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AUTHOR'S AFFILIATIONS
Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Indonesia[1]

CORRESPONDING AUTHOR
Pratika Yuhyi Hernanda
Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Indonesia
E-mail:
yuhyi_h@yahoo.com

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Systematic Literature Review of Early Estrogen Exposure and its Relation to Breast Cancer in Woman

Ni Putu Manik Suryaningsih[1], Roethmia Yaniari[1] , Pratika Yuhyi Hernanda[1]*

Abstract

Breast cancer cell begins in the ductal epithelium and its lobes, where abnormal cell growth that is excessive, uncoordinated, and susceptible to metastasis accumulates. This study set out to find out how far early estrogen exposure influences the risk of having breast cancer in women. This systematic literature review was done by collecting sources related to the investigated variables which are menarche age, age at first birth, and hormonal contraception use. We collect from a variety of sources such as Google Scholar, PubMed, and Proquest to draw conclusions by grouping the odds ratio (OR) and their 95% CI. Data from the research articles, including author, year, title, and research results in the form of p-value, OR, and 95% CI, were collected from 35 articles published between 2011 and 2022 for this study. The data analysis revealed women with menarche age at less than 12 years old are more likely to have breast cancer (range of OR 0.80 – 26.8), meanwhile women who give birth more than 30 years old are also more likely to have breast cancer (range of OR 1.26 – 6.47) and duration of hormonal contraception use > 5 years were also give more chance to breast cancer development (range OR 0.51 – 9.06). This review analysis highlighted the increased probability of the incidence of breast cancer in women related to the duration of hormonal contraception use, the age of menarche, and the age at first birth.

Keywords: age at first birth, breast cancer, contraception, menarche

Review Article

INTRODUCTION

In Indonesia, the most prevalent type of cancer was also breast cancer, with 58,256 cases or 16.7% of the total 348,809 cancer cases (Rasjidi, 2010). The exact cause of breast cancer is still unknown. However, there are a number of risk factors for breast cancer, the most important of which are hormonal ones. These factors include having menstruation too early, using hormonal contraception too early, being born too young, having a family history of disease, and leading unhealthy lifestyles. The hormone estrogen is one of the hormones thought to raise the risk of developing breast cancer. where a significant increase in the hormone estrogen will disrupt the body's physiological processes (Setiowati et al., 2016)

Studies have shown that a woman's risk of developing breast cancer is related to her exposure to hormones that are produced by her ovaries (estrogen and progesterone). Reproductive factors that increase the duration and/or levels of exposure to ovarian hormones, which stimulate cell growth and have been associated with an increase in breast cancer risk. These factors include early onset

of menstruation, late onset of menopause, and factors that may allow breast tissue to be exposed to high levels of hormones for longer periods of time, such as later age at first pregnancy and hormonal contraception (Ahmad, 2019).

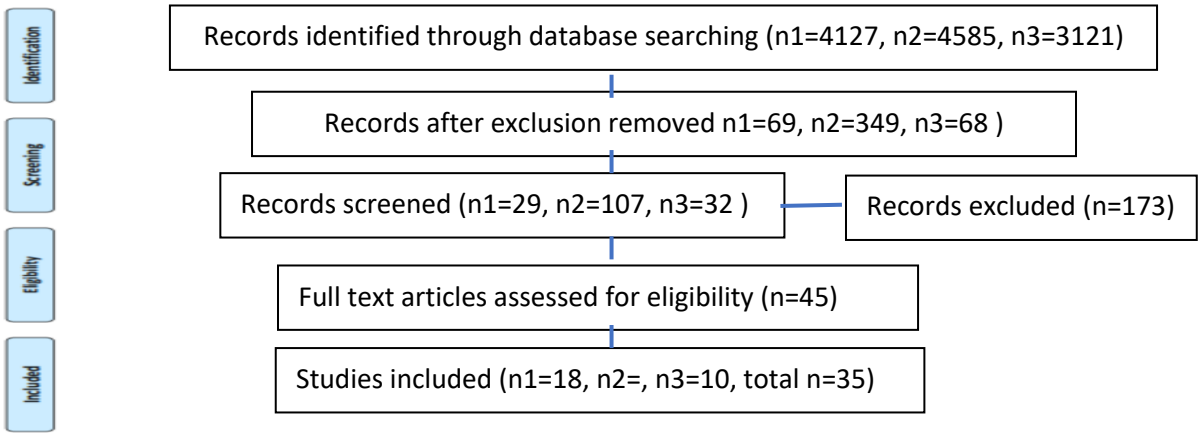
The process of shedding the endometrial wall that has not been fertilized occurs during the menstrual cycle. Menarche is the first period of menstruation. According to Dewi and Hendrati (Dewi & Hendrati, 2015), a woman's normal age of menarche will increase her exposure to the hormone estrogen, which will have an effect on the growth and development of cells in certain areas.

