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Original Research Paper

Surgery

THE DIFFERENCES OF THE LIPID PROFILE LEVEL IN SUBTYPES OF BREAST CANCER

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ABSTRACT

Background and Aim : Breast cancer is the leading cause of cancer death among woman. Changes in lipid metabolism have been reported in many types of cancer. Lipids have been involved in the regulation of proliferation, differentiation, apoptosis, inflammation, autophagia, motility and membrane homeostasis. The purpose of this study is to determine the differences levels of lipid profiles in subtypes of breast cancer.

Methods: We include all breast cancer patients who treated at polyclinics and patient wards of Oncology Surgical Science Department of general hospital of H. Adam Malik Medan since October 2018 to February 2019. Data such as age, age at the onset of menarche, menopausal status, body mass index (bmi), parity status, family history of breast cancer, previous history of breast cancer, histopathological findings, tumour grade, stage of cancer, genetic subtypes, lipid profile were collected.

Results: From 151 patients, The median age of this study was 51.0 (18-82) years. The mean age at the menarche onset was 12.61 (±1.291) years. Patients who were already menopause that represented approximately 78.8% of the total study population. Forty three (28,5%) patients have BMI of 25.0-29.9. Most of the subjects had one to two children around the study period accounting for 53 (35.1%) and 75 (49.7%) patients, respectively. A total of 127 (84%) subjects did not report any history of breast cancer occurred in their family members. The results showed that approximately 90% of the subjects had undergone at least one operative management for breast cancer. Majority of the samples were categorized as IDC histologic subtypes with 114 (75.5%) patients, poorly differentiated cancer with 87 (57.6%) patients, diagnosed with stage III and IV breast cancer which 104 (68.8%) patients, have Luminal A cancer with 81 (53.6%) patients. From the analysis, the only significant finding was for the difference in total cholesterol levels among those with TNBC (p-value of 0.002).

Conclusions: There was no difference found in the level of lipid profile as in breast cancer subtype. There is a difference in tumor patient TNBC subtype with normal total cholesterol value and abnormal total cholesterol value.

KEYWORDS : Breast cancer subtype, breast cancer, lipid profile

INTRODUCTION

Cancer is one of the main causes of death throughout the world.[1] In 2012, around 8,2 million deaths caused by cancer. Breast cancer is the leading cause of cancer death among woman. Data from American Cancer Society (2015) shows that 231.840 new cases of breast cancer and 40.290 deaths caused by breast cancer. In Indonesia, breast cancer is the second most common cancer after cervical cancer. The prevalence of breast cancer in Indonesia is 0,5% in 2013, and Yogyakarta has the highest prevalence of breast cancer with 2,4%.[2,3] In the period of 2011 to 2013, 1.427 cases of breast malignancy were recorded at the department of Surgery, Oncologist Sub-Division of RSUP H. Adam Malik (Divisi Bedah Onkologi, 2013).

In the development of oncology medical science, it was found that breast cancer is not a single disease, but instead several diseases that have different traits and responses to existing therapeutic modalities. This disease is referred as a subtype in breast cancer. These subtypes in breast cancer have risk factors based on epidemiology, various types of the disease's course, and different responses to systemic or local therapies. To find out the subtype of breast cancer, an additional examination is needed, and it is called immunohistochemical examination. The existence of differences in subtypes of breast cancer requires health workers to manage therapy to be given to patients, based on existing clinical evidence, in order to achieve the expected targets.[4]

Diet can also be a factor in the incidence of variations in breast cancer among women of different races and ethnicities.[5] Various opinions have been found regarding the relationship between fat consumption and breast cancer risk. From several epidemiological studies it has been shown that there is an association between increased fat consumption and an increased risk of breast cancer. Environmental studies have also shown that there is a connection between increased fat consumption and an increased risk of breast cancer over time in various countries.[6] On the basis of this background, authors were interested in examining the differences of the level of lipid profiles in breast cancer subtypes.

