 ± 8.32	55.32 ± 11.32
30-39	4 (5.0)	3 (3.8)		
40-49	10 (12.5)	11 (13.8)		
50-59	16 (20.0)	13 (16.3)		
60-69	9 (11.3)	10 (12.5)		
70-79	0 (0.0)	2 (2.5)		
80-89	0 (0.0)	2 (2.5)		
Histopathology				
Invasive Ductal Carcinoma (IDC)	31 (38.8)	29 (36.3)		
Invasive Lobular Carcinoma (ILC)	8 (10.0)	12 (15.0)		
Highest Diameter of Tumor (T)				
T1	1 (1.3)	2 (2.5)		
T2	9 (11.3)	8 (10.0)		
T3	20 (25.0)	19 (23.8)		
T4	9 (11.3)	12 (15.0)		
Node (N)				
N0	5 (6.3)	7 (8.8)		
N1	20 (25.0)	21 (26.3)		
N2	13 (16.3)	9 (11.3)		
N3	1 (1.3)	4 (5.0)		
Distant Metastasis (M)				
M0	29 (36.3)	22 (27.5)		
M1	10 (12.5)	19 (23.8)		
Stage				
I	1 (1.3)	2 (2.5)		
II	6 (7.5)	3 (3.8)		
III	22 (27.5)	17 (21.3)		
IV	10 (12.5)	19 (23.8)		

Normality distribution of the age and overexpression of IGF1R

The normality test of the age data and overexpression of

IGF1R was done with the Kolmogorov-Smirnov test. In this analysis, the distribution of the age data was normal ($p = 0.200$) while the distribution of the overexpression data of IGF1R was not normal ($p = 0.0001$). The result of this analysis is shown in table 2.

Table 2. Kolmogorov-Smirnov Test for Age and Overexpression of IGF1R Data

Characteristics	Type 2 DM	P-value
Age	Yes	0.200*
	No	0.200*
Over expression of IGF1R	Yes	0.0001*
	No	0.0001*

* p-value is considered significant if less than 0.05

Relationship of the overexpression of IGF1R with type 2 DM

Among the type 2 DM group, there were 28 patients had overexpression of IGF1R, while there were 14 patients with overexpression of IGF1R in the group without type 2 DM and 27 patients in the group without type 2 DM did not have overexpression of IGF1R. The relationship between these two groups was analyzed with chi-square, which showed that there were significant differences of overexpression IGF1R incident between the type 2 DM group and the group without type 2 DM ($p = 0.001$, OR: 4.9; 95% CI 1.898 – 12.697). The summary of the result is shown in Table 3.

Table 3. The Relationship of the Over expression of IGF1R with Type 2 DM

		Type 2 DM		P value
		Yes	No	
Overexpression of IGF1R	Yes	28	14	0.001*
	No	11	27	

* p-value is considered significant if less than 0.05

Relationship of the overexpression of IGF1R with samples characteristics

We also further analyzed the relationship between the overexpression of IGF1R and the sample characteristics. The characteristics included in this analysis was the score of “N and M” in TNM staging more than 0, and the type of histopathology of the breast cancer. The analysis was done with chi-square and the result is shown in table 4.

Table 4. The Relationship of the Overexpression of IGF1R with Sample Characteristics

Characteristics	P-value
Node (N) Score > 0 Yes vs. No	0.286*
Distant Metastasis (M) Yes vs. No	0.049*
Histopathology Type IDC vs. ILC	0.438*

* p-value is considered significant if less than 0.05

DISCUSSION

Breast cancer is a malignant tumor that starts from cells found in the breast. These malignant tumors can enlarge and invade surrounding tissue or spread to tissue far from the breast (The American Cancer Society, 2012). Breast cancer can be divided into ductal and lobular types. The most common type of breast cancer is the invasive ductal type which accounts for 75% (Cassidy et al., 2002).