Women's risk of developing breast cancer is also influenced by their age at first birth. The amount of estrogen a woman is exposed to is higher the older she is when she gives birth to her first child. The older a woman gives birth, the longer exposure to estrogen (Sari & Gumayesty, 2016). In addition, it will have an effect on breast cells' maturation, which are susceptible to mutation processes caused by carcinogenic compounds (substances that promote cancer cell growth. Women who have a first full-term pregnancy before age 20, the risk of developing breast cancer is about half that of women whose first full-term pregnancy occurs after the age of 30 (Bernstein, 2002). Women who are older than 30 when they give birth to their first child have a higher risk of breast cancer than women who have never given birth (Kelsey et al., 1993).

Therefore, we would like to assess from the literatures how far these estrogen exposures which are age of menarche, age at first giving birth and duration of hormonal contraception use influence the probability of having breast cancer in woman.

METHODS

This systematic literature review draws conclusions by grouping data and uses data collection techniques from a variety of sources, such as Google Scholar, PubMed, and Proquest with keyword breast cancer, menarche, hormonal contraception, and age at first giving birth. To assess the influence of the investigated variables in breast cancer woman, we use the Odds Ratio (OR) (and its 95% CI) which is the ratio of the probability of an event (investigated variables) occurring in breast cancer group to the probability of non-investigated variables occurring in breast cancer. The parameter analysis was variably across study therefore we did not use other parameters instead of OR because we would like to use the same parameter for all study.



The inclusion criteria of the literature search were 1) Journal publication time range from year of 2011 – 2021, 2) The theme or content of the research journal regarding the relationship between early estrogen exposure and the incidence of breast cancer in women, 3) It has a full text journal, and 4) Original research journal. Moreover, the exclusion criteria were journal below year of 2011, a review and case study journal and not journal of interest based on the keyword search.

By recording the characteristics of research articles, including author, year, title, and research results in the form of p-value, OR, and 95% CI, 35 articles from the years 2011 to 2022 were used in this study. Variables investigated were 1) menarche age, 2) age at first giving birth and 3) hormonal contraception use.

RESULT

35 articles from databases such as Google Scholar, PubMed, and Proquest from 2011 to 2022 were used in this study for the systematic literature review. The table of characteristics and distribution of each variable displays the characteristics of research articles that include the author, year, title, and research results in this study.

Menarche Age

Eighteen journals were analyzed for the impact of menarche at less than 12 years old in breast cancer; The highest was OR 26.8 means that woman who had menarche at 12 years old or less had 26.8 times more likely to develop breast cancer than woman who had menarche more than 12 years old. Twelve articles reported a link between the age of menarche and the incidence of breast cancer; One person stated that there was a connection, but that it had no bearing on the rate of breast cancer; and 5 reported that there was no correlation between the incidence of breast cancer and menarche at the age of 12. The table 1 provides a graph of the distribution of OR dan their 95% CI for menarche age in breast cancer women.

