

THE RISK FACTORS OF BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: The risk factor is described as something that develops the risk of breast cancer. A woman can develop breast cancer due to the various causes. It can be affected by behavior, substance or environmental condition. The purpose of this systematic review is to determine the risk factors of breast cancer. The method of writing this article is systematic review, where the articles were published from 2015 to 2020 that focused on assessing the risk factors of breast cancer. Assessment of the methodological quality of each article was carried out using PRISMA checklist. The results of the analysis of breast cancer risk factors in women are age (p value = 0.0001), family history (p value = 0.0001), age at menarche (p value = 0.036), age at menopause (p value = 0.05), age at first full term pregnancy (p value = 0.033), menopausal status (p value = 0.001), parity (p value = 0.001), breastfeeding (p value = 0.028), oral contraceptive (p value = 0.03), BMI (p value = 0.0001), active smoker (p value = 0.051), and alcohol intake (p value = 0.001). Based on the review conducted, there is a strong correlation between age, family history, age at menarche, age at menopause, age at first full term pregnancy, parity, usage of oral contraceptive, body mass index and alcohol that are very much associated as risk factors of breast cancer. However, smoking has no significant correlation to breast cancer.

Keywords: Women, Breast Cancer, Risk Factors.

1. INTRODUCTION

National Cancer Institute concluded that, cancer is the name given to a group related disease.¹ In all types of cancer some of the body's cells start to isolate without delaying and transmitting into surrounding tissues. ¹ One of the most common cancer is breast cancer where it is very high in number among women and very rare in men. Based on the World Health Organization (WHO), breast cancer is the most widely recognized cancer among women around the world and it's taking away a huge number of women's lives every year. In the year of 2017, WHO had showed that the deaths of breast cancer in Indonesia was 21,287 of total deaths per year.²

Risk factor is defined as something that increases the risk of developing breast cancer. Many various causes may affect a woman's risk of developing breast cancer. It can be affected by behavior, substance or environmental condition. Most breast cancer happens in women.³ Age is the main risk factors of breast cancer. Another main reason in risk factor of breast cancer is the family history. Use of oral contraceptives also plays a part in breast cancer growth. Other risk factors including, the first occurrence of menstruation, age at menopause, age at first pregnancy, menopausal status, parity, short term breast feeding, body mass index (BMI), alcohol consumption and smoking.⁴ In any case, there have been a few common developments in the capacity to foresee and change breast cancer risk.⁵

According to the statistic of United States, an expected 276,480 new cases of obtrusive breast cancer are required to be analyzed in women in 2020 alongside 48,530 new cases of non-intrusive breast cancer. Around 2,550 new cases of obtrusive breast cancer are required to be analyzed in men in 2018. A man's lifetime danger of breast cancer is around 1 of every 1,000.⁶

Based on GLOBOCAN Cancer, breast cancer positions as the fifth reason for death which is around 522,000 deaths. More advanced countries represent around one-half of all breast cancer cases and 38% of deaths. Rates of breast cancer are high in Northern America, Australia/New Zealand, and Northern and Western Europe; middle in Central and Eastern Europe, Latin America, and the Caribbean; and the lowest cases are in Africa and Asia.⁷ The range in death rates between world areas is not as much as that for occurrence in view of the great survival of breast cancer in developed areas, with rates extending from 6 for each 100,000 in Eastern Asia to 20 for every 100,000 in Western Africa (GLOBOCAN Cancer, 2012).⁷

2. MATERIALS AND METHODS

Protocol and Registration

A comprehensive overview in the form of a systematic review and meta-analysis of the risk factors of breast cancer. The protocol in this study uses The Center for Review and Dissemination and The Joanna Briggs Institute Guideline as a guide in assessing the quality of the studies to be summarized. An evaluation of a systematic review, the PRISMA checklist is used to assess the completion of a research that have been found and adjusted to the objectives of the systematic review (Moher, 2009).⁸

Information Sources

The data used in this systematic review were secondary data, which was not obtained from direct observations, but it was obtained from the results of research that had been conducted by previous researchers. The literature search was carried out in October - November 2020. The data comes from various sources and relevant literature, namely using search engines such as Google Scholar, PubMed and NCBI without any time restrictions. This medium provides an easy way to widely browse medical journals which index most of the medical and scientific articles published globally. The literature obtained was then filtered based on predefined inclusion and exclusion criteria.