MATERIAL AND METHODS

Population of study and variables

This study is an observational analytic research with cross sectional study design. We include all breast cancer patients who treated at polyclinics and patient wards of Oncology Surgical Science Department of general hospital of H. Adam Malik Medan since October 2018 to February 2019. Inclsion criteria were breast cancer patients with invasive ductal carcinoma and their variants or invasive lobular carcinoma that confirmed by histopathology. Data such as age, age at the onset of menarche, menopausal status, body mass index (bmi), parity status, family history of breast cancer, previous history of breast cancer, histopathological findings, tumour grade, stage of cancer, genetic subtypes, lipid profile were collected.

DATA COLLECTION

Data such as age, age at the onset of menarche, menopausal status, body mass index (bmi), parity status, family history of breast cancer, previous history of breast cancer, histopathological findings, tumour grade, stage of cancer, genetic subtypes, lipid profile were collected.from medical records of patients with breast cancer who treated at polyclinics and patient wards of Oncology Surgical Science Department of general hospital of H. Adam Malik Medan. Data of lipid profile levels were retrieved from serum that taken from patient's veins. Immunohistochemical examination was done to determine the classification of breast cancer subtypes.

Statistical analysis

Data that has been collected, processed, and presented descriptively in the form of tables, diagrams and narratives. The relationship between variables is obtained by using the Chi square test on the SPSS program ver. 20.

RESULTS

From 151 patients, it was found that majority of patients were in the 46-55 years age group with a total of 51 (33.8%) patients, followed by 40 (26.5%) patients in the 56-65 years age group. The remaining were 12 (7.9%) patients aged ≤35 years, 32 (21.2%) patients aged 36-45 years, and 16 (10.6%) patients were included in the >65 years age group. The median age of this study was 51.0 (18-82) years.

Table 4.1. Sample Distribution Based on Age

Age Group	Number (%)	Median (Min-Max)
≤35	12 (7.9)	51.0 (18-82)
36-45	32 (21.2)	
46-55	51 (33.8)	
56-65	40 (26.5)	
≥66	16 (10.6)	
Total	151 (100)	

Regarding the onset of menarche, the age ranged from 10 to 16 years with the following details of 6 (3.3%), 20 (13.2%), 54 (35.8%), 39 (25.8%), 21 (13.9%), 7 (4.6%), and 5 (3.3%) subjects reported their menarche onset at the age of 10, 11, 12, 13, 14, 15, and 16, respectively. The mean age at the menarche onset was 12.61 (±1.291) years.

Table 4.2. Sample Distribution Based on Age at the Onset of Menarche

Age	Number (%)	Mean (SD)
10	5 (3.3)	12.61 (±1.291)
12	54 (35.8)	
13	39 (25.8)	
14	21 (13.9)	
15	7 (4.6)	
16	5 (3.3)	
Total	151 (100)	

According to menopausal status, from 151 patients in total, there were 119 patients who were already menopause that represented approximately 78.8% of the total study population, whereas the remaining 32 (21.2%) subjects were still in their reproductive period.

Table 4.3. Sample Distribution According to Menopausal Status

Menopause	Number	Percentage (%)
Yes	119	78.8
No	32	21.2
Total	151	100

As for the body mass index (BMI) calculation, from 151 subjects included in the analysis, a number of 19 (12.6%); 25 (16.6%); 38 (25.2%); 43 (28.5%); and 26 (17.2%) subjects were found to have BMI of <18.5; 18.5-22.9; 23.0-24.9; 25.0-29.9; and ≥30.0 kg/m2, respectively.

Table 4.4. Sample Distribution According to Body Mass Index (BMI) Calculation

BMI	Number	Percentage (%)
<18.5	19	12.6
18.5-22.9	25	16.6
23.0-24.9	38	25.2
25.0-29.9	43	28.5
≥30.0	26	17.2
Total	151	100

When stratified based on their parity status, most of the subjects had one to two children around the study period accounting for 53 (35.1%) and 75 (49.7%) subjects, respectively. On the other hand, 16 (10.6%) and 7 (4.6%) patients had three and four children, respectively.