Table 1. Menarche age analysis and its relation to breast cancer in woman

No.	(Author)	Title	Results		
			P *value*	OR	95% CI
1.	(Setiadharma, Kuntjoro, & Utomo, 2019)	Hubungan Penggunaan Kontrasepsi Hormonal Terhadap Kejadian Tumor Payudara: Studi Pada Wanita Yang Melakukan Pemeriksaan Ultrasonografi Payudara Di RSUP Dr. Kariadi Dan RS Ken Saras, Semarang	0.742	1.556	0.419 – 5.779
2	(Dewi & Hendrati, 2015)	Analisis Risiko Kanker Payudara Berdasar Riwayat Pemakaian Kontrasepsi Hormonal dan Usia Menarche	0.031	3.492	1.118 – 10. 911
3.	(Al-Insyirah, 2016)	Faktor-Faktor Yang Berhubungan Dengan Kejadian Kanker Payudara Di Poliklinik Onkologi RSUD Arifin Achmad Provinsi Riau	0.028	2.12	1.13 – 3.96
4.	(Setiowati et al., 2016)	Hubungan antara Pemakaian KB Hormonal dengan Kejadian Kanker Payudara di Poli Onkologi Satu Atap RSUD Dr. Soetomo, Februari–April 2015	0.474	1.363	0.568 – 2.823
5.	(Syarlina, Azamris, Suchitra, & Harahap, 2019)	Hubungan Interval Waktu Antara Usia Menarche Dan Usia Saat Melahirkan Anak Pertama Cukup Bulan Dengan Kejadian Kanker Payudara Di RSUP Dr.M. Djamil Padang Pada Tahun 2014-2017	0.742	1.556	0.419 – 5.779

(*Continue on next page*)

6.	(*continued*) (Anggorowati, 2013)	Faktor Risiko Kanker Payudara Wanita	0.00	6.66	2.84 – 15.65
7.	(Priyatin, Ulfiana, & Sumarni, 2013)	Faktor Risiko yang Berpengaruh Terhadap Kejadian Kanker Payudara Di RSUP Dr. Kariadi Semarang	-	2.638	0.735 – 9.644
8.	(Yulianti, Santoso, & Sutinigsih, 2016)	Faktor-Faktor Risiko Kanker Payudara (Studi Kasus Pada Rumah Sakit Ken Saras Semarang)	0.0001	1.04	1.04 – 1.04
9.	(Purwanti & Syukur, 2021)	Faktor Risiko yang Berhubungan dengan Kejadian Kanker Payudara Wanita	0.375	1.5	0.4 – 4.9
10.	(Iqmy, Setiawati, & Yanti, 2021)	Faktor Risiko Yang Berhubungan Dengan Kanker Payudara	0.000	55.163	2.348 – 11.351
11.	(Paratiwi, 2021)	Faktor Risiko Yang Berhubungan Dengan Kejadian Kanker Payudara Wanita Di RSUD Dr. Achmad Mochtar Bukittinggi	0.014	33.083	1.330 – 7.149
12.	(Yulianti et al., 2016)	Faktor-Faktor Risiko Kanker Payudara (Studi Kasus Pada Rumah Sakit Ken Saras Semarang)	0.051	0.812	0.331 – 1.989
13.	(Indrati, 2005)	Faktor – Faktor Risiko Yang Berpengaruh Terhadap Kejadian Kanker Payudara Wanita	-	3.6	1.08 – 12.04
14.	(Ardiana & Negara, 2013)	Analisis Faktor Risiko Reproduksi yang Berhubungan dengan Kejadian Kanker Payudara pada Wanita	0.015	4.41	1.33 – 14.63
15.	(Harahap & Lumbanraja, 2018)	Faktor Risiko Kanker Payudara Pada Wanit Usia Subur di RSUD Dr. Pirngadi Medan	0.00	4.487	2.080 – 9.682
16.	(Ahsani & Machmud, 2019)	Hubungan Riwayat Reproduksi dengan Tumor Payudara pada Perempuan Usia Muda di Indonesia (Analisis Riset PTM 2016)	0.021	1.29	1.24 – 1.98
17.	(Husada, 2019)	Hubungan Usia Menarche Dengan Kejadian Kanker Payudara Pada Wanita Usia 25-50 Tahun Di Rumah Singgah Yayasan Kanker Payudara Indonesia (YKPI) Jakarta	0.007	0.800	0.587 – 1.091
18.	(Sukmayenti & Sari, 2019)	Analisis Determinan Kanker Payudara Pada Wanita Di RSUP Dr. M. Djamil Padang Tahun 2018	0.000	226.8	-