Search Strategy

Search for articles or journals done by entering keywords as follows ((breast cancer) AND (age OR family history OR oral contraceptives OR age at menarche OR age at menopause OR age at first pregnancy OR menopausal status OR parity OR breastfeeding OR body mass index OR obesity OR alcohol consumption OR smoking)) and Boolean operator such as (AND, OR NOT, or AND NOT), which are used to specify a search, making it easier to find the articles or journals used. The keywords used on this systematic review are based on the Medical Subject Heading (MeSH).

Selection

Based on literature findings from the search for journals and using MeSH-matched keywords, 1023 articles corresponded to these keywords. The screening was then made on the basis of the title that was adjusted to the theme of systematic review and eliminated as many as 972 articles as they were unacceptable and the remaining articles were 51. And thereafter, a reselection was subsequently conducted based on the abstract studies and suitability of the 39 articles based on the abstract and the whole text, and 8 articles could then be included in a systematic review, in compliance with the requirements for eligibility.

Assessment of Risk Bias in Individual Studies

In order to evaluate the consistency of the methodology of each sample (n = 8), The Joanna Briggs Institute (JBI) Critical Appraisal was used for several types of study such as randomized control and trial studies, systematic reviews and qualitative research to analyze. In order to determine the quality of the research, the JBI Critical Appraisal assessment checklist provided several questions. The scoring criteria are given a "yes," "no" or "not valid" score, each criterion with a "yes" scoring is set to one point and each criterion to zero, then each scoring is counted and applied. Critical appraisal for assessing eligible studies is made by the researcher themselves. When the study score achieved at least 50% by fulfilling the critical appraisal criteria with the cut-off point agreed upon by the researcher, then the study is taken into consideration in the inclusion criteria. In order to prevent the validity of the results and the analysis findings, the researcher ruled out poor-quality studies. 8 studies obtained scores greater than 50% for the final screening. This allows for a systematic review to be done.

Summary Measures

The search results for articles based on protocol and registration have been obtained and used to summarize this systematic review. In this systematic review, the data that will be presented are the risk factors of the study based on the articles that has been found, which summarizes 8 articles from the references in this study. Research risk factors include: age frequency distribution, family history, usage of oral contraceptives, the age at first menstruation (menarche), age at menopause, age at first pregnancy, menopausal status, parity, history of breastfeeding, body mass index (BMI), alcohol consumption and smoking.

Result Synthesis

The result synthesis used in this systematic review is a descriptive method focused on the themes that have been determined and described in the systematic review. The study uses descriptive analysis to describe and explain regarding the research results define in the literature through a narrative. The relevant data evaluated by the review questions, which includes: author, country, year, background, theoretical framework, research objectives, study design, sample size, reliability and validity, analysis and statistical techniques and analysis of results. A narrative technique was used in this systematic review with the primary objective of collecting data on the effectiveness of variables and develop a clear textual narrative regarding similarities and differences between studies.

