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The Relations Between Breast Cancer and Hormonal Contraception Acceptor At RSUP Dr. Mohammad Hoesin Palembang in 2021

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ABSTRACT

Introduction. Breast cancer is a non-communicable disease that has become a health problem in the world. One of the risk factors for breast cancer is hormonal factors that can be obtained from the use of hormonal contraception. This study describes the relationship between the incidence of breast cancer and the use of hormonal contraception at RSUP Dr. Mohammad Hoesin Palembang in 2021. **Method.** This is an observational analytic study with a case-control design. The data used are secondary data and primary data. The sample are women with breast cancer and benign breast tumors at RSUP Dr. Mohammad Hoesin Palembang in 2021who met the inclusion criteria. **Results.** There was a significant relationship between the use of hormonal contraceptives (p = 0.003), duration of the use of hormonal contraceptives>5 years (p = 0.004), the type of injectable hormonal contraceptive (p = 0.001), the type of hormonal pills (p = 0.018) and a family history (p = 0.001). Meanwhile, there was no significant relationship between the type of hormonal contraceptive implant (p = 0.724), parity (p = 1.000), and age at menarche (p = 0.129),with the incidence of breast cancer. **Conclusion.** There is a significant relationship between the use of hormonal contraception, duration of use of hormonal contraception >5 years, type of injectable hormonal contraceptive use, type of use of hormonal contraceptive pills, and family history of breast cancer with breast cancer incidence.

1. Introduction

Breast cancer is a malignancy in breast tissue originating from the ductal or lobular epithelium. According to WHO data in 2020, there are 2.3 million women diagnosed with breast cancer with 685,000 deaths globally. By the end of 2020 there were 7.8 million women diagnosed with breast cancer in the last 5 years, making it the most common cancer in the world.[1]

Data from the Global Cancer Observatory in 2020 stated that there were 68,858 incidents of breast cancer (16.6%) out of a total of 396,914 new cases of cancer in Indonesia. With, the number of deaths has reached more than 22,000 cases.[2] According to data from the Indonesian Ministry of Health regarding the profile of non-communicable diseases in 2016, South Sumatra Province occupies the first position with the highest number of breast cancer cases, namely 2,299 cases.[3]

The etiology of breast cancer is still not known with certainty, but there are several factors that can increase the risk of developing breast cancer, including: age, BRCA1 and BRCA2 gene mutations, family history of breast cancer, reproductive history, menopausal age over 55 years and menarche before 12 years of age. Research also shows risk factors contributing to breast cancer due to long-term use of hormonal contraceptives containing progesterone and combinations (progesterone and estrogen).[4]

The percentage of acceptors of hormonal contraception based on data from the Central Statistics Agency (BPS) for 2021 shows that in Palembang there were 235,603 participants with a percentage of contraceptive use of 34.7% injections, 22.7% pills and 16.7% implants. Based on these data it can be concluded that the interest of Family Planning (KB) acceptors in Palembang City is quite high. Given the many incidences of breast cancer that are related to hormones, the use of hormonal contraception has received a lot of attention.[5]

The hormonal content in hormonal contraception is in the form of synthetic progesterone hormone or its combination. The combination of these two hormones can cause proliferative effects, one of which is on the mammary glands. In women with breast cells that have been exposed to mutagens, in the long term it can cause a promotive process which is then followed by a progressive one leading to

invasion and metastasis.[6]

Based on previous research conducted by the New England Journal of Medicine in 2017, regarding the effect of hormonal contraception on breast cancer risk, it was stated that compared to women who had never used hormonal contraception, the relative risk of breast cancer in current users increased by 1.2 times. The study also stated that the risk of breast cancer increased with the duration of use of hormonal contraception for more than 5 years.[7]

2. Methods

This research is an observational analytic study with a case-control design. This research was carried out in October-November 2022 at the Medical Record Installation of RSUP Dr. Mohammad Hoesin Palembang. The sample of this study were women with breast cancer and benign breast tumors who met the inclusion criteria at RSUP Dr. Mohammad Hoesin Palembang in 2021 which is calculated using the minimum sample formula so that 54 samples per group are obtained. Sampling in this study was carried out by simple random sampling technique.