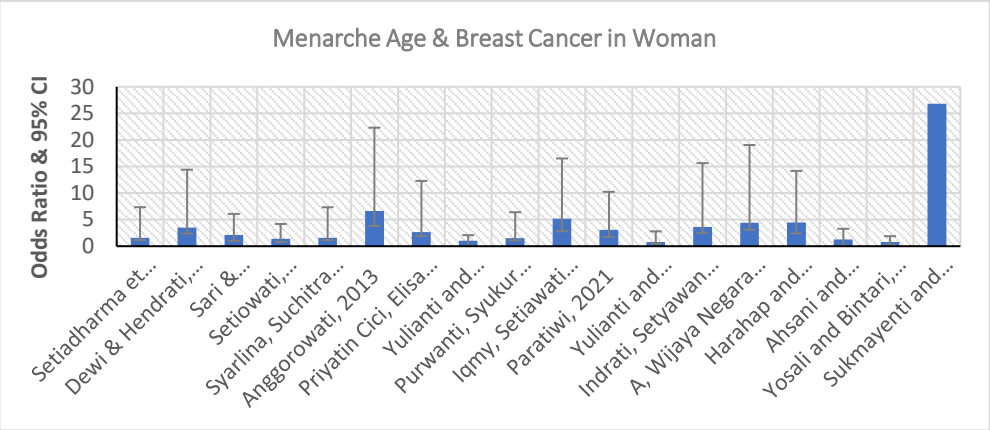


Figure 1. The OR and 95% CI distribution of age at menarche and its relation to breast cancer in woman in the searched literatures

Age at First Giving Birth

Seven journals were analyzed. There were significant correlations between the incidence of breast cancer and the age at which a woman gave birth for the first time, which the cut off was 30 years old. Moreover, only two of those journals report no association between them. The highest OR was 6,473 means women who first give birth at > 30 years old are 6,473 times more likely to have breast cancer than women who first give birth < 30 years old. Below is the table and graph of the distribution of OR of age at first birth in relation to breast cancer incidence in women.

Table 2. Age at first time gave birth analysis and its relation to breast cancer in woman

No.	Author	Title	Results		
			P *value*	OR	95% CI
1.	(Anggorowati, 2013)	Faktor Risiko Kanker Payudara Wanita	0.00	4.99	1.90 – 13.87
2.	(Tirtawati, 2014)	Risiko Kanker Payudara pada Kehamilan Pertama Wanita Usia diatas 30 Tahun	0.001	5.0	1.78 – 14.10
3.	(Priyatin et al., 2013)	Faktor Risiko yang Berpengaruh Terhadap Kejadian Kanker Payudara Di RSUP Dr. Kariadi Semarang	-	2.634	0.626 – 11.078
4.	(Yulianti et al., 2016)	Faktor-Faktor Risiko Kanker Payudara (Studi Kasus Pada Rumah Sakit Ken Saras Semarang)	0.0001	1.32	1.31 – 1.34
5.	(Iqmy et al., 2021)	Faktor Risiko Yang Berhubungan Dengan Kanker Payudara	0.000	6.473	2.668 – 15.705
6.	(Ahsani & Machmud, 2019)	Hubungan Riwayat Reproduksi dengan Tumor Payudara pada Perempuan Usia Muda di Indonesia (Analisis Riset PTM 2016)	0.187	1.26	0.89 – 1.76
7.	(Astri, Rivaí, Desfita, & Yunita, 2020)	Determinan Kejadian Kanker Payudara Pada Wanita Di Rsud Arifin Achmad Provinsi Riau Tahun 2019	0.001	3.091	1.620 – 5895