3. RESULTS

Study Selection

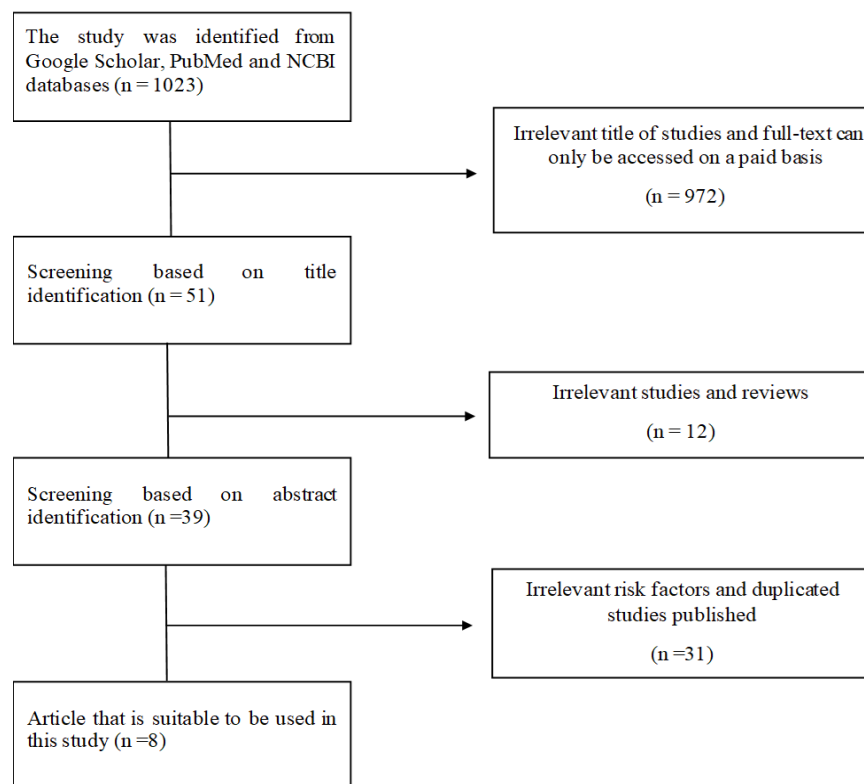


Figure 1. Flow Chart of Literature Search for The Risk Factors of Breast Cancer

Study Characteristic

Out of 8 included studies, 5 studies were case-control studies, 2 meta-analysis studies, and 1 retrospective cohort studies from the period 2015 to 2020. A population of 6 countries in the study of the 8 articles included in this systematic review. In India, 2 studies were carried out, namely at hospital in India. Moreover, 2 studies were carried out in Iran, one in Malaysia, one in Philippines, one in Morocco, and one in Iraq. A number of data collection techniques were used such as interviews, questionnaires and clinical examinations. The characteristics of the articles used in this study shown in Table 2.

Table 2 Characteristics of Studies Reviewed

First Author, Year	Region	Type of Study	Risk Factors	Number of Cases	Sample Control
Mohite et al., 2015	India	Case-control	Age, Oral contraceptive, Age at menarche, Parity, Menopausal status, Breastfeeding	217	217
Aich et al., 2016	India	Case-control	Age, Age at menarche, Age at menopause, Parity, Age of first full term pregnancy, Menopausal status, Breastfeeding, BMI	1463	1440
Tan et al., 2018	Malaysia	Case-control	Age, Family history, Oral contraceptives, Age at menarche, Age at menopause, Parity, Age of first full term pregnancy, Menopausal status, Breastfeeding, BMI, Smoking, Alcohol	3683	3980
Argenal et al., 2019	Philippines	Meta-analysis	Family History, Age at menarche, Parity, Age of first full term pregnancy, BMI, Smoking, Alcohol		480 -10953
Ghalib et al., 2019	Iran	Retrospective cohort	Age, Family History, Age at menarche, Age at Menopause, Parity, Age of first full term pregnancy, Menopausal status, Breastfeeding, BMI	338	676
Houda et al., 2019	Morocco	Case-control	Age, Family History, Menopausal status, BMI, Smoking, Alcohol	305	305
Baiee et al., 2020	Iraq	Case-control	Family history, Age at menarche, Age at menopause, Smoking	100	200
Shamshirian et al., 2020	Iran	Meta-analysis	Age, Family History, Oral contraceptives, Age at menarche, Age of first full term pregnancy, Menopausal status, Breastfeeding, BMI, Smoking	54347	93 - 25592

