



## CHARACTERISTICS OF BREAST CANCER PATIENTS ACCOMPANIED BY TYPE 2 DIABETES MELLITUS

### Surgery

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### ABSTRACT

**Background:** Breast cancer is the woman's leading cause of death in the world to date (DeSantis et al, 2016). Type 2 diabetes mellitus has been recognized as a risk factor for several types of cancer, including breast, liver and pancreatic cancer. Insulin resistance and high insulin levels in type 2 DM are mitogenic for breast cancer cells. Insulin receptors are also often expressed in breast cancer (Yerrabothala et al, 2014). Therefore, the author is interested to discover how the characteristics of breast cancer patients accompanied by type 2 diabetes in H. Adam Malik Medan General Hospital.

**Methods:** This study is a descriptive study with a cross sectional design, with a sample of 318 breast cancer patients associated with type 2 diabetes at H. Adam Malik Medan General Hospital from January 2013 to December 2017 who met the inclusion and exclusion criteria. Data taken from medical records. Data that has been collected, processed, and presented descriptively in the form of tables and diagrams using the SPSS program ver. 22.

**Results:** In this study 318 breast cancer patients accompanied by type 2 DM were found from a total of 3137 breast cancer patients in H. Adam Malik Medan General Hospital (proportion: 10.13%). The majority of patients were aged 46-55 years old by 121 (38.1%) patients, menarch at the age of 12 as many as 136 (42.8%) patients, 247 (77.7%) patients had menopause, had BMI 23.0 -24.9 kg/m<sup>2</sup> as many as 88 (27.7%) patients, had two children by 155 (48.7%) patients, did not have a family history of breast cancer as many as 264 (83%) patients, almost 90% of patients had underwent surgery, had histopathological type of Invasive Ductal Carcinoma (IDC) as many as 231 (72.6%) patients, had grade III tumor by 182 (57.2%) patients, stage III and IV by 110 (69, 2%) patients each, and had TNBC subtypes of 179 (56.3%) patients.

**Conclusion:** The majority of breast cancer patients accompanied by type 2 DM were aged 46-55 years old, menarch at the age of 12, 247 (77.7%) patients had menopause, had BMI 23.0 -24.9 kg/m<sup>2</sup>, had two children, did not have a family history of breast cancer, had underwent surgery, had histopathological type of Invasive Ductal Carcinoma (IDC), had grade III tumor, stage III and IV, and had TNBC subtypes.

### KEYWORDS

Breast cancer, diabetes mellitus

### Introduction

Cancer is one of the leading causes of death throughout the world. (DeSantis et al, 2016). In 2012, around 8.2 million deaths were caused by cancer (Kemenkes RI, 2015). Breast cancer causes the death of the number one woman in the world today. Data from the American Cancer Society (2015) estimated 231,840 new cases of breast cancer and 40,290 deaths caused by breast cancer. In Indonesia, breast cancer is ranked second after cervical cancer. The breast cancer prevalence in Indonesia is 0.5% in 2013 (Kemenkes RI, 2015). In the subdivision of Surgical Oncology at RSUP H. Adam Malik, the number of cases of breast malignancies recorded in the period 2011-2013 was 1,427 cases (Division of Surgical Oncology, 2013).

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

Glucose is the main fuel for cells in the body, including cancer cells. Higher blood glucose levels certainly provide enough fuel for cancer cells, stimulate proliferation, and accelerate the development of cancer cells. Hyperglycemia is the initiator of tissue damage in diabetes. The mechanism of hyperglycemia destroys tissue is through changes in acute acute cellular glucose metabolism, or through chronic accumulation of glycated biomolecules and advanced glycation end products (AGE). The interaction between AGE and its specific receptors often causes oxidative stress which leads to an increase in proinflammatory signals by activating the transcription factors of nuclear factor (NF) -BB and the formation of reactive oxygen species (ROS) in cells. In diabetes, hyperglycemia is responsible for the occurrence of endothelial dysfunction and aberrant neoangiogenesis, which suggests that hyperglycemia can support angiogenesis in cancer (Chang et Yang, 2016).

There are several mechanisms related to the relationship of breast

cancer and DM. First, cancer patients with diabetes experience increased tumor cell proliferation and metastasis in an environment of hyperinsulinemia and hyperglycemia. Research has found that high insulin or insulin-like growth factors can trigger the formation of cancer cells and tumor growth. Another potential pathway is acute exposure to hyperglycemia can increase endothelial cell permeability due to increased generation of reactive oxidative species and structural changes in the basement membrane, which ultimately increases the likelihood of metastasis (Peairs et al, 2011).

Most studies of the relationship between diabetes and breast cancer are carried out in the Western world (Wu et al., 2015). In the study of Liao et al (2010) showed that DM was a poor prognostic factor for breast cancer. Similar to the study by Hardefeldt et al (2012), results showed that DM was a risk factor for breast cancer. Because DM is one of the risk factors for breast cancer, the researchers are interested in examining how the characteristics of breast cancer patients are accompanied by type 2 DM in H. Adam Malik General Hospital, Medan.