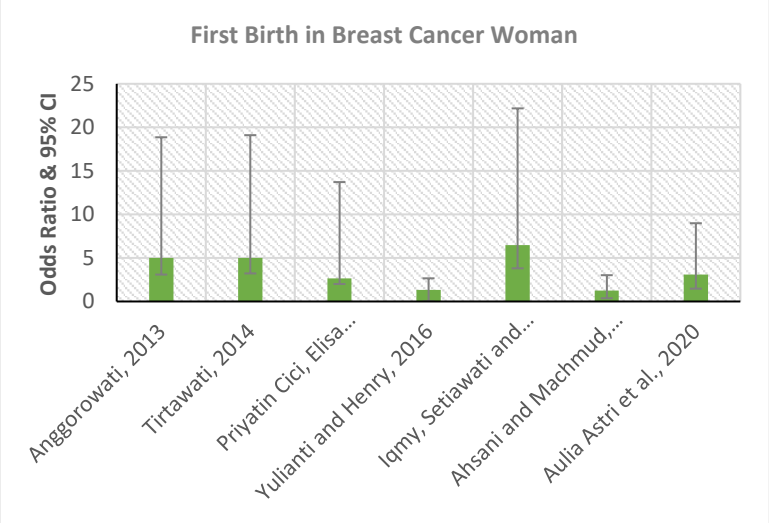


Figure 2. The OR and 95% CI distribution of age at first birth and its relation to breast cancer in woman in the searched literatures

Duration of Hormonal Contraception Use

There were 10 journals that were analyzed to investigate the relation of the duration of contraception use which is more than ≥ 5 years to the incidence of breast cancer in woman. Only one journal said that there was no relationship between duration use of contraception ≥ 5 years even increases the risk of not getting breast cancer. The highest OR 9.06 showed that women that use hormonal contraception >5 years are 9.06 times more likely to have breast cancer than women who do not use hormonal contraception. The table 3 showed the characteristics of research articles in the literature about duration of hormonal contraception use and its relation to the incidence of breast cancer based on the OR value and 95% CI.

Table 3. Characteristics of research articles in the literature study variable length of use of contraception analysis of early estrogen exposure on the incidence of breast cancer in women

No.	(Author)	Title	Results		
			P *value*	OR	95% CI
1.	(Dewi & Hendrati, 2015)	Analisis Risiko Kanker Payudara Berdasar Riwayat Pemakaian Kontrasepsi Hormonal dan Usia Menarche	0,028	3,266	1,136 – 9,390
2.	(Anggorowati, 2013)	Faktor Risiko Kanker Payudara Wanita	0,69	1,75	0,35 – 8.71
3.	(Al-Insyirah, 2016)	Faktor-Faktor Yang Berhubungan Dengan Kejadian Kanker Payudara Di Poliklinik Onkologi RSUD Arifin Achmad Provinsi Riau	0.008	2.65	1.34 – 5.24
4.	(Alsammarraie, Mubarak, Alnuaimi, & Kamal, 2020)	Association of Oral Contraceptions use with Breast Cancer and Hormone Receptor Status in Iraqi Women	0.07	1.57	0.96 – 2.56
5.	(Priyatin et al., 2013)	Faktor Risiko yang Berpengaruh Terhadap Kejadian Kanker Payudara Di RSUP Dr. Kariadi Semarang	-	0.513	0.201 – 1.306
6.	(Andini, Qodir, & Azhar, 2017)	Hubungan Lama Penggunaan Kontrasepsi Hormonal dengan Kejadian Kanker Payudara pada Pasien di Poliklinik Bedah Onkologi	0.000	6.362	2.713 – 14.919

		RSUP Dr. Mohammad Hoesin Palembang pada September – Oktober 2016			(*continue on next page*)
	(continued)				
7.	(Paratiwi, 2021)	Faktor Risiko Yang Berhubungan Dengan Kejadian Kanker Payudara Wanita Di RSUD Dr. Achmad Mochtar Bukittinggi	0.158	1.926	0.865 – 4.290
8.	(Nissa, Widjajanegara, & Purbaningsih, 2017)	Kontrasepsi Hormonal sebagai Faktor Risiko Kanker Payudara di RSUD Al-Ihsan Bandung	0,001	9,06	9,10 – 11,4
9.	(Awaliyah, Pradjatmo, & Kusnanto, 2017)	Penggunaan kontrasepsi hormonal dan kejadian kanker payudara di rumah sakit Dr. Sardjito	0,0003	3,55	1,70 – 7,40
10.	(Ahsani & Machmud, 2019)	Hubungan Riwayat Reproduksi dengan Tumor Payudara pada Perempuan Usia Muda di Indonesia (Analisis Riset PTM 2016)	0,000	0,72	0,69 – 0,88

