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Meta Analysis
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Meta Analysis: Correlations between Age at Menarche, Parity, and Hormonal Contraceptive Use with Breast Cancer in Women of Reproductive Age

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ABSTRACT

Background: Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide. The implementation of the program in reducing the incidence of breast cancer is focused on prevention based on evidence of risk factors. This study aims to estimate factors that influence the incidence of breast cancer in women of productive age.
Subjects and Method: This study used systematic review and meta-analysis using PICO. Population: Women of productive age. Interventions: menstruation at ≥13 years, parity (multipara) and using hormonal contraceptives. Comparison: menstruation at <13 years, parity (nullipara) and not using hormonal contraceptives. Result: breast cancer. The articles used in this study came from 2 databases, namely Google Scholar and BMC. The keywords of the article were "menarche" AND "parity" AND "risk factor" AND "breast cancer". The articles included in this study were full paper articles, used case control study designs, publication year ranged from 2014-2023, and measure of association was in Adjusted Odds Ratio. Articles were analyzed using the Review Manager 5.4 application.
Results: Thirteen case-control studies indicated that women who menstruated at ≥13 years old lowered the likelihood of breast cancer by 0.69 times (aOR=0.69; 95% CI= 0.57 to 0.84; p= 0.001). Eleven case-control studies indicated that multiparous parity lowered the likelihood of breast cancer by 0.49 times (aOR=0.49; 95% CI= 0.34 to 0.72; p= 0.001). Eleven case-control studies indicated that using contraception increased the likelihood of breast cancer by 1.47 times (aOR=1.47; 95% CI= 1.12 to 1.93; p= 0.006).
Conclusion: Menstruation age <13 years old, parity (nullipara) and use of hormonal contraceptives are predictors in breast cancer cases in women of productive age.

Keywords: risk factors, menarche, parity, breast cancer.

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BACKGROUND

Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide, surpassing lung cancer by accounting for 2.3 million new cases and 684,679 deaths (Sung et al., 2021).

Every 3 minutes one woman is diagnosed with breast cancer, with a total of one million cases per year (Babita, 2014). The burden of breast cancer is geographically varied with an increased incidence in high-income countries. Despite its low burden, the disease ranks second only to cervical cancer in many sub-Saharan African countries (Bray et al., 2018). Based on a study, several factors may lead to breast cancer including eating habits, lack of physical activity, smoking, family history, alcohol consumption, obesity (Balekouzou et al., 2017).

Another study states that nulliparity, delayed first parity, and lack of breastfeeding are risk factors for breast cancer (Hassen et al., 2022). The implementation of the program in reducing the incidence of breast cancer is focused on prevention based on evidence of risk factors. Based on the description above, researchers are interested in summarizing the research evidence of primary studies that are the risk of breast cancer in women of productive age.

SUBJECTS AND METHOD

1. Study Design

This study used articles published during the period of 2014 to 2023. Articles selection was conducted using PRISMA Flowchart. The keywords used in article searches were "menarche" AND "parity" AND "risk factor" AND "breast cancer".

2. Steps of Meta-Analysis

1) Formulating PICO includes P = women of productive age, I = menstruation at >13 years old, parity (multipara) and using hormonal contraceptives, C = menstruation at ≤13 years old, parity (nullipara) and not using hormonal contraceptives, O = breast cancer.
2) Searching primary study articles from a variety of electronic and non-electronic journals.
3) Conducting screening and critical appraisal of primary study articles
4) Performing extraction and synthesis of output forecast data into RevMan 5.4.
5) Presenting results and drawing conclusions.

3. Inclusion Criteria

The inclusion criteria used in this study were namely a full text article with a cross-sectional study design, an article published in English during the period of 2014 to 2023, analysis of menstrual age, parity and hormonal contraceptive use through the end of the study was reported using adjusted odds ratios (aOR).

4. Exclusion Criteria

The exclusion criteria used in this study were namely an article that previously underwent meta-analysis, non-cross-sectional design, the final result of the study was not reported in adjusted odds ratio (aOR) and the sample was <100 participants.

5. Operational Definition of Variable

Article search is conducted by taking into account the eligibility criteria determined using the PICO model.

Menstruation: A natural cycle in the female body in which the inner lining of the uterus is periodically released. This process involves the release of blood and tissue from the uterus through the reproductive tract and out of the body through the vagina. Menstruation generally occurs in women who have reached reproductive age, usually starting in adolescence and lasting until menopause.

Parity: Number of pregnancies and number of live or dead births a woman has experienced.

Hormonal contraceptives: A method of birth control that uses hormones to prevent pregnancy. This method involves administering hormones such as estrogen and progestin in the form of pill, injection, or implant.

Breast Cancer: A condition in which abnormal cells grow uncontrollably in breast tissue.

6. Instrument

The instrument used in this study was PRISMA Flow Chart with primary study quality assessment for case control design of Meta-analysis study.

7. Data Analysis

Data processing was carried out upon the collected articles using the Review Manager application. Data processing was presented in the form of forest plot and funnel plot.

RESULTS

The searching process for articles to be synthesized, also the process of reviewing and selecting articles using the PRISMA Flow Diagram were presented in Figure 1. The initial search process resulted in 30,786 articles, after removing duplicate articles, 17,300 articles were generated, then after the process of removing article duplicates, the next step was to check the relevance of the title and design of the study to generate 1,396 articles. After that, an articles verifying process was conducted according to inclusion criteria and exclusion criteria and obtained a total of 2,759 articles. The screened articles subsequently underwent a critical appraisal and generated 16 articles.