The inclusion criteria in this study were female patients with breast tumors and the exclusion criteria were patients with incomplete medical record data (if the results of histopathological examination were not included) and patients who did not agree to be interviewed.

In this study, secondary data was used in the form of patient medical records followed by primary data in the form of interviews with patients at RSUP Dr. Mohammad Hoesin Palembang.

The research data will be processed using the SPSS statistics 24 application. Univariate analysis is used to describe the frequency of each research variable. Next, a bivariate analysis will be carried out on the dependent and independent variables to analyze the significance value of the relationship between the two variables. The test used in the bivariate analysis is the Chi-Square Test.

3. Result

Table 1 shows that based on age it is known that the majority of breast cancer subjects are >35 years old (75.9%). Based on parity, most were not nullipara (92.6%). Based on the age of menarche, most were ≥12 years (75.9%). Based on a family history of breast cancer, the majority did not (63%). Based on smoking history, the majority did not smoke (100%).

Table 1. Characteristics of Subjects in the Department of Surgical Oncology Dr. Mohammad Hoesin Palembang in 2021

Characteristic	Benign Breast Tumor		Breast Cancer		Total
	n	%	n	%	n(%)
Age					
<20 years	1	1,9%	0	0%	1(0,9%)
20-35 years	14	25,9%	13	24,1%	27(25%)
>35 years	39	72,2%	41	75,9%	80 (74,1%)
Total	54	100%	54	100%	108 (100%)
Parity					
Nullipara	3	5,6%	4	7,4%	7 (6,5%)
Non Nullipara	51	94,4%	50	92,6%	101 (93,5%)
Total	54	100%	54	100%	108 (100%)
Age Menarche					
<12 years	6	11,1%	13	24,1%	19 (17,6%)
≥12 years	48	88,9%	41	75,9%	89 (82,4%)
Total	54	100%	54	100%	108 (100%)
History of Breast Cancer in Family					
Yes	5	9,3%	20	37%	25 (23,1%)
No	49	90,7%	34	63%	83 (76,9%)
Total	54	100%	54	100%	108 (100%)
Smoking					
Yes	0	0%	0	0%	0 (0%)
No	54	100%	54	100%	108 (100%)
Total	54	100%	54	100%	108 (100%)

Table 2. Distribution of the Use of Hormonal Contraceptives by Research Subjects in the Department of Surgical Oncology, Dr. Mohammad Hoesin Palembang in 2021

Characteristic	Benign Breast Tumor		Breast Cancer		Total
	n	%	n	%	n(%)
Use of of Hormonal Contraception					
Yes	26	48,1%	42	77,8%	68 (63%)
No	28	51,9%	12	22,2%	40 (37%)
Total	54	100%	54	100%	108 (100%)
Duration of Hormonal Contraception					
>5 years	12	22,2%	25	46,3%	37 (34,3%)
≤5 years	14	25,9%	17	31,5%	31 (28,7%)
No	28	51,9%	12	22,2%	40 (37%)
Total	54	100%	54	100%	108 (100%)
Type of Hormonal Contraception					
Injection	8	14,8%	23	42,6%	30 (27,8%)
Implant	13	24,1%	8	14%	21 (19,4%)
Pill	5	9,3%	11	20,4%	16 (14,8%)
No	28	51,9%	12	22,2%	41 (38%)
Total	54	100%	54	100%	108 (100%)

Table 2 shows that the majority of breast cancer patients had a history of using hormonal contraception (77.8%), with a duration of using hormonal contraception >5 years (46.3%), with a history of using injectable hormonal contraception (42.6%).

Table 3. shows the relationship between the use of hormonal contraception with the incidence of breast cancer. The results of this study showed that out of 108 research subjects, subjects with a history of using hormonal contraception, 42 people (61.8%) had breast cancer and 26 people (38.2%) had benign breast tumors. Whereas in subjects with a history of not using hormonal contraception, 12 people (30%) had breast cancer and 28 people (70%) had benign breast tumors. The results were obtained using the chi-square test (p-value = 0.003; OR = 3.769; CI = 1.636-8.684) which means that there is a significant relationship between the use of hormonal contraception and a 3.769 times greater risk of developing breast cancer.