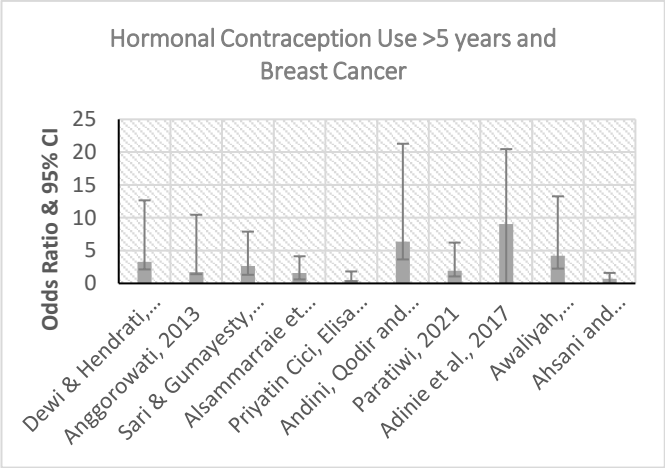


Figure 3. The distribution OR dan 95% CI of duration of contraception use >5 years and its relation to the incidence of breast cancer in woman

DISCUSSION

Estrogen is the most studied hormone because there is epidemiological evidence that long-term exposure to estrogen can increase the incidence of breast cancer in women. Research results showed that there is a significant relationship between an early age at menarche or less than 12 years with the incidence of breast cancer. According to researchers, women who have their first menstruation < 12 years old indirectly have a longer duration of exposure to the hormone estrogen than normal, so the risk of developing breast cancer is higher (Harahap & Lumbanraja, 2018).

The menarche age variable in this study has the highest OR values among the three studied variables. The data analysis revealed woman with menarche age at 12 years old or below have more risk to have breast cancer (range of OR 0.80 – 26.8. This is because in earlier menarche age, women are exposed to estrogen earlier. Menarche typically takes place between the ages of 12 and 13. The age difference at menarche's onset is influenced by a number of factors, including lifestyle, environment, and genetics (Ningrum & Rahayu, 2021). One of study reported found that women who reach menarche too early, around the age of 12 years old, they are more exposed to the estrogen hormone. Estrogen has potential to initiate abnormal cell development (Dewi & Hendrati, 2015). The role of estrogen, its metabolites, and the division of epithelial cells are sparked by estrogen stimulation, as the development of breast cancer. The earlier she begins menstruating, the longer she stays

exposed to estrogen and developing breast cancer cells (Al-Insyirah, 2016). Another research reported that there is no significant influence between the age of menarche on the incidence of breast cancer. However, the researcher stated that an early age at menarche still contributes to an increased risk of breast cancer because it affects the decline in the function of steroid hormones. The hormone estrogen is a steroid hormone that will be formed at an early age if you experience menstruation too early (Purwanti & Syukur, 2021).

This study's findings are consistent with previous studies. According to the findings of this study, a woman's risk of developing breast cancer will rise if she experiences her first menstrual period at a younger age—less than 12 years—than the average age. This is because the length of time that breast tissue is exposed to chemicals, estrogen, or radiation increases with woman's rate of menstruation (Mail & Yuliani, 2021).

Age at first delivery was also investigated in this study because it is related to the time of a women were exposed to estrogen. Breast cells in type I and type II (immaturity) are more susceptible to mutations from carcinogenic precursor compounds the longer they are present (Mail & Yuliani, 2021). There is a statistically significant correlation between the incidence of breast cancer in women and the age at which they gave birth for the first time (more than 30 years) (Tirtawati, 2014). This is due to the period in between menarche and first pregnancy, hormonal and tissue imbalances occur. The breasts are very sensitive to this, so this period is the beginning of development of breast cancer (Anggorowati, 2013). As a result, mitosis, the process by which cells multiply, moves quickly, which can cause cancer cells to form. There is a relationship between the age at birth of the first child ≥ 30 years and the incidence of breast cancer at the Regional General Hospital dr. Hi. Abdul Moeloek, Lampung Province in 2016 (Iqmy et al., 2021). In this research, it was stated women who have never given birth over the age of 30 years have a risk that is 6.73 times greater than those under 30 years of age.