Individual-related Risk Factors

About 12 risk factors for breast cancer have been identified, according to the studies included. These includes age, family history, age at menarche, age at menopause, age at first full term pregnancy, menopausal status, parity, breastfeeding, oral contraceptive, BMI, smoking status and alcohol intake in women with breast cancer. Of all studied variables, age (p value = 0.001), family history (OR: 5.73, p value = 0.001), age at menarche between 12 to 15 years (OR: 0.55, p value = 0.036), age at menopause lesser than 45 years (OR: 2.48, p value = 0.05), age at first full term pregnancy between 21 to 29 years (OR: 0.690, p value = 0.033), menopausal status (OR: 1.52, p value = 0.001), parity (numbers of children more than 5) (OR: 1.49, p value = 0.001), breastfeeding (OR: 1.4, p value = 0.028), oral contraceptive (OR:1.64, p value = 0.03), BMI that shows overweight women (OR: 1.78, p value = 0.001), active smoker (OR: 1.70, p value = 0.051), and alcohol intake (OR: 0.52, p value = 0.001). The table below shows the odds ratio between the risk factors and breast cancer.

Table 3 Odds ratios for the association between risk factors and breast cancer.

Risk Factor	OR	P-Value	Sample Size		Study	Design
			Cases	Control		
Age < 31 31 – 40 41 – 50 51 – 60 > 60		0.001	72 429 568 272 122	183 409 420 279 149	Aich et al	Case-control
Family History No Yes	5.73	0.001	243 62	292 13	Houda et al	Case-control
Age at Menarche (years) < 12 years Between 12 to 15 years ≥ 15 years	1.31 0.55 0.81	0.000 0.036 0.201	5 2 5	- 2 4	Shamshirian et al	Meta-analysis
Age at Menopause ≤ 45 years 46 – 50 years 51 – 55 years ≥ 56 years	2.48 1.071 3.720 5.833	0.05 0.012 0.036	7 21 61 7	17 49 41 3	Baiee et al Ghalib et al Ghalib et al Ghalib et al	Case-control Retrospective cohort Retrospective cohort Retrospective cohort

Age at First Full Term Pregnancy						
< 18 years		0.001	290	500	Aich et al	Case-control
21 – 29 years	0.690	0.033	123	176	Ghalib et al	Retrospective cohort
30 – 34 years	1.01	0.032	113	-	Argenal et al	Meta-analysis
Menopausal Status						
Pre-menopausal	1.52	0.001	1149	1550	Tan et al	Case-control
Post-menopausal			1771	2408		
Parity (No. of children)						
0	1		66	43	Ghalib et al	Retrospective cohort
1 - 2	0.878	0.638	62	46	Ghalib et al	Retrospective cohort
3 - 4	0.594	0.027	113	124	Ghalib et al	Retrospective cohort
≥ 5	1.49	0.001	370	449	Tan et al	Case-control
Breastfeeding						
Yes	1.4	0.028	1289	1305	Aich et al	Case-control
No			174	135		
Oral Contraceptive						
No			148	169	Mohite et al	Case-control
Yes	1.64	0.03	69	48		
BMI						
Normal weight			72	118	Houda et al	Case-control
Overweight	1.78	0.001	119	109		
Obese	2.39		114	78		
Smoking Status						
Active smoker	1.70	0.051	3	-	Shamshirian et al	Meta-analysis
Passive smoker	1.68	0.442	3	-	Shamshirian et al	Meta-analysis
Non-smoker		0.1	285	293	Houda et al	Case-control
Ex-smoker	2.22	0.1	7	6	Houda et al	Case-control
Alcohol Intake						
No		0.01	287	300	Houda et al	Case-control
Yes	3.76		18	5	Houda et al	Case-control
Less than 1 glass per week	0.45	0.001	98	279	Tan et al	Case-control
1 glass per week or more	0.52	0.001	71	169	Tan et al	Case-control