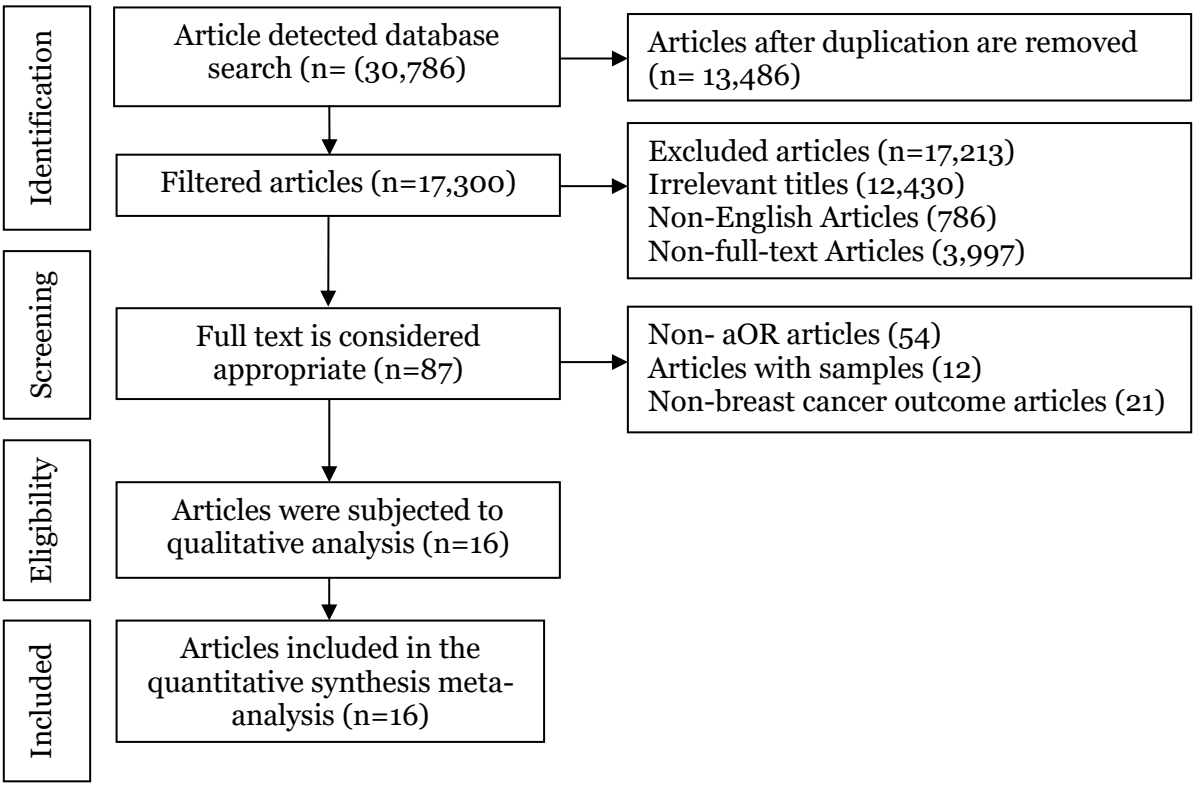

Figure 1. PRISMA Flow Diagram Results

Based on Figure 2 show that a total of 16 articles that met the critical appraisal were included in the quantitative synthesis using meta-analysis. Based on Figure 2, a total of 16 study articles were observed. 4 articles were from Africa, 2 articles were from America, and 10 articles were from Asia.

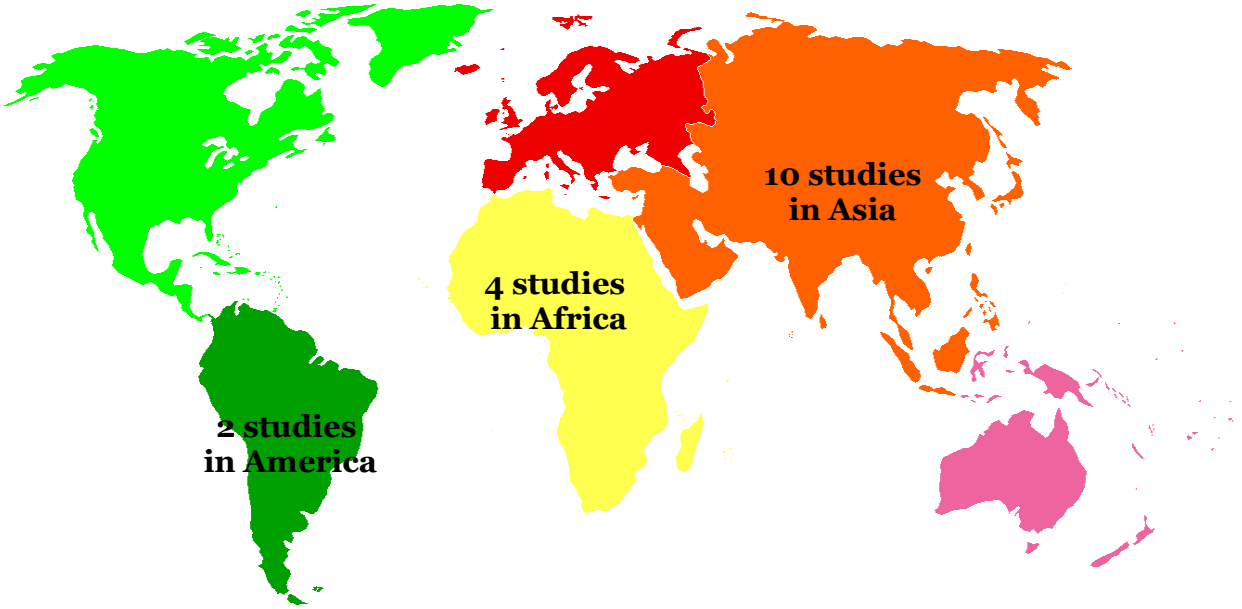

Figure 2. Map of the Research Area study of the effect of menstrual age, parity and hormonal contraceptives on breast cancer in women of productive age

Table 1. Critical appraisal of the effect of menstrual age, parity and hormonal contraception on breast cancer in women of productive age

Author (Year)	Appraisal Criteria													Total
	1a	1b	1c	1d	2a	2b	3a	3b	4	5	6a	6b	7	
Nguyen et al. (2016)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Sepandi et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Tan et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Khalis et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Balekouzou et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Alipour et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Paul et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Bensaber et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Monteiro et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Bui et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Ma et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Dung et al. (2016)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Hassen et al. (2022)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Trieu et al. (2017)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Baset et al. (2021)	2	2	2	2	2	2	2	2	2	2	2	2	2	26
Nag et al. (2023)	2	2	2	2	2	2	2	2	2	2	2	2	2	26

Description of question criteria:

1. **Formulation of research questions in the acronym PICO**

a. Is the population in the primary study the same as the population in the PICO meta-analysis?

b. Is the operational definition of the intervention, i.e. exposed status in the primary study the same as the definition intended in the meta-analysis?

c. Is the comparison, i.e. unexposed status used by the primary study the same as the definition intended in the meta-analysis?

d. Are the outcome variables studied in the primary study the same as the definitions intended in the meta-analysis?