### Methods

This study was a descriptive study with a cross sectional study design, with a sample of 318 breast cancer patients accompanied by type 2 DM in the Surgical Oncology Division of the Department of Surgery at the USU Medical Faculty H. Adam Malik General Hospital Medan from January 2013 to December 2017 that met the criteria inclusion and exclusion. The inclusion criteria of this study were type 2 DM patients with breast cancer and breast cancer patients with type 2 DM. While the exclusion criteria were incomplete data and had a history of other malignancies.

Data taken in the form of age, age of menarche, age of menopause, BMI, parity, family history, history of surgery, stage, histopathology, grading, and tumor subtypes. Data taken from medical records. Data that has been collected, processed, and presented descriptively in the form of tables or diagrams using the SPSS program ver. 22. Explanation of tables and diagrams will be presented in narrative form.

## Result

In this study 318 breast cancer patients were accompanied by type 2 diabetes mellitus from a total of 3137 breast cancer patients in H. Adam Malik General Hospital Medan from January 2013 to December 2017. This means that the proportion of breast cancer patients accompanied by type 2 DM at H. Adam Malik Hospital Medan from January 2013 to December 2017 at 10.13%.

The majority of patients aged 46-55 years were 121 (38.1%) patients, menarche at 12 years old as many as 136 (42.8%) patients, 247 (77.7%) patients had menopause, had BMI 23.0 -24.9 kg / m<sup>2</sup> as many as 88 (27.7%) patients, had two children 155 patients (48.7%), had no family history of breast cancer as many as 264 (83%) patients, almost 90% of patients had undergone surgery, a histopathological type of Invasive Ductal Carcinoma (IDC) with a total of 231 (72.6%) patients, had tumor III grading with a total of 182 (57.2%) patients, including stage III and IV respectively 110 (69.2%) patients, had TNBC subtypes of 179 (56.3%) patients. The characteristics of this research sample can be seen in table 1.

**Table 1. Characteristics of the study sample**

Characteristics	Frequency (n)	Percentage (%)
Age (years) (Mean (SD))	51,87 (±10,117)	
≤35	16	5,0
36-45	71	22,3
46-55	121	38,1
56-65	81	25,5
≥66	29	9,1
Menarche age (years) (Mean (SD))	12,43 (±1,288)	
10	9	2,8
11	56	17,6
12	136	42,8
13	61	19,2
14	27	8,5
15	20	6,3
16	9	2,8
Menopause		
Ya	247	77,7
Tidak	71	22,3
BMI (kg/m <sup>2</sup> )		
<18,5	36	11,3
18,5-22,9	53	16,7
23,0-24,9	88	27,7
25,0-29,9	87	27,4
≥30,0	54	17
Parity		
1	112	35,2
2	155	48,7
3	35	11,0
4	16	5,0
Family History with Breast Cancer		
Yes	54	17,0
No	264	83,0
Operational History for Cancer		
Yes	278	87,4
No	40	12,6
Histopathology		
IDC	231	72,6
ILC	87	27,4
Grading		
I	45	14,2
II	91	28,6
III	182	57,2
Stadium		
I	27	8,5
II	71	22,3
III	110	34,6
IV	110	34,6
Subtype		
Luminal A	62	19,5
Luminal B	29	9,1
HER2 overexpression	48	15,1
TNBC	179	56,3
<b>Total</b>	<b>318</b>	<b>100</b>

## Discussion

Breast cancer is malignancy in breast tissue that can originate from the ductal epithelium or lobule. This cancer is most often found in women where as many as 22% of new cases of cancer in women are breast cancer and is one of the main causes of cancer-related deaths in the world (Ministry of Health, 2017; Suprabawati, 2017).

The incidence of breast cancer in Indonesia and the world (Europe-United States) tends to increase. Breast cancer is an important public health problem, due to its high mortality and morbidity (Ramli M, 2015; Indrati R, 2005). In 2018 there were 2,088,849 (11.6%) cases of breast cancer in the world with a mortality rate of 626,679 (6.6%) cases (Globocan, 2018).

Diabetes mellitus is a general term for metabolic disorders whose main finding is chronic hyperglycemia. The cause is a disorder of insulin secretion or a disruption of the function of insulin itself or both. (American Diabetes Association, 2014; Kerner, 2014). In Indonesia, from 1980 to 2000, there was an increase in the prevalence of diabetes mellitus from 1.7% in 1982 and then in 2013 to 5.7% and in 2001 it increased to 12.8% (PERKENI, 2011)

Some hypothetical mechanisms might explain the relationship between diabetes mellitus and the risk of breast cancer. Breast cancer is a malignancy related to hormones, and diabetes mellitus can cause hormonal changes that encourage the development of this cancer (Weiderpass, 1997). The mechanism underlying the relationship between diabetes and the risk of breast cancer may be related to changes in circulating insulin concentrations, insulin-like growth factor (IGFs) and endogenous hormones. Whereas in type 2 diabetes is usually associated with insulin resistance and increased pancreatic insulin secretion for a long time. A meta-analysis found an association between diabetes mellitus and breast cancer, of which 20 studies analyzed found 15 showed an increased risk of breast cancer in women with diabetes and 8 of them showed statistically significant results (Larsson, 2007). In other studies data obtained up to 10-20% that type 2 diabetes mellitus is associated with the risk of breast cancer (Wolf, 2005). Another meta-analysis indicated women with type 2 diabetes had a 23% higher risk of developing breast cancer than women who did not have diabetes mellitus. This increase is seen in postmenopausal women (Liao, 2011).