Risk of Study Bias

Based on the quality analysis of the JBI Critical Appraisal Tools, the study quality of each article that has been determined as the source of systematic review, and so there were 8 articles that were compatible with the systematic review. The findings of the literature which were reviewed and determined in a systematic review are as follows:

Table 4 Result of Study Assessment for Systematic Review using The JBI Critical Appraisal Tools

Citation	Criteria										Result
	1	2	3	4	5	6	7	8	9	10	
Mohite et al., 2015	✓	✓	✓	✓	✓		✓	✓	✓	✓	9/10
Aich et al., 2016	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10/10
Tan et al., 2018	✓	✓	✓	✓	✓	✓	✓		✓	✓	9/10
Argenal et al., 2019	✓	✓	✓		✓	✓		✓	✓		7/10
Ghalib et al., 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10/10
Houda et al., 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10/10
Baiee et al., 2020	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10/10
Shamshirian et al., 2020	✓	✓	✓		✓		✓	✓	✓		7/10

The findings of the 8 studies meeting the criteria for this systematic review shown in (Table 4) are 5 case-control articles, 2 meta-analysis articles, and 1 retrospective cohort articles. Based on these findings, the cohort study was given a total quality score of seven to ten points on the checklist after a critical assessment was conducted using the JBI critical appraisal method. Based on the overall researched reviewed, almost all research showed important data analysis and assessment findings on the risk factors of breast cancer. The high risk of bias is attributed to other factors that lead to breast cancer risk factors, thereby being a confounding factor in the research

4. DISCUSSION

Summary of Evidence

A risk factor is a cause that affects the probability that an individual developing a disease, particularly cancer. Women with breast cancer are more likely to have one or more risk factors than women who does not have breast cancer. Age is very much associated as risk factor for breast cancer ($p < 0.001$). In this systematic review, the researcher showed that the age group of 41 to 50 years has the highest incidence of breast cancer, whereas the lowest breast cancer incidence age is less than 31 years. Similar findings also have been observed.⁹

Family history has been a major contributing factor in breast cancer. Women with positive family history are significantly related to breast cancer ($p < 0.001$). In the study conducted by Houda et al (2019), confirms that family history plays an important role in increasing the risk of developing breast cancer in women.¹⁰ This observed that women with family history of breast cancer is likely to imply a genetic predisposition. A woman who has a first-degree female relative who is considered as her mother, sister or daughter with breast cancer has double the risk of a women without the family history. Provided that she has more than one first- degree female relative with a history of breast cancer, her risk is around 3-4 times higher.¹¹ The importance of family history of breast cancer rises with the quantity of relatives affected in breast cancer and the relationship of the affected family members with the breast cancer patient.

Menarche means the first menstrual period in a women's life, it is a pubertal improvement in young girls. Based on the findings in Shamshirian et al (2020), age at menarche more than 15 years has a protective impact on breast cancer, whereas age at menarche less than 12 years is significantly related to breast cancer ($p < 0.001$).¹² Age at menopause has a strong correlation with breast cancer for those who have menopause more than 51 years ($p < 0.05$). Menopause happens as the ovaries ends the making of hormones and the level of hormones, likely estrogen and progesterone in the body drops. This makes a woman quit bleeding. In the study conducted by Ghalib et al (2019), woman who has early menstruation and late menopause has been said that the cells are exposed to hormones for a longer period of time.¹³ Thus, this increases the risk of breast cancer. Women who have a normal menopause after the age of 55 are twice as prone to get breast cancer as women who encounter menopause before the age of 45. Women with late menarche and early menopause lower the risk of breast cancer. Furthermore, based on the findings of Tan et al (2018), the risk of breast cancer in postmenopausal women was increased by 52% than premenopausal. It is however specifically related to ages at menopause and possibly because some drugs used to relieve symptoms of menopause.¹⁴