Based on the relationship between the duration of hormonal contraceptive use and the incidence of breast cancer, in subjects with a history of using hormonal contraception >5 years, 25 people (67.6%) had breast cancer, and 12 people (32.4%) had benign breast tumors. Furthermore, in subjects with a history of using hormonal contraception ≤5 years, 17 people (54.8%) had breast cancer and 14 people (45.2%) had benign breast tumors. The results of the study using the chi-square test showed that the duration of hormonal contraceptive use was >5 years (p-value = 0.004; OR = 4.861; CI = 1.852-12.759) indicating a significant relationship between the duration of hormonal contraceptive use >5 years and the risk of 4.861 times. greater risk of developing breast cancer. Whereas duration ≤ 5 years was not significantly related to breast cancer (p-value = 0.062).

Based on the relationship between the type of hormonal contraception and the incidence of breast cancer, in subjects with a history of using injectable hormonal contraception, it was found that 23 people (74.2%) had breast cancer and 8 people (25.8%) had benign breast tumors. Furthermore, in subjects with a history of using implant-type hormonal contraception, 8 people (38.1%) had breast cancer and 13 people (61.9%) had benign breast tumors. Meanwhile, in subjects with a history of using pill-type hormonal contraception, 11 people (68.8%) had breast cancer and 5 people (31.3%) had benign breast tumors. The results of the study with the chi-square test showed that the type of injectable hormonal contraception (p-value = 0.001; OR = 6.708; CI = 2.345-19.189) indicated that there was a significant relationship between injecting hormonal contraception with a 6.708 times greater risk of developing breast cancer. The type of hormonal contraceptive pill is significantly associated with a 5.133 times greater risk of developing breast cancer (p-value = 0.018; OR = 5.133; CI = 1.464-18.006). The type of hormonal contraceptive implant was not significantly related to the incidence of breast cancer (p-value = 0.724).

Table 3. Relationship of Hormonal Contraception with Breast Cancer

Characteristic	Benign Breast Tumor		Breast Cancer		Total	*p-value*	OR (CI)
	n	%	n	%	n(%)		
Use of Hormonal Contraception							
Yes	26	38,2%	42	61,8%	68 (100%)	0,003	3,769 (1,636-8,684)
No	28	70%	12	30%	40 (100%)		
Duration of of Hormonal Contraception							
≤5 years	14	45,2%	17	54,8%	31 (100%)	0,062	2,833 (1,065-7,539)
>5 years	12	32,4%	25	67,6%	37 (100%)	0,002	4,861 (1,852-12,759)
No	28	70%	12	30%	40 (100%)		
Type of of Hormonal Contraception							
Injection	8	25,8%	23	74,2%	31 (100%)	0,001	6,708 (2,345-19,189)
Implant	13	61,9%	8	38,1%	21 (100%)	0,724	1,436 (0,473-4,359)
Pill	5	31,3%	11	68,8%	16 (100%)	0,018	5,133 (1,464-18,006)
No	28	70%	12	30%	40 (100%)		
Total	54	50%	54	50%	108 (100%)		

Table 4. shows the relationship based on parity with the incidence of breast cancer. The results of this study showed that of the 108 study subjects, in subjects with a history of nulliparous parity, 4 people (57.1%) had breast cancer and 3 people (42.9%) had benign breast tumors. Whereas in subjects with a history of non-nullipara parity, 50 people (49.5%) had breast cancer and 51 people (50.5%) had benign breast tumors. The results of the study with the chi-square test obtained a p-value = 1.000 (> 0.05) which indicated that there was no significant relationship between parity and the incidence of breast cancer.

Based on the relationship between the age of menarche and breast cancer, in subjects with menarche <12 years, 13 people (68.4%) had breast cancer and 6 people (31.6%) had benign breast tumors. Whereas in subjects with menarche ≥ 12 years, 41 people (46.1%) had breast cancer, and 48 people (53.9%) had benign breast tumors. The results of the study with the chi-square test obtained a p-value (> 0.05).