2. Methods for selecting a study subject

a. In cross-sectional analytical study, did researcher randomly select samples from the population (random sampling)?
b. Alternatively, if in a cross-sectional analytic study, the sample was not randomly selected, did the researcher select the sample based on the status of the outcome or based on intervention status?

3. Methods for measuring exposure (intervention) and outcome variables

a. Were both exposure and outcome variables measured with the same instruments in all primary studies?
b. If variables were measured on a categorical scale, were the cut-offs or categories used the same across primary studies?

4. Design-related bias

If the sample was not randomly selected, have researchers made efforts to prevent bias in choosing study subjects? For example, selecting subjects based on outcome status was not affected by exposure status (intervention), or in selecting subjects based on exposure status (intervention) was not affected by outcome status

5. Methods to control confusion (confounding)

Whether primary study researchers have made efforts to control the effect of confusion (e.g., performing a multivariate analysis to control for the effect of several confounding factors)?

6. Statistical analysis methods

a. Did the researchers analyze the data in this primary study with multivariate analysis models (e.g., multiple linear regression analysis, multiple logistic regression analysis)?
b. Did the primary study report measure of effect or association of the results of the multivariate analysis (adjusted OR)?

7. Conflict of interest

Was there no possibility of conflict of interest with the research sponsor, which caused bias in concluding study results?

Assessment Instructions:

1. Total number of questions = 13 questions. A score of "2" is given for each "Yes" answer to each question. A score of "1" is for each "Undecided" answer. A score of "0" is for each "No" answer.
2. Maximum total score= 13 questions x 2= 26.
3. Minimum total score= 13 questions x 0= 0. So, the total score ranges for a primary study between 0 and 26.

If the total score of a primary study >= 22, then the study can be included in the meta-analysis. If the total score of a primary study.

Table 2. Description of the primary studies of the effect of menstruation at ≥13 years old on breast cancer in women of productive age (n = 32,253)

Author (Year)	Country	Sample	P	I	C	O
			Population	Intervention	Comparison	Outcome
Moradinazar et al. (2019)	Iran	620	Healthy women and women with breast cancer	Menstruation ≥13 years	Menstruation <13 years	Breast cancer
Baset et al. (2021)	Afghanistan	402	Women with breast cancer aged >30 years	Menstruation ≥13 years	Menstruation <13years	Breast cancer
Tan et al. (2018)	Malaysia	7,663	Women aged 40-74 years	Menstruation ≥13 years	Menstruation <13years	Breast cancer
Nag et al (2023)	India	1,146	Women aged 18-70 years	Menstruation ≥13 years	Menstruation <13years	Breast cancer

Author (Year)	Country	Sample	P	I	C	O
			Population	Intervention	Comparison	Outcome
Khalis et al. (2018)	Morrocco	474	Patients diagnosed with breast cancer and healthy women	Menstruation ≥13years	Menstruation <13years	Breast cancer
Trieu et al. (2017)	Vietnam	788	Women diagnosed with cancer	Menstruation ≥13 years	Menstruation <13years	Breast cancer
Hassen et al. (2022)	Ethiopia	460	Women with breast cancer aged >18 years and healthy women	Menstruation ≥13 years	Menstruation <13years	Breast cancer
Sepandi et al. (2014)	Iran	12,047	Women diagnosed with breast cancer and healthy women	Menstruation ≥13 years	Menstruation <13years	Breast cancer
Nguyen et al (2016)	Vietnam	1,798	Women with invasive breast cancer aged 25-75 years	Menstruation ≥13 years	Menstruation <13years	Breast cancer
Bui et al. (2022)	Vietnam	958	Women aged 21-79 from inpatient and outpatient	Menstruation ≥13 years	menstruation <13years	Breast cancer
Balekouzouet al. (2017)	China	522	Women aged >15 years who showed breast cancer	Menstruation ≥13 years	menstruation <13years	Breast cancer
Ma et al. (2017)	USA	5,106	Women aged 20-64 years	Menstruation ≥13 years	menstruation <13years	Breast cancer
Dung et al. (2016)	Vietnam	269	Women with breast cancer and healthy women	Menstruation ≥13years	menstruation <13years	Breast cancer

Table 3. Adjusted Odd Ratio data of the effect of menstruation at ≥13 years on breast cancer in women of productive age (n = 32,253)

Author (year)	aOR	95% CI	
		Upper Limit	Lower Limit
Moradinazar et al. (2019)	0.62	0.29	1.25
Baset et al. (2021)	0.83	0.72	0.92
Tan et al. (2018)	1.04	0.94	1.16
Nag et al. (2023)	1.31	0.91	1.88
Khalis et al. (2018)	0.62	0.42	0.92
Trieu et al. (2017)	0.43	0.21	0.83
Balekouzou et al. (2017)	0.18	0.07	0.44
Hassen et al. (2022)	0.31	0.17	0.56
Bui et al. (2022)	0.37	0.13	0.92
Ma et al. (2017)	0.75	0.53	1.08
Sepandi et al. (2014)	0.40	0.16	0.95
Nguyen et al. (2016)	1.05	0.95	1.16
Dung et al. (2016)	0.47	0.31	0.71