Older gestational age and delivery are related to the menstrual cycle. Where the menstrual cycle in women who are older in pregnancy and childbirth will experience more menstruation before pregnancy. During the menstrual cycle, FSH (Follicle Stimulating Hormone) will stimulate the growth of primary follicles in the ovaries. In general, the follicles will develop into de Graff follicles which will play a role in the formation of estrogen (Durmaz, 2017). This excessive or abnormal menstrual cycle will result in several changes in the breast tissue due to the presence of the hormone estrogen. These changes trigger abnormalities in the cell regeneration process, apart from that, older gestational age and childbirth can be a promoter of breast duct cell tumors transforming into more malignant ones which will increase the risk of breast cancer. A similar study by Priyatin et al. also reported an influence of age at first birth ≥ 30 years on the incidence of breast cancer in women (Priyatin et al., 2013).

The process of upregulating estrogen receptors causes an increase in the amount of estrogen in a woman's body. The estrogen hormone and progestin, which cause hormonal imbalances in the body, are contained in hormonal contraceptions. After four years, using hormonal contraception especially the pills with combination of estrogen - progesteron results in a buildup of estrogen, which will continue to rise. Additionally, prolonged hormonal contraception will lead to obesity due to the accumulation of estrogen and an increase in the number of adipocytes in the body. Estrogen production and exposure to more estrogen will both raise excessive fat storage and breast cell proliferation. Fat deposition is influenced by estrogen, and the body will store more fat when estrogen levels are high (Awaliyah et al., 2017).

Because fat deposition reduces *Sex Hormone Binding Globulin* (SHBG), or estrogen binding protein, more estrogen can circulate in the bloodstream and reach various body cells through receptors. In the breast glands, one of the most important receptors for the estrogen hormone, more estrogen will bind to its receptors in the breast glands over time, affecting the activity of the CYP17 and CYP19 genes and potentially disrupting mRNA splicing. Genetic errors in the BRCA1, BRCA2, HER2/NEU, or p53 genes will accumulate when this process continues to occur excessively and abnormally, resulting in atypical hyperplasia that eventually leads to breast cancer. In a study that was

carried out by 2017 demonstrated that women's rates of breast cancer increased when they used contraceptions for less than five years. Women who have used hormonal contraception for more than five years are at a greater risk (OR = 4.22, 95% CI = 1.70 – 7.40) than those who have not use hormonal contraception (Awaliyah et al., 2017). This is due to the widespread use of hormonal contraceptions, which, when used for an extended period of time, raise a woman's body's levels of estrogen and progesterone. Breast cancer risk can be increased by this increase in estrogen and progesterone levels.

CONCLUSION

The results showed a range of OR value revealed 0.80 – 26.8 for menarche age at <12 years old, a range of OR 1.26 – 6.47 for age at first birth > 30 years old and a range OR 0.51 – 9.06 for duration hormonal contraception use > 5 years. This review analysis highlighted the relation between the incidence of breast cancer in women and the duration of use of contraception, age at menarche, and age at first birth.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this study

ACKNOWLEDGEMENT

It is hoped that future researchers will be able to carry out further research related to early estrogen exposure because the number of studies on estrogen exposure is not many, so it is very relevant for scientific fields as well as information for the public. For the community, it can be used as well as the importance of knowing the extent to which early exposure to estrogen is at risk for the incidence of breast cancer in women. For related institutions, namely the Faculty of Medicine, Wijaya Kusuma Surabaya University, it is hoped that this research can be used as a library archive at the institution and a facility for all students to find references for research related to the analysis of early estrogen exposure on the incidence of breast cancer in women.

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