Of the 318 samples obtained in this study, women with diabetes mellitus who had breast cancer had the most age in the range of ages 36 to 65 which can be seen in table 4.1. In table 4.3, it can also be seen the incidence of breast cancer with DM is common in menopausal patients with 247 people (77.7%). In a study conducted by Lipscombe and colleagues, the same results were found in this study, which also concluded that female patients of post-menopausal age who had diabetes mellitus had a greater risk of developing breast cancer (Lipscombe, 2006). In this study, the age distribution of menarches tended to be higher in the age group ≤13 years, with a 10-year distribution of 9 people (2.8%), 11 years as many as 56 people (17.6%), 12 years old as many as 136 (42.8%), and age 13 as many as 61 people (19.2%). This is in line with a study in the form of a meta-analysis conducted by Zahmatkesh et al in 2016.

In this study 141 patients had BMI > 25, which was divided into BMI 25.0-29.9 as many as 87 people (27.4%) and ≥30.0 as many as 54 people (17%). Obesity has been linked to breast cancer by various studies. This is in line with the research conducted by Neuhouser et al. In 2015 where in his study taken from 3388 patients, there was an association between obesity and an increased risk of breast cancer with a value of p < 0.001. Multiparity is believed to reduce the risk of breast cancer (Babalou, 2017). In table 4.5, it can be seen that the majority of samples have a one-time parity status of 112 patients (35.2%) and 2 times as many as 155 patients (48.7%). Table 4.6 shows 264 patients (83.0%) did not have a family history diagnosed with breast cancer, this contradicts a study conducted by Brewer et al. In 2017 on 113,000 samples in the United Kingdom using the family history score and found the relationship between family history and the increased risk of breast cancer with a value of p < 0.0001. While in table 4.7 can be seen the number of samples who have a history of surgery for breast cancer previously there were 278 patients (87.4%).

More than 95% of breast cancers are adenocarcinoma. Invasive ductal carcinoma (IDC) is the most common form of invasive breast cancer with an incidence of 55% of breast cancer (Makki, 2015). This

supports the results of the study which obtained 231 patients (72.8%) out of 318 patients having IDC histopathology.

In this study, Poorly Differentiated was the most tumor grading with 182 patients (57.2%). Diabetes can directly affect the severity of breast cancer by changing the regulation of endogenous sex hormones and activation of IGF and insulin signaling pathways (Wolf, 2005). In this study, from 318 samples, 110 patients had stage III breast cancer and 110 patients had stage IV breast cancer. The research conducted by Srokowski found that in patients with diabetes mellitus the data tended to have breast cancer at a later stage compared to patients not diagnosed with diabetes mellitus (Srokowski, 2009). Estrogen receptors, progesterone receptors, HER-2, and Ki67 have become predictive and prognostic which are very important for breast cancer (Subik, 2010). In addition, there are studies on the expression of genes Luminal A and Luminal B. In this study, 318 patients were examined for subtypes, found that the majority of patients had TNBC subtypes of 179 (56.3%) patients, and minorities had Luminal B subtypes in a number of 62 (19.5%) patients. In line with the study by Bronsveld, it was shown that premenopausal women with diabetes tended to have TNBC subtypes and basal likes, which are associated with poor prognosis (Bronsveld et al, 2017). This result is different from the research from Behrouzi, et al., Which states that in patients with diabetes the luminal A gene subtype becomes the majority of the results with 61.1%. Whereas in Luminal B, HER2, and TNBC with a proportion of 8.8%; 12.0%; and 18.1% (Behrouzi, 2017). An earlier study showed an increase in estrogen levels in women with diabetes, that is, postmenopausal women will be more often affected by ER-positive breast cancer (Rose et Vona-Davis, 2012).

The weakness of this study is that the research data is taken from medical records and is retrospective. In addition, the author also had difficulty in retrieving research data in the H. Adam Malik Hospital Hospital Information System (SIRS) in Medan, because in SIRS only 5 people with breast cancer were recorded accompanied by type 2 DM, so the author had to manually record the patient.

## Conclusion

The majority of breast cancer patients are accompanied by type 2 DM aged 46-55 years, menarch at 12 years of age, menopause, BMI 23.0-24.9 kg / m<sup>2</sup>, have one to two children, no family history of breast cancer, ever surgery, histopathological type Invasive Ductal Carcinoma (IDC), tumor III grading, including stage III and IV, and TNBC subtypes.

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