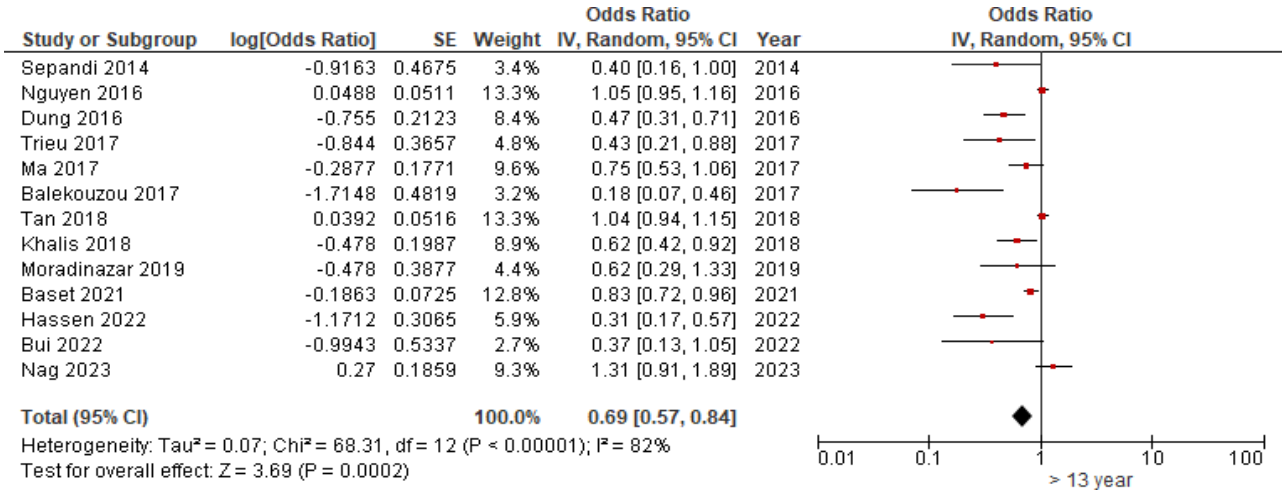

Figure 3. Forest plot of the effect of menstruation age ≥13 years on breast cancer in productive age

Forest plot in Figure 3 shows that women who menstruated at ≥13 years could reduce the risk of breast cancer by 0.94 times compared to women with menstrual age <13 years, and this result was statistically significant (aOR=0.69; 95% CI= 0.57 to 0.84; p= 0.002). The forest plot also shows high heterogeneity of effect estimates across primary studies I^2 = 82%; p<0.001. The calculation of the average effect estimates was carried out with a random effect model approach.

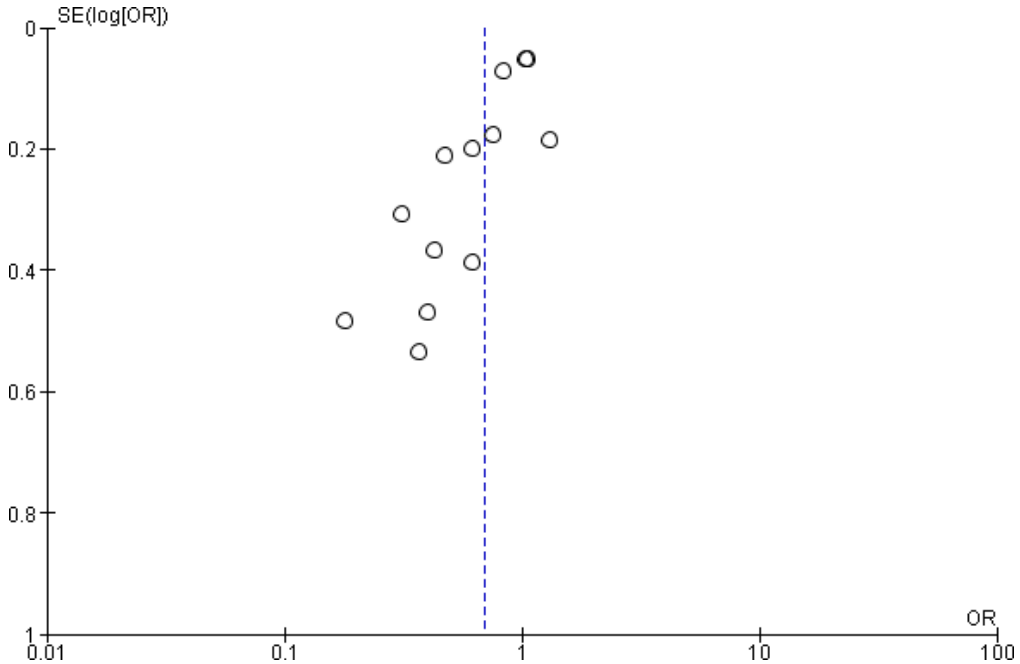

Figure 4. Funnel plot of the effect of menstruation at age ≥13 years on breast cancer in productive age

The funnel plot results in Figure 4 show that the distribution of effect estimates is uneven. The distribution of effect estimates shows that the distribution of effect estimates tends to lie more to the left of the average vertical line of effect estimates than

to the left. Thus, funnel plot figure shows publication bias. Because the distribution of effect estimates is located to the left of the average vertical line in the same direction as the diamonds in the forest plot, publication bias tends to reduce the actual effect (underestimate).

Table 4. Description of the primary studies of the effect of parity on breast cancer cases in productive age (n = 31,114)

Author (Year)	Country	Sample	P	I	C	O
			Population	Inter-vention	Compa-rison	Outcome
Nguyen et al . (2016)	Vietnam	1,798	Women with invasive breast cancer aged 25-75 years	Multipara	Nullipara	Breast cancer
Sepandi et al. (2014)	Iran	12,047	Women diagnosed with breast cancer and healthy women	Multipara	Nullipara	Breast cancer
Tan et al . (2018)	Malaysia	7,663	Women aged 40-74 years	Multipara	Nullipara	Breast cancer
Khalis et al . (2018)	Morrocco	474	Patients diagnosed with breast cancer and healthy women	Multipara	Nullipara	Breast cancer
Alipour et al. (2019)	Iran	499	Women aged 40-75 recruited from the residents of north-eastern Iran	Multipara	Nullipara	Breast cancer
Bensaber et al. (2021)	geria	484	Women undergoing treatment at the hospital and hospital visitors	Multipara	Nullipara	Breast cancer
Monteiro et al. (2019)	Brazil	63	Women aged between 25-43.	Multipara	Nullipara	Breast cancer
Bui et al. (2022)	Vietnam	958	Women aged 21 to 79	Multipara	Nullipara	Breast cancer
Ma et al. (2017)	USA	5,106	Women aged 20-64	Multipara	Nullipara	Breast cancer