Table 4. Relationship of Other Factors with Breast Cancer

Characteristic	Benign Breast Tumor		Breast Cancer		Total	*p-value*	OR (CI)
	n	%	n	%	n(%)		
Parity							
Nullipara	3	42,9%	4	57,1%	7 (100%)	1,000	1,360 (0,290-6,388)
Non Nulipara	51	50,5%	50	49,5%	101 (100%)		
Total	54	50%	54	50%	108 (100%)		
Age Menarche							
<12 years	6	31,6%	13	68,4%	19 (100%)	0,129	2,537 (0,885-7,273)
≥12 years	48	53,9%	41	46,1%	89 (100%)		
Total	54	50%	54	50%	108 (100%)		
History of Breast Cancer in Family							
Yes	5	20%	20	80%	25 (100%)	0,001	5,765 (1,971-16,860)
No	49	59%	34	41%	83 (100%)		
Total	54	50%	54	50%	108 (100%)		
Smoking							
Yes	0	0%	0	0%	0 (0%)	Cannot be calculated	Cannot be calculated
No	54	50%	54	50%	108 (100%)		
Total	54	50%	54	50%	108 (100%)		

This means that there is no significant relationship between the age of menarche and the incidence of breast cancer. Based on the relationship between a family history of breast cancer and the incidence of breast cancer, 20 people (80%) had breast cancer and 5 people (20%) had a family history of breast cancer. suffering from a benign breast tumor. Whereas in subjects with no family history of breast cancer, 34 people (41%) had breast cancer, and 49 people (59%) had benign breast tumors. The results obtained using the chi-square test (p-value = 0.001; OR = 5.765; CI = 1.971-16.860) indicated that there was a significant relationship between a family history of breast cancer and a 5.765 times greater risk of developing breast cancer.

Based on the relationship between smoking history and the incidence of breast cancer, in subjects with a non-smoking history, 54 people (50%) had breast cancer and 54 people (50%) had benign breast tumors. While there were no subjects with a history of smoking. The results of the study with the chi-square test cannot be calculated.

4. Discussion

In this study, it was found that the majority of breast cancer patients were >35 years old (72.2%). The results of this study are in line with research conducted by Areckcsueng et al, which found that the majority of breast cancer patients were >40 years old (83.5%).[8] (BRK-IAIP) which states that the age of 35-44 years is at great risk of developing breast cancer. Another study conducted by Sun et al stated that around 85% of breast cancer cases occurred in women aged 50 years and over, while 5% occurred in women under 40 years.[9] The incidence of breast cancer increases with age, with

a rapid rate at reproductive age. and proceed at a slower rate.

In this study, it was found that the majority of breast cancer subjects had a history of using hormonal contraception (77.8%). These results are in line with research conducted by Arekcsueng et al who said there were (71.1%) breast cancer patients using hormonal contraception.[8]

The results of this analysis using the Chi-square test showed that the use of hormonal contraception was significantly associated with the incidence of breast cancer with a risk of 3.769 times compared to non-users of hormonal contraception (p-value = 0.003; OR = 3.769; CI = 1.636-8.684). This study is in line with research conducted by Ditya et al which stated that there was a significant relationship between the incidence of breast cancer and the use of hormonal contraception with a risk of 2.304 times (p-value = 0.007; OR = 2.304; CI = 1.255-4.232).[10] The results of this study also in line with research by Putri et al which stated that there was a significant relationship between the use of hormonal contraception and the incidence of breast cancer with a greater risk of 2.81 (p-value = 0.013; OR = 2.81; CI = 2.04-3, 59).[11] The results of this study are also in line with a study published by the New England Journal of Medicine in 2017 which stated that there was a significant relationship between the effect of using hormonal contraception and the risk of breast cancer with a risk of 1.2 times greater (p-value = 0.002; RR = 1 .2; CI = 1.14-1.26).[7]

The content of estrogen and progesterone in hormonal contraceptives can increase the risk of cell mutations during the division phase. Progesterone stimulates the normal human breast epithelium through a paracrine mechanism, making it a risk factor for breast cancer as it promotes pre-neoplastic development through stimulation of cyclical proliferation of mammary stem cell pools or hidden tumor-initiating cells in the mature breast epithelium. Estrogen plays a role in fat deposition, therefore more estrogen levels are associated with increased levels of fat in the body. Fat can cause a decrease in sex hormone-binding globulin (SHBG) estrogen-binding protein so that circulating levels of estrogen in the blood will enter cells through their receptors and experience an increase.[12–14]

The results of this study showed that out of a total of 37 women with a history of duration of hormonal contraceptive use >5 years, 25 (67.6%) had breast cancer. Studies say that the risk of breast cancer can increase with the duration of use of hormonal contraception for more than 5 years and have an increased risk for at least 5 years after stopping therapy.[13]