Table 4.5. Sample Distribution According to Parity Status

Parity	Number	Percentage (%)
1	53	35.1
2	75	49.7
3	16	10.6
4	7	4.6
Total	151	100

According to the data from clinical history taking, the subjects reported a detailed history of breast cancer among their first- and second-degree relatives from bother maternal and paternal sides. A total of 127 (84%) subjects did not report any history of breast cancer occurred in their family members; on the contrary, family history of breast cancer existed in the remaining 24 subjects.

Table 4.6. Sample Distribution According to Family History of Breast Cancer

Family history of breast cancer	Number	Percentage(%)
Yes	24	15.9
No	127	84.1
Total	151	100

The data regarding the history of previous breast cancer surgeries were obtained from all of the subjects. The results showed that approximately 90% of the subjects had undergone at least one operative management for breast cancer. On the other hand, only 9.9% who never went under the knife for any breast cancer surgeries.

Tabel 4.7. Sample Distribution According to Their Previous History of Breast Cancer Surgery

History of Breast Cancer Surgery	Number	Percentage (%)
Yes	136	90.1
No	15	9.9
Total	151	100

Following a histopathological investigation conducted by an anatomical pathologist, a series of histopathological data regarding the histologic subtypes of the tumour. Majority of the samples were categorized as Invasive Ductal Carcinoma (IDC) histologic subtypes that were found in 114 (75.5%) subjects, followed by 37 (24.5%) subjects with Invasive Lobular Carcinoma (ILC).

Table 4.8. Sample Distribution According to Histopathological Findings

Histologic Subtype	Number	Percentage (%)
IDC	114	75.5
ILC	37	24.5
Total	151	100

In addition to their histopathological features, the tumours were also classified based on the breast cancer grading system into well differentiated, moderately differentiated, and poorly differentiated. Poorly differentiated cancer were the most common type of tumour found in 87 (57.6%) subjects, followed by 41 (27.2%) with moderately differentiated, and 23 (15.2%) with well differentiated tumours.

Table 4.9. Distribution of Tissue Samples According to the Tumour Grading System

Grading	Number	Percentage (%)
Well Differentiated	23	15.2
Moderately Differentiated	41	27.2
Poorly Differentiated	87	57.6
Total	151	100

Of the total study population, majority of subjects were diagnosed with stage III and IV breast cancer which accounted for 104 (68.8%)

subjects. Whilst, the remaining 47 subjects were diagnosed with stage I (10 subjects; 6.6%) and stage II (37 subjects; 24.5%) breast cancer.

Table 4.10. Distribution of Tissue Samples According to the Stage of Cancer

Stage	Number	Percentage (%)
I	10	6.6
II	37	24.5
III	52	34.4
IV	52	34.4
Total	151	100

Genetic analysis stratified the cancer into several genetic subtypes, including Luminal A, Luminal B, HER-2 overexpression, and triple negative breast cancer (TNBC). From 151 individuals, 81 (53.6%) were found to have Luminal A cancer, 16 (10.6%) with Luminal B, 13 (8.6%) with HER-2 overexpression, as well as 41 (27.2%) with TNBC.

Table 4.11. Distribution of Tissue Samples According to Genetic Subtypes

Subtypes	Frequency	Percentage (%)
Luminal A	81	53.6
Luminal B	16	10.6
HER2 overexpression	13	8.6
TNBC	41	27.2
Total	151	100

Lipid profile evaluation was conducted in all 151 patients, and 75 (49.7%) of them showed abnormal lipid profile, while the results from remaining 76 (50.3%) patients indicated normal lipid profile.