Table 5. Adjusted Odd Ratio data of effect of parity on breast cancer in women of productive age (n = 31,114)

Author (Years)	aOR	95% CI	
		Upper Limit	Lower Limit
Nguyen et al. (2016)	0.17	0.05	0.63
Sepandi et al. (2014)	0.27	0.12	0.59
Tan et al. (2018)	1.20	0.85	1.69
Khalis et al. (2018)	0.26	0.13	0.50
Balekouzou et al. (2017)	0.50	0.28	0.89
Alipour et al. (2019)	0.87	0.80	0.95
Paul et al. (2020)	0.35	0.18	0.66
Bensaber et al. (2021)	0.14	0.05	0.39
Monteiro et al. (2019)	2.25	0.26	19.09
Bui et al. (2022)	0.60	0.23	1.47
Ma et al. (2017)	0.76	0.43	1.36

Forest plot in Figure 5 show that nulliparous women could increase breast cancer cases by 0.49 times compared to women with multiparous parity, and this result was statistically significant (aOR= 0.49; 95% CI= 0.34 to 0.72; p= 0.001). The forest plot showed high heterogeneity in the effect estimates across primary studies I^2 = 81%; p<0.003. Thus, the calculation of the average effect estimates was carried out with a random effect model approach.

The result of the funnel plot in Figure 6 shows that the distribution of effect estimates is uneven. It shows that the distribution of effect estimates tends to lie more to the left of the average vertical line of effect estimates than to the left. Thus, this funnel plot image shows the presence of publication bias. Because the distribution of effect estimates is located to the left of the average vertical line in the same direction as the diamonds in the forest plot, publication bias tends to reduce the actual effect (underestimate).

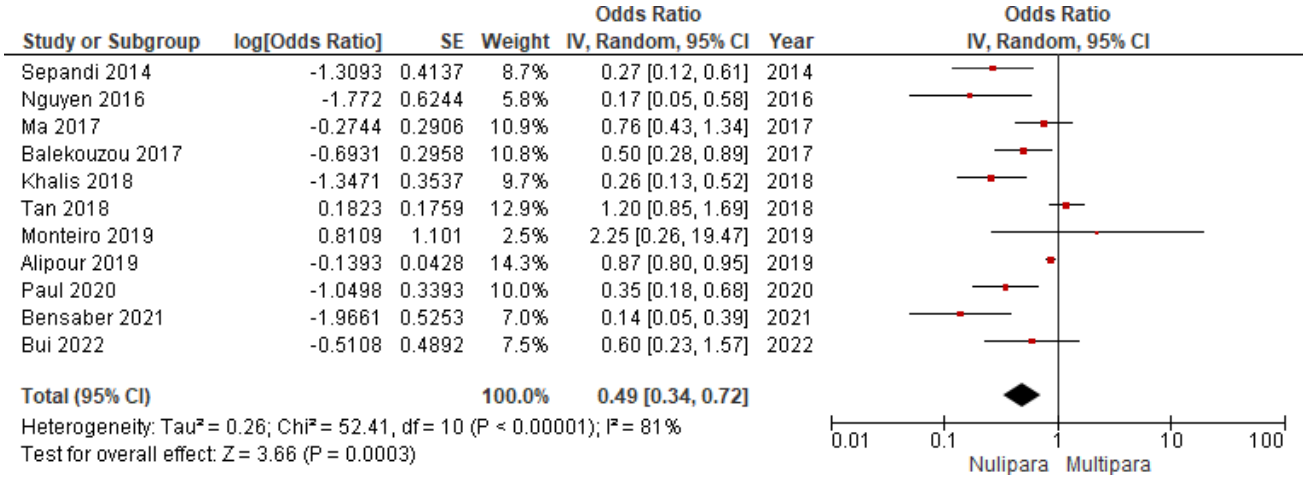

Figure 5. Forest plot of effect of parity on productive age breast cancer

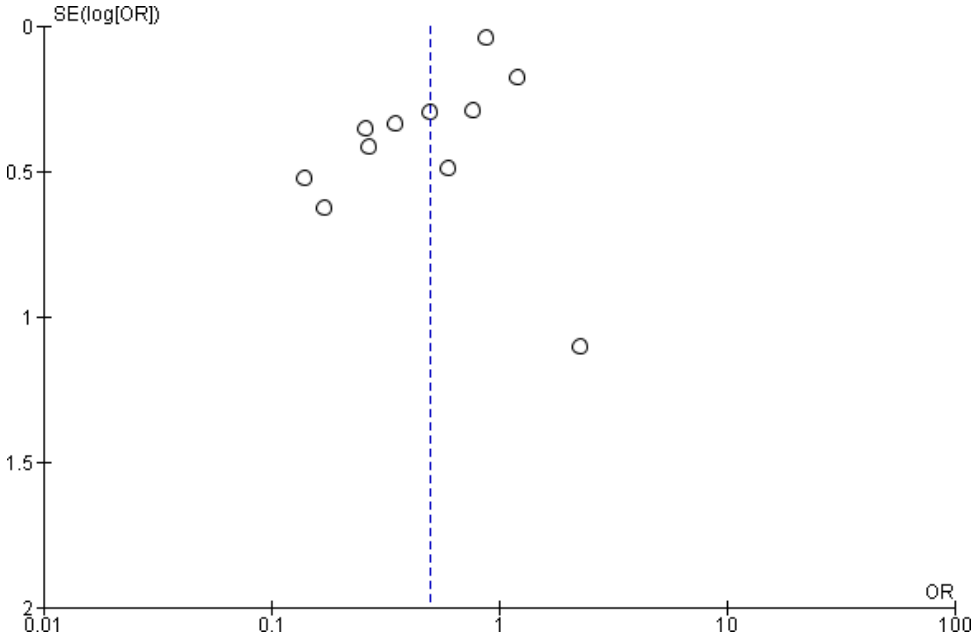

Figure 6. Funnel plot of the effect of parity on breast cancer in women of productive age