This study used the Chi-square test to show that the duration of hormonal contraceptive use >5 years was significantly associated with the incidence of breast cancer with a risk of 4.861 times greater (p-value = 0.004; OR = 4.861; CI = 1.852-12.759). The results of this study are in line with research conducted by Karisya, where there was a significant relationship between the length of use of hormonal contraception >5 years and the incidence of breast cancer with a risk of 6.362 times (p-value = 0.000; OR = 6.362; CI = 2.713-14.919).[15]

This study is also in line with research conducted by Nuratul et al which stated that there was a significant relationship between the length of use of hormonal contraception and the incidence of breast cancer with a 2.25 times higher risk (p-value = 0.037; OR = 2.25; CI = 1 .04-4.84).[16]

A history of using hormonal contraception for a long time can disrupt the balance of the hormone estrogen in the body, causing abnormal cell changes. Another study conducted by Karim et al also stated that there was a significant relationship between long-term use of hormonal contraception and the risk of developing breast cancer with a p-value = 0.001 (<0.05).[17]

The results of this study showed that the majority of breast cancer subjects used injectable hormonal contraception as many as 22 people (40.7%). In contrast to the study of Sweeney et al which stated that most breast cancer sufferers in America used pill-type hormonal contraception (49%).[18] widely used on the grounds that it is more practical and inexpensive. The Central Statistics Agency (BPS) for 2021 shows that in Palembang there are 235,603 participants who accept family planning with a percentage of contraceptive use of 34.7% for injections, 22.7% for pills, and 16.7% for implants.[5]

This study used the Chi-square test to show that the type of injectable hormonal contraception is significantly associated with the incidence of breast cancer with a greater risk of 6.708 (p-value = 0.001; OR = 6.708; CI = 2.345-19.189). These results are in line with another study conducted by Dian et al which stated that there was a significant relationship between injectable hormonal contraceptive types and the incidence of breast cancer with a risk of 2.2 times higher (p-value = 0.010; OR = 2.2 ; CI = 1 .2-4.2).[19] And the type of hormonal contraceptive pill is significantly associated with a 5.133 higher risk of breast cancer (p-value = 0.018; OR = 5.133; CI = 1.464-18.006). These results are in line with previous research conducted by Putri et al which stated that there was a significant relationship between the type of hormonal contraceptive pill and the incidence of breast cancer with a 2.76 times higher risk (p-value = 0.020; OR = 2.76; CI = 1.00). 1.89-3.63).[11] Another study conducted by Nuratul et al stated that there was a significant relationship between the use of hormonal contraceptive pills and a 1.66 times higher risk of developing breast cancer (p-value = 0.001; OR = 1.66; CI = 1.21-2.28).[16]

The most commonly used injectable and oral contraceptives are a combination of estrogen and

progesterone. There is a theory that explains the effect of estrogen and progesterone in causing breast cancer, increased levels of these two hormones due to exposure to exogenous hormones, one of which is obtained from the use of hormonal contraception can cause hormonal imbalances. There are two theories explaining how estrogen and progesterone cause breast cancer. The first theory states that there is an increased risk of cell mutations during the division phase due to increased cell proliferation. The second theory explains the role of the hormones estrogen and progesterone in directly stimulating the growth of cancer stem cells in the mammary gland ducts through increasing breast cell proliferation and inhibiting the process of apoptosis which in the long-term results in mutations in the genes that regulate mRNA splicing, namely CYP17 and CYP19 in the mammary gland.[20]

Another study says that estrogen is the hormone that plays the most important role in breast growth. Too much estrogen levels can cause the body to overload and the function of the estrogen receptors to die. Estrogen can act as a mitogen to stimulate increased mitosis in the breast glands and can also act directly as a carcinogen by damaging DNA which in turn causes mutations and the formation of cancer cells.[21]

In this study, the highest parity distribution of breast cancer subjects was non-nulliparous (92.6%). These results are in line with research conducted by Arekcsueng et al which said that the majority of breast cancer subjects were in the non-nulliparous group (96.9%).[8]

The results of this study showed that out of a total of 7 women with a history of nullipara, 4 (57.1%) had breast cancer. Based on the theory, nulliparas are more at risk of causing breast cancer than women who have children[22]