According to the lipid parameters presented in the following table, the median total cholesterol, triglyceride, LDL cholesterol, and HDL cholesterol levels in the abnormal group were 182 (80-259), 151 (34-684), 125 (28-246), and 34 (9-67), respectively. Whereas, the results for the normal group showed the median or mean total cholesterol, triglyceride, LDL cholesterol, and HDL cholesterol levels were 181 (105-199), 128 (36-313), 79 (±12.6), dan 68 (60-161), respectively.

Table 4.12. Distribution According to Their Lipid Profile

Lipid Profile	Frequency (%)	Mean (±SD) / Median (Min-Max)
Abnormal Lipid Group	75 (49.7)	
Total cholesterol		182 (80-259)
Triglyceride		151 (34-684)
LDL		125 (28-246)
HDL		34 (9-67)
Normal Lipid Group	76 (50.3)	
Total cholesterol		181 (105-199)
Triglyceride		128 (36-313)
LDL		79 (±12.6)
HDL		68 (60-161)

Among those with normal and abnormal lipid parameters, the subtypes of breast cancer were compared. From the comparison, it was noted that the luminal A subtype was found in 37 and 45 patients with abnormal and normal lipid profile, respectively. The luminal B cancer was found in 8 patients with both normal and abnormal lipid profile. HER-2 overexpression was found in 7 patients with abnormal lipid profile and 6 patients with normal lipid profile. TNBC expression was found in 23 and 18 patients with abnormal and normal lipid parameters, respectively. Table 4.13 shows the results from Chi-Square analysis for the comparison between random lipid profile and breast cancer subtypes which indicated no difference between the two groups owing to the p-value = 0.733.

Tabel 4.13. Cross-Tabulation between Random Lipid Profile and Breast Cancer Subtypes

Breast Cancer Subtypes	Lipid Profile		p-value[a]
	Abnormal	Normal	
Luminal A	37	44	0.733
Luminal B	8	8	
HER2 overexpression	7	6	
TNBC	23	18	

[a]Statistical analysis using Chi-Square test, with p<0,05 is considered significant.

This study also evaluated the difference in random lipid profile among the respective subtypes (Table 4.14). From the analysis, the only significant finding was for the difference in total cholesterol levels among those with TNBC (p-value of 0.002).

Table 4.14. The Difference in Profile Lipid among Different Breast Cancer Subtypes

	Lipid Profile (n(%))		p-value
Luminal A			
Total cholesterol	Abnormal	19 (23.4)	0.054
	Normal	62 (76.5)	
Triglyceride	Abnormal	23 (28.3)	0.325
	Normal	58 (71.6)	
LDL	Abnormal	27 (33.3)	0.304
	Normal	54 (66.7)	
HDL	Abnormal	35 (43.2)	0.628
	Normal	46 (56.7)	
Luminal B			
Total cholesterol	Abnormal	3 (18.8)	0.575
	Normal	13 (81.2)	
Triglyceride	Abnormal	4 (25)	0.627
	Normal	12 (75)	
LDL	Abnormal	6 (37.5)	0.971
	Normal	10 (62.5)	
HDL	Abnormal	7 (43.7)	0.913
	Normal	9 (56.3)	
HER2 overexpression			
Total cholesterol	Abnormal	4 (30.7)	0.251
	Normal	9 (69.3)	
Triglyceride	Abnormal	4 (30.7)	0.738
	Normal	9 (69.3)	
LDL	Abnormal	6 (46.2)	0.553
	Normal	7 (53.8)	
HDL	Abnormal	7 (53.8)	0.504
	Normal	6 (46.2)	
TNBC			
Total cholesterol	Abnormal	1 (2.5)	0.002
	Normal	40 (97.5)	
Triglyceride	Abnormal	7 (17)	0.162
	Normal	34 (83)	
LDL	Abnormal	17 (41.5)	0.497
	Normal	24 (58.5)	
HDL	Abnormal	19 (46.3)	0.844
	Normal	22 (53.7)	