Table 6. Description of primary studies effect of hormonal contraceptives on breast cancer in women of productive age (n = 27,405)

Author (Year)	Country	Sample	P	I	C	O
			Population	Inter-vention	Compa-rison	Out-come
Nguyen et al. (2016)	Vietnam	1,798	Women with invasive breast cancer aged 25-75 years	Using oral contraceptives (pills)	Not using contracep-tives	Breast cancer
Moradinazar et al. (2019)	Iran	620	Women with breast cancer and healthy women	Using hormonal contraceptives	Not using contracep-tives	Breast cancer
Sepandi et al. (2014)	Iran	12,047	Women diagnosed with breast cancer and healthy women	Using oral contraceptives (pills)	Not using contracep-tives	Breast cancer
Tan et al. (2018)	Malaysia	7,663	Women aged 40-74 years	Using oral contraceptives (pills)	Not using contracep-tives	Breast cancer
Khalis et al. (2018)	Morrocco	474	Patients diagnosed with breast cancer and healthy women	Using oral contraceptives (pills)	Not using contracep-tives	Breast cancer
Trieu et al. (2017)	Vietnam	788	Women diagnosed with cancer	Using hormonal contraceptives	Not using contracep-tives	Breast cancer
Balekouzou et al. (2017)	China	522	Women aged >15 years who indicated breast cancer	Using hormonal contraceptives	Not using contracep-tives	Breast cancer
Fararouei et al. (2018)	Iran	1,010	Women aged 40-50	Using hormonal contraceptives	Not using contracep-tives	Breast cancer
Alipour et al. (2019)	Iran	499	Women aged 40-75 recruited from residents of northeastern Iran	Using oral contraceptives (pills)	Not using contracep-tives	Breast cancer
Paul et al. (2020)	Cameroon	1,500	Women aged 18 years and over with a diagnosis of breast cancer	Using hormonal contraceptives	Not using contracep-tives	Breast cancer
Bensaber et al. (2021)	Algeria	484	Women undergoing treatment at the hospital and hospital visitors	Using hormonal contraceptives	Not using contracep-tives	Breast cancer

Table 7. Data on Adjusted Odd Ratio of the effect of hormonal contraceptives on breast cancer (n = 27,405)

Author (Years)	aOR	95% CI	
		Upper Limit	Lower Limit
Nguyen et al (2016)	2.03	0.94	4.42
Moradinazar et al (2019)	2.02	1.20	3.30
Sepandi et al (2014)	1.09	0.75	1.58
Tan et al (2018)	0.99	0.88	1.11
Khalis et al (2018)	1.11	0.74	1.66

Author (Years)	aOR	95% CI	
		Upper Limit	Lower Limit
Trieu et al (2017)	2.3	1.30	3.90
Balekouzou et al (2017)	0.62	0.41	0.93
Fararouei et al (2018)	1.77	1.32	2.38
Alipour et al (2019)	3.17	1.27	7.95
Paul et al (2020)	1.56	0.68	3.19
Bensaber et al (2021)	2.55	1.45	4.50

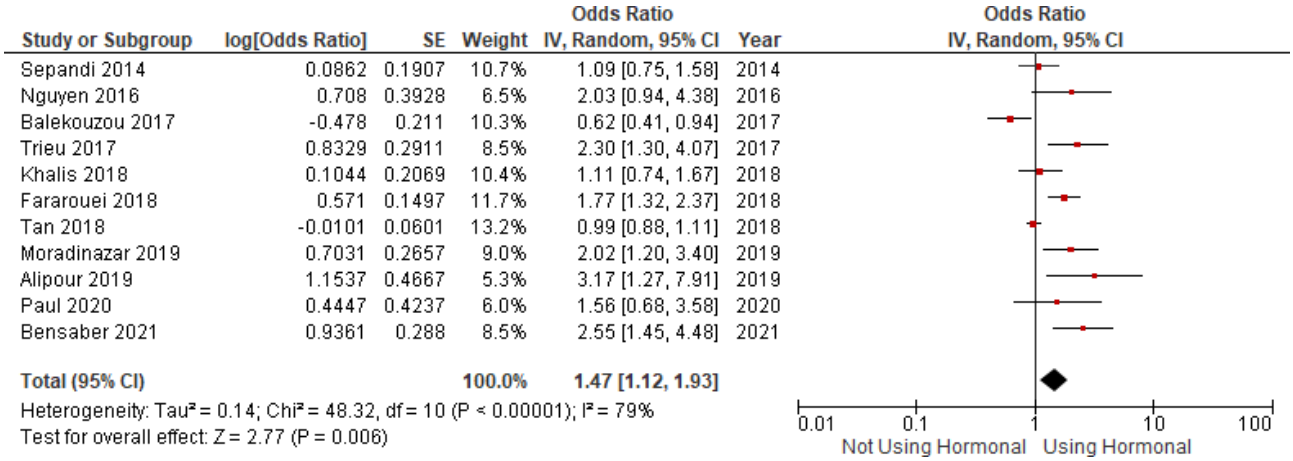

Figure 7. Forest plot of the effect of hormonal contraceptives on breast cancer in women of productive age

Forest plot in Figure 7 show that individuals taking hormonal contraceptives could increase the incidence of breast cancer by 1.47 times compared to individuals not using hormonal contraceptives and this result was statistically significant (aOR= 1.47; 95% CI= 1.12 to 1.93; p= 0.006). The forest plot showed high heterogeneity in the effect estimates across primary studies I^2 = 79%; p = 0.001. Thus, the calculation of the average effect estimation was carried out with a random effect model approach.