Based on age, Agustina's research in 2018 states that the most age range is at the age of 45-49 years (Agustina, 2018). Furthermore, the Wahidin study in 2018 found that about 80% of the total sample of the study was in the range of 40 years and over with each of the 40-49 years age range of 38.1% and ≥ 50 years of 42.3% (Wahidin, 2018). In a previous study, Rizki

stated that around 51.87% of the research samples were in the range of 46 to 55 years (Rizki, 2019). Similar results were obtained in this study, where the mean age in the DM and non-DM groups was 52.33 ± 8.32 years compared to 55.32 ± 11.32 years with the majority of ages from 40-69 years with a total of 69 patients (86.25%) respectively from ages 40-49, 50-59, and 60-69 respectively were 21 patients (26.3%), 29 patients (36.3%), and 19 patients (23.8%).

For the type of breast cancer that was assessed histopathologically, 60 samples (75.15) were obtained with the type of invasive ductal carcinoma, while the remaining 20 samples (25.0%) were obtained. In the 2003 Christopher study, of a total of 190,000 cases, approximately 72.8% (138,000) cases were invasive ductal carcinoma. (Christopher, 2003). Also, the 2015 Xin study found similar results. Where in the study, obtained 85% of ductal carcinoma histopathology types.

IGF/IR group is an important growth factor system in the body that has a robust anti-apoptotic effect and plays a role both in the development of organisms and defenses so that the normal function of cells in the body continues to run normally. This IGF/IR group also has a vital role in the development of cancer, while at the same time the IGF/IR axis influences the risk of diabetes and IGF-1 can play a role in reducing blood sugar levels (Chan, 2008; LeRoith, 2003; Schneider, 2011; LeRoith, 2007).

IGF1R expression shows the difference between groups of breast cancer with diabetes mellitus and without diabetes mellitus. In the breast cancer group with diabetes mellitus, a higher expression of IGF1R was obtained. As is well known, insulin resistance will have an impact on chronic hyperinsulinemia and insulin can indirectly increase IGF-1 production in the liver (Amiel, 1984; Leung, 2000). Thus, chronic hyperinsulinemia is associated with elevated levels of IGF-1 (LeRoith, 2003; Renehan, 2004). In addition, increased insulin levels cause an increase in hybrid receptors and cause insulin to bind to IGF1R (Vigneri, 2009). Some of the statements above indicate that the IGF signal will be actively associated with insulin resistance status in diabetes mellitus.

A previous study from Xin in 2015 found a significant difference in the expression of IGF1R between patients suffering from diabetes mellitus compared with no diabetes mellitus with a p-value of 0.044. 26 DM patients had high IGF1R expression and 14 patients who had low IGF1R expression. Whereas in patients without DM, 17 patients with high IGF1R expression were compared with 23 patients with low IGF1R expression (Xin, 2015). Similar results were obtained in this study, where we found 28 patients with diabetes mellitus and high IGF1R expression. Whereas in patients who did not suffer from diabetes mellitus and low IGF1R expression, showed a total of 27 patients. This result shows a statistically significant difference with a p-value of 0.001.

This study also performed a comparison between tumor diameter and IGF1R expression, but the results were not statistically significant with the odds ratio has a range of 0.198-26.181 and a p-value of 0.602. Similar research results were also obtained from the 2015 Xin study which received an odds ratio of 0.057-1.945 with a p-value of 0.221 (Xin, 2015). Furthermore, it was also assessed whether there was a nodal metastasis with an odds ratio of 0.138-1.818 and a p-value of 0.286, which indicated that it was not statistically significant. Research from Xin (2015) also obtained an odds ratio of 0.276-8.804 with a p-value of 0.615 (Xin, 2015). The last thing assessed in this study is the type of histopathology between IDC and ILC with a p-value that is not statistically significant, namely 0.438 with an odds ratio between 0.239-1.863.

CONCLUSION

In this study, it was found that there was a significant

difference in the expression of IGF1R in breast cancer patients suffering from and not type 2 diabetes mellitus. Furthermore, it could be a predictor of breast cancer, especially in patients with diabetes mellitus.

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