Nulliparous women have a 30% greater risk of developing breast cancer when compared to multiparous women. The risk of developing breast cancer for nulliparous women is higher than for women who already have children, this is due to the longer exposure time to the hormone estrogen. Increased estrogen levels, especially during a woman's fertile period, if not accompanied by hormonal changes during pregnancy can increase the chances of growth of cells in the glands that have been damaged and cause cancer, one of which is in the breast glands.[22]

This study used the Chi-square test to show that parity was not significantly related to the incidence of breast cancer with a p-value = 0.696 (>0.05). The results of this study are in line with research conducted by Sukmayenti et al which stated that there was no significant relationship between parity and the incidence of breast cancer with a p-value = 0.476 (> 0.05).[23] This could happen because parity is not the only risk factor of developing breast cancer but there are still other risk factors that influence it such as history of breastfeeding, age of menarche, age of menopause, etc.

Early menarche can increase the duration of exposure to the hormone estrogen in a woman's body. This estrogen hormone has an important role in triggering abnormal cell growth in certain parts of the body. This can affect the proliferation of tissues in the human body, including breast tissue. Estrogen can act as a promoter for certain types of cancer, one of which is breast cancer, with high estrogen levels during the menstrual period will increase the risk of breast cancer in women with early menarche.[22]

However, the results of this study using the Chi-square test showed that there was no significant relationship between menarche and breast cancer with a p-value=0.129 (>0.05). The results of this study are in line with research conducted by Mudhawaroh et al which stated that there was no significant relationship between the age of menarche and breast cancer with a p-value = 0.666 (> 0.05).[24] The occurrence of breast cancer where there are other factors that can affect the incidence of breast cancer.

Family history of breast cancer is one of the important factors causing breast cancer. Studies say that women with mothers or sisters with breast cancer are more susceptible to breast cancer. Based on research conducted in England in 2011 it was found that women with first-degree families who suffer from breast cancer are at risk 1.75 times greater for suffering from breast cancer compared to women without a family history. The risk is 2.5 times greater in women with two or more first-degree relatives with a history of breast cancer.[25] This is associated with inherited susceptibility through mutations in breast cancer-related genes such as BRCA1, BRCA2, HER2, EGFR, c-Myc and p53.[9]

The results of this study showed that out of 25 women with a family history of breast cancer, 20 (80%) had breast cancer. Someone with a family history of breast cancer has a higher risk of developing breast cancer.[20]

The results of this study using the Chi-square test showed that there was a significant relationship between a family history of breast cancer and the incidence of breast cancer with an increased risk of 5.765 times (p-value = 0.001; OR = 5.765; CI = 1.971-16.860). The results of this study are consistent with research conducted by Emy which stated that there was a significant relationship between a family history of breast cancer and the incidence of breast cancer with a risk of 6.44 times greater than those without a history of breast cancer (p-value = 0.001; OR = 6.44; CI = 2.9-13.9). 26 This study is also in line with research conducted by Nuratul which showed a significant relationship between a family history of breast cancer and the incidence of breast cancer with (p-value = 0,0272; OR = 1.93; CI = 1.03-3.67).[16]

The results of this study using the Chi-square test showed that the relationship between smoking history and the incidence of breast cancer cannot be calculated. However, research conducted by Sun et al mentioned the relationship between smoking and the incidence of breast cancer, mentioning that mutagens in the content of cigarette smoke have been detected in the breast fluid of women who are not breastfeeding. So far, accumulating evidence suggests that smoking, especially at an early age, increases the risk of developing breast cancer.[9]

5. Conclusion

There was a significant relationship between the use of hormonal contraception (p = 0.003), the duration of use of hormonal contraception >5 years (p = 0.004), the type of use of injectable hormonal contraception (p = 0.001), the type of use of hormonal contraception pills (p = 0.018), and history breast cancer in families with breast cancer incidence (p = 0.001) with breast cancer incidence in Dr. Mohammad Hoesin Palembang in 2021. There was a non-significant relationship between the type of hormonal contraceptive implant (p = 0.724), parity (p = 1.000), and age at menarche (p = 0.129), with the incidence of breast cancer at RSUP Dr. Mohammad Hoesin Palembang in 2021.

6. Acknowledgements

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