DISCUSSION

Breast cancer is a form of cellular malignancy affecting the breast tissue that can originate from both ductal and lobular epithelial cells. This cancer is most frequently found among women where around 22% of newly diagnosed cancer in women is breast cancer and it is known to be one of the leading cause of cancer-related death worldwide.[2,7]

Breast cancer incidence is still increasing both in Indonesia and worldwide (Europe-United States). Breast cancer is still considered a substantial health issue, owing to its high rates of mortality and morbidity. [8,9] In 2018, a total of 2.088.849 (11.6%) breast cancer cases were recorded across the globe with the incidence of breast cancer-related mortality reaching 626.679 (6.6%) cases.[10]

Our results showed that 69 patients had the BMI of >25 kg/m^2 that were further subcategorized into 43 (28.5%) patients with BMI of 25.0-29.9 kg/m^2 and 26 (17.2%) patients with BMI of ≥30.0 kg/m^2.

Obesity has been linked with the incidence of breast cancer in various population-based studies. This theory is in accordance with the study conducted by Neuhouser *et al.*, in 2015 reported that from 3388 patients included in the analysis, they found a significant association between obesity and increased risk of breast cancer with the p-value <0.001. Moreover, multiparity is believed to reduce the risk of breast cancer development (Babalou, 2007).[11] Table 4.5 shows that the majority of study population had one or two children which accounted for 53 (35.1%) and 75 (49.7%), respectively. From table 4.6, it is noted that 127 (84.1%) patients did not report any family history of breast cancer diagnosis which is contradicted with the results from the study by Brewer *et al.,* in 2017, reporting that from 113,000 English participants, using family history score, family history of breast cancer is significantly associated with increased risk of breast cancer with the p-value of <0.0001. Table 4.7 shows that a total of 136 (90.1%) patients had at least one prior history of breast cancer surgery.

More than 95% of breast cancer is found to be adenocarcinoma. Invasive ductal carcinoma (IDC) is the most common malignant form of breast cancer with the incidence reaching 55% of all breast cancer cases.[12] This data also supports our finding where IDC was confirmed in 114 (75.5%) out of 151 patients included in the analysis according to histopathological investigation. Our results showed that poorly differentiated tumour was the most common tumour grade which was found in 87 (57.6%) patients.

Adipose tissue is known to contribute in body's metabolic and hormonal function, and excessive adipose tissue accumulation will cause subsequent tissue hypoxia and increased oxidative stress which are believed to trigger cancer development. Adipose tissue consists of white and brown adipose tissues. Adipose tissue could undergo proliferation that results in hypertrophy and hyperplasia; should the proliferation continue and exceed the limit for normal proliferation rates, it could lead to tissue hypoxia and the final results would be tissue necrosis and increased oxidative stress.[13] The damage occurs at the cellular and tissue levels can result in inflammation that recruits various inflammatory cells, cytokines and mediators leading to carcinogenesis.[14]

Alterations in lipid metabolic pathway in cancer has been an interesting topic for decades. Lipid involves in the regulation of cellular proliferation, differentiation, apoptosis, inflammation, autophagy, motility, and cell membrane homeostasis. This regulation process should be strictly regulated to reach homeostasis.[15] Malignant breast tissue proliferation in women has been linked to the alteration of plasma lipid and lipoprotein levels.[16] HDL cholesterol level is known to correlate with a more extensive breast tissue dysplasia as well as with family history of breast cancer diagnosis.[17] Contrarily, lower HDL cholesterol level among breast cancer sufferers aged under 50 years old had never been discovered in the previous reports. However, several studies have reported significant association between HDL cholesterol and breast cancer.[18]