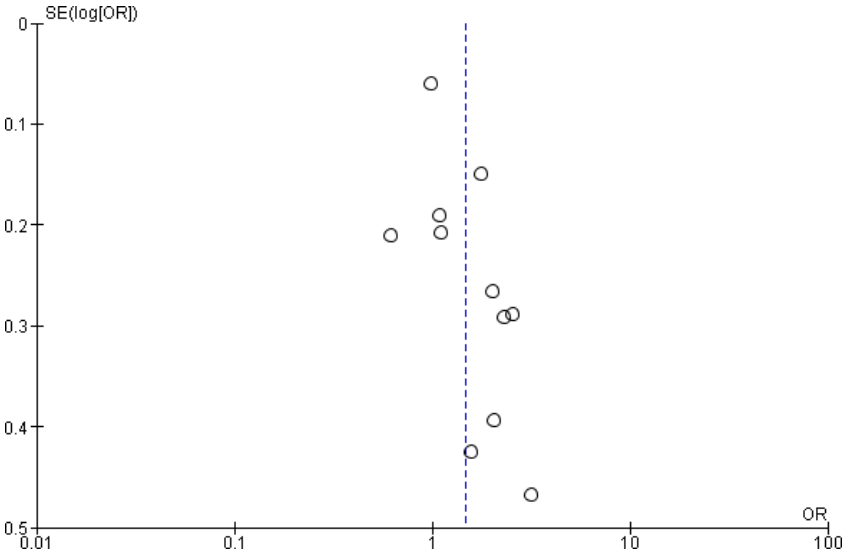

Figure 7. Funnel plot of the effect of hormonal contraceptives on breast cancer in women of productive age

The funnel plot result in Figure 8 shows that the distribution of effect estimates is uneven. indicates that the distribution of effect estimates tends to lie more to the right of the average vertical line of effect estimates than to the right. Thus, this funnel plot image indicates the presence of publication bias. Because the distribution of effect estimates tends to be located to the right of the average vertical line which is in the same direction as the location of the average effect estimate (diamond) located on the right, publication bias tends to overestimate the actual effect (overestimate).

DISCUSSION

This meta-analysis study analyzed factors that affect breast cancer in productive age. This study used aOR statistics of multivariate analysis results which aims to get the same final results for the study to be analyzed.

1. The effect of menstruation at ≥13 years on breast cancer in women of productive age

This study showed that menstrual age ≥13 years has a low probability of breast cancer at productive age of 0.69 times and this result was statistically significant (aOR= 0.69; 95% CI= 0.57 to 0.84; p= 0.001). This suggests that menarche age <13 years increases the risk of breast cancer.

The result of this study is in line with a study by Khalis et al. (2018) which shows that early menarche (≤13 years) is significantly associated with an increased risk of breast cancer.

The biological explanation for this association is based on early and prolonged exposure of the breast epithelium to estrogen produced during periods of ovarian activity. By the time a woman begins to menstruate, the ovarian cycle that produces estrogen begins. Therefore, the amount of exposure to estrogen and progesterone in a woman during her lifetime is a risk factor. The longer a woman is exposed, the higher the risk for breast cancer. Early menstrual age is associated with the length of exposure to the hormone estrogen and progesterone in women which affects the process of tissue proliferation and atrophy including breast tissue.

This is in accordance with the theory introduced by Desen (2013) that early menarche causes an increased risk of breast cancer in women who menstruate before the age of 12 years. The age difference in the occurrence of menarche is influenced by several factors, namely hormonal, genetic, nutritional, environmental, physical activity and psychic states. The sooner a woman experiences puberty, the longer her breast tissue can be exposed to harmful elements that can trigger cancer such as chemicals, estrogen and radiation.

The results of a study by Ardiana et al. (2013) states that women who have risk factors <12 years give significant results have a 4.41 times risk of breast cancer compared to women whose menarche is at the age of >12 years (OR= 4.41; 95% CI = 1.33 to 14.63).

2. The effect of parity on breast cancer in women of productive age

This study showed that multiparous had a low probability of breast cancer in women of productive age of 0.49 times and this result was statistically significant (aOR= 0.49; 95% CI= 0.34 to 0.72; p= 0.001). This suggests that nullipara parity has a high risk of breast cancer incidence. Women who have never been pregnant may have higher hormone levels in the long run, which can increase their risk of breast cancer. The results of this study are in line with a study of Khalis et al. (2018) which states that nulliparity is significantly associated with an increased risk of breast cancer.

This is in line with Rahayu and

Arania's (2018), which states that patients with a parity at risk, namely nullipara and primipara, have 4.9 times risk of breast cancer compared to patients with a non-parity- at risk (multipara and Grande multipara). High incidence occurs in the nullipara state, while low incidence occurs in the multiparous state (decreases with each birth). Nullipara and primipara increase the occurrence of breast cancer compared to women who are multiparous. High levels of estrogen during a woman's reproductive years, especially if not punctuated by hormonal changes in pregnancy, appear to promote the growth of genetically damaged cells that lead to cancer. This is also because nulliparous women never breastfeed, level of estrogen and progesterone of women who breastfeed will remain low during breastfeeding thereby reducing the effect of these hormones on tissue proliferation including breast tissue.

This is in line with the result of a study by Ardiana et al (2013) women with parity 1 to 2 increased risk of breast cancer incidence (OR= 6.38; 95% CI = 1.57 until 25.90).

3. The effect of hormonal contraceptives on breast cancer in women of productive age

This study showed that using hormonal contraceptives had a high probability of breast cancer in productive age of 1.47 times and this result was statistically significant (aOR=1.47; 95% CI= 1.12 to 1.93; p= 0.006). Prolonged hormonal use can disrupt the balance of the hormone estrogen in the body, resulting in normal cell changes to be abnormal. Desen (2013) explains that the hormonal effects of oral contraceptives on the breast are complex.

In premenopausal women, the mechanism of estrogen control is regulated by the pituitary. Which then regulates the production of estrogen in the ovaries and only a small part comes from other organs. The content of estrogen and progesterone in contraception will give an excessive proliferative effect on the breast glands. While in postmenopausal women, estrogen is mainly produced from aromatization of adrenal and ovarian androgens in extragonadal tissues such as liver, muscle, and fat tissue.

The results of a study by Setiowati et al. (2016) indicates that using hormonal birth control has a 2.99 times greater risk of breast cancer than those who do not use hormonal birth control (OR= 2.99; 95% CI= 1.52 to 5.86; p=0.001).

The result of this study is supported by another study conducted by Al-Amri et al. (2015) that there is a significant association between the use of oral contraceptives and the occurrence of breast cancer with a value of p = 0.042. The study was conducted in Saudi Arabia using a case control study design.