The altered lipid profile in patients with breast cancer has been identified in the previous study by Shah *et al*., (2008). The alteration is caused by abnormal lipid metabolism associated with the pathogenesis of the tumour and the host-tumour interaction. The cancer cells tend to differently metabolize lipid compared with the normal cells. Cholesterol is an important element of the lipoprotein fractions such as LDL, HDL, and VLDL. Seventy five percent of the total cholesterol are distributed in the form of LDL. Positive correlation between total cholesterol and LDL levels have been observed. Lower LDL and HDL levels observed in this study are attributed to lower antioxidant capacity due to increased ROS level as the LDL cholesterol is more susceptible to ROS-induced oxidation that results in lipid peroxidation. HDL is an important lipid fraction possessing the ability to object the oxidative damage of LDL that further prevent the formation of lipid peroxidation.[19]

The lipoprotein lipase activity within the white adipose tissue is reduced in cancer host that contributes to the development of hypertriglyceridemia. Since the precursor of HDL cholesterol is believed to originate from the lipolysis products of triglyceride and the lipoprotein lipase activity is reduced in cancer, an increase in plasma triglyceride level is considered one of the factors associated with lower HDL concentration. Additionally, higher plasma triglyceride level can lead to reduction in sex hormone-binding globulin which subsequently results in the elevation of free estradiol levels that also increases the risk of developing breast cancer.[19]

Previous studies reported the presence of lipid profile alterations, including increased triglyceride, LDL, and VLDL levels, in patients with breast cancer. As for the HDL and total cholesterol levels, there were no significant difference between non- and breast cancer sufferers.[20] In contrary, there were also some studies reporting negative correlation between LDL level and neoplastic transformation. It is presumed that in carcinogenesis, neoplastic cells tend to increase LDL utilization by increasing LDL receptor activation leading to reduced LDL level.[21]

A meta-analysis investigating the correlation between lipid profile and incident breast cancer reported no significant association between cholesterol level and breast cancer.[22] Meanwhile, our study tried to see the relationship between lipid profile and breast cancer subtypes, namely luminal, HER2, and TNBC. Our results are in agreement with the previous results showing that there is no significant difference in the two groups studied albeit hypothetically, the pathologic mechanism could explain the relationship between lipid profile and breast cancer risk, particularly in regard to its subtypes. Increased HDL cholesterol levels in CETP genetic variant is linked with the risk of breast cancer development with positive estrogen receptor.[23]

In this study, we also found a significant difference between total cholesterol level and TNBC subtype; however, no such difference was found for HDL, triglyceride, and LDL. Different results were reported by Lofterød (2018), HDL/total cholesterol ratio possesses protective effects on overall mortality only in patients with TNBC. Low HDL level is linked with a more aggressive tumour. Lower HDL level is inversely associated with interleukin (IL)-6 activity. Moreover, IL-6 and IL-8 can induce tumour development within TNBC cells. Interestingly, it is known that HDL possesses anti-tumorigenic properties through regulation of angiogenesis that involves reduction in vascular endothelial growth factor (VEGF) expression that subsequently decrease its potential for metastasis. In addition, there are also several mechanisms in which triglyceride takes part in tumour proliferation, growth, and metastases in TNBC cases by acting as the energy reservoir, and serving as the source for fatty acid oxidation (FAO), an important energy source for cellular proliferation and migration.[24]

As for the difference among the subtypes, this study has several limitations, including the cross-sectional design used in this study would interfere with data collection as the data can only be obtained once at a time that can possibly be the source of bias for the results.

CONCLUSIONS

There was no difference found in the level of lipid profile as in breast cancer subtype (p-value 0,733). Since October 2018 to February 2019, there are breast cancer patients recorded in RSUP H Adam Malik Medan, 75 patients (49,7%) that has abnormal lipid profile and 76 other patients (50,3%) that has the normal lipid profile. In this study we found that breast cancer subtype in RSUP H Adam Malik Medan, since October 2018 to February 2019 there are 81 (53,6%) Luminal A subtypbe, 16 (10,6%) Luminal B, 13 (8,6%) HER2 *overexpression,* and 41 (27,2%) TNBC. There is a difference in tumor patient TNBC subtype with normal total cholesterol value and abnormal total cholesterol value (pValue: 0,002).

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