AUTHOR CONTRIBUTION

Khairina Nur Hidayati was the main researcher who designed the research, conducted article searches and analyzed data. Hanif Wildan Purnama collected articles and analyzed the data. Anna Nugrahani reviewed article documents.

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CONFLICT OF INTEREST

There was no conflict of interest in this study.

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REFERENCES

Al-Amri FA, Saeedi MY, Al-Tahan FM, Ali AM, Alomary SA, Arafa M, Ibrahim AK, Kassim KA (2015). Breast cancer

corrrelates in a cohort of breast screening program participants in Riyadh, KSA. J Egypt natl canc Inst. 27 (77-82). doi : 10.1016/j.jnci.2015.04.002.

Alipour S, Omranipour R, Malekzadeh R, Poustchi H, Pourshams A, Khoshnia M, Gharavi A, et al. (2019). Case-control study of breast cancer in Northeast of Iran: The Golestan Cohort Study. Arch Iran Med. 22(7): 355-360. doi: https://pubmed.ncbi.nlm.nih.gov/31679377/.

Ardiana, Negara HW, Sutisna M (2013). Analisis faktor risiko reproduksi yang berhubungan dengan kejadian kanker payudara pada wanita. 1(2). doi: 10.24198/jkp.v1i2.58

Babita R, Kumar N, Karwasra RK, Singh M, Malik JS, Kaur A (2014). Reproductive risk factors associated with breast carcinoma in a tertiary care hospital of North India: A case-control study. Adv.Cancer Res. 51, 251-255. doi: https://doi.org/10.4103/0019509X.146759.

Balekouzou A, Yin P, Pamatika CM, Bekolo CE, Nambei SW, Djeintote M, Kota K, Mossoro-Kpinde CD, et al. (2017). Reproductive risk factors associated with breast cancer in women in Bangui: a case-control study. BMC Womens Health. 17(1). doi: 10.1186/s12905-017-0368.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6). doi: 10.3322/caac.214.

Desen W (2013). Buku ajar onkologi klinis, edisi 2. Balai Penerbit FKUI: Jakarta.

Dung PDY, Mello-Thoms C, Peat JK, Do TD, Brennan PC. Inconsistencies of Breast Cancer Risk Factors between the Northern and Southern Regions of Vietnam. Asian Pac J Cancer Prev. doi: 10.22034/APJCP.2017.18.10.2747.

Fararouei M, Iqbal A, Rezaian S, Gheibi Z, Dianatinasab A, Shakarami S, Dianatinasab M (2019). Dietary habits and physical activity are associated with the risk of breast cancer among young iranian women: a case-control study on 1010 premenopausal women. Clin Breast Cancer. doi: 10.1016/j.clbc.2018.10.011.

Hassen F, Enquselassie F, Ali A, Addissie A, Taye G, Tsegaye A, Assefa M (2022). Association of risk factors and breast cancer among women treated at tikur anbessa specialized hospital, Addis Ababa, Ethiopia: a case-control study. BMJ Open. 12 (9). doi: 10.1136/bmjopen-2021-060636.

Khalis M, Charbotel B, Chajes V, Rinaldi S, Moskal A, Biessy C, Dossus L, et al. (2018). Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco. PLoS One. 13(1). doi: 10.1371/journal.pone.0191333.

Ma H, Ursin G, Xu X, Lee E, Togawa K, Duan L, Lu Y, et al. (2017). Reproductive factors and the risk of triple-negative breast cancer in white women and African-American women: a pooled analysis. Breast Cancer Res. 2017 Jan 13;19(1):6. doi: 10.1186/s13058-016-0799-9.

Moradinazar M, Marzbani B, Shahebrahimi K, Shahabadi S, Marzbani B, Moradinazar Z (2019). Hormone therapy and factors affecting fertility of women under 50-year-old with breast cancer. Breast Cancer (Dove Med Press). 11: 309-319. doi: 10.2147/BCTT.S218394.

Nguyen J, Le QH, Duong BH, Sun P, Pham HT, Ta VT, Kotsopoulos J, Narod SA, Ginsburg O (2016). A Matched case-

control study of risk factors for breast cancer risk in Vietnam. Int J Breast Cancer. doi: 10.1155/2016/7164623.

Paul ENJ, Henri E, Valere MK, Sara SND, Emile MT. (2020). Risk Factors for Breast Cancer in the City of Douala: A Case Control Study. Adv Cancer Res. 9 :66-77. doi: https://doi.org/10.4236/-abcr.2020.93006.

Rahayu SA dan Arania R (2018). Hubungan usia dan paritas dengan kejadian kanker payudara di Rsud Dr. H. Abdul Moeloek Bandar Lampung tahun 2017. Jurnal ilmu kedokteran dan kesehatan. 5 (1).

Sepandi M, Akrami M, Tabatabaee H, Rajaeefard A, Tahmasebi S, Angali KA, Rezaianzadeh A, Talei A (2014). Breast cancer risk factors in women participating in a breast screening program: a study on 11,850 Iranian females. Asian Pac J Cancer Prev. 5(19):8499-502. doi: 10.7314/apjcp.2014.15.19.-8499.

Setiowati DAI, Tanngo EH, Soebijanto RI. (2015). Hubungan antara pemakaian kb hormonal dengan kejadian kanker payudara di poli onkologi satu atap RSUD Dr. Soetomo, Februari–April 2015. Indonesian Journal of Cancer. 10 (1). doi : 10.33371/ijoc.v10i1.409.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021). Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. (3): 209-249. doi: 10.3322/-caac.21660.

Tan MM, Ho WK, Yoon SY, Mariapun S, Hasan SN, Lee DS, Hassan T, et al. (2018). A case- control study of breast cancer risk factors in 7,663 women in Malaysia. PLoS One. 13(9). doi: 10.1371/journal.pone.0203469.

Trieu PD, Mello-Thoms C, Peat JK, Do TD, Brennan PC (2017). Inconsistencies of breast cancer risk factors between the Northern and Southern regions of Vietnam. Asian Pac J Cancer Prev. 18(10):2747-2754. doi: 10.22034/-APJCP.2017.18.10.