The Aich et al (2016) study, reported that women who have their first child before the age of 18 has around one third of the risk of breast cancer.⁹ The results are similar to the research carried out by Ghalib et al (2019) and Argenal et al (2019), early age at first full term pregnancy has a protective impact on breast cancer ($p < 0.001$), while moderately older age woman more than 35 years at first birth presents a relative risk of breast cancer ($p < 0.05$).^{13,15} While pregnancy, breast cells develop very quickly. On the off chance, that there is any hereditary damage in the breast cells, it's copied as the cells develop. This gradually increases hereditary damage in the cells can lead to breast cancer. The possibility of having such hereditary damage runs up with age. This may help clarify why women who have their first child at a later age have a higher risk of breast cancer than women who have their first child at a younger age.¹⁶

Based on the research by Ghalib et al (2019), risk of breast cancer in women who has no children (nulliparous) is two times higher than in women who has children (parous) (p value < 0.001).¹³ Indeed, the study in Tan et al (2018) shows that, the more a woman give birth, the lower her risk of breast cancer.¹⁴ After the first child, every childbirth brings down risk of breast cancer.¹⁷

In the study conducted by Aich et al (2016) analyzed that women who never breastfed their children are more at risk for breast cancer as compared to those who had breastfeed (p value < 0.001) and the correlation has been found to be significant.⁹ Breastfeeding decreases a woman's risk of breast cancer, especially woman who breastfeed for more than 2 years, thus it reduces the number of menstrual cycles, and also lowers the estrogen levels in the body. These effects have been shown to be associated with a reduction in risk of breast cancer. Besides that, breastfeeding has major effects on breast cells that causes them to differentiate, or mature to produce milk. Furthermore, breastfeeding gives numerous advantages to the newborn child, including less scenes of diarrhea, ear contaminations, and lower respiratory diseases and a lower danger of sudden newborn child death, diabetes and asthma. In comparison, woman with short breastfeeding duration or never breastfeed, is common in developed countries which has greater risk of developing breast cancer.¹⁸

Research demonstrated by Mohite et al (2015), that woman with usage of oral contraceptive pills as contraceptives hormones are 1.6 times more likely to develop breast cancer (p value < 0.05) than those who does not use oral contraceptive pills. Hormone replacement is a risk factor of breast cancer, likely due to the usage of estrogen alone or

combined with progesterone which increases the effect of breast cancer compared with progesterone itself. However, it appears that woman who have stopped oral contraceptive pills for a period of 10 years are not at a higher risk of developing breast cancer.¹⁹

In this study, body mass index (BMI) has been strongly associated to breast cancer (p value < 0.001). Obesity is a common risk factor in both premenopausal and postmenopausal woman for breast cancer. For women, being overweight or obese after menopause increases the risk of breast cancer. Women were set into weight classifications based on their BMI, a measure of body fat that considers height and weight. In the study of Houda et al (2019), multivariate odds ratio was 1.78 for overweight women (BMI 25.0-29.9) and obese women was 2.39 (BMI > 30.0) contrasted with women in the normal weight range.¹⁰ Fat tissue contains an enzyme called aromatase that convert hormones, androgens to estrogens.²⁰ Having more fat tissue can rise the possibility of getting breast cancer by raising estrogen receptor- positive breast cancers more than estrogen receptor-negative. Moreover, women who are overweight have a tendency to have higher amounts of insulin. Higher insulin levels have high risk of breast cancer.²¹ However, being overweight or obese before menopause decreases the breast cancer.

Based on the research by Shamshirian et al (2020) and Houda et al (2019), the population of woman who smoke was poor.^{10,12} In this study, smoking was considered to have no significant effect on breast cancer (p value > 0.05). Nonetheless, numerous studies have shown that woman with cigarette exposure may increase the risk of breast cancer, whereas exposure to secondhand smoke has also been shown a slight increase in breast cancer. According to an investigation, women who starts smoking at their early age of their childhood has higher risk (about 24%) of developing breast cancer.

The studies of Houda et al (2019) and Tan et al (2018) has researched that there is adequate proof that alcohol causes risk of breast cancer (p value < 0.001).^{10,14} One practical explanation behind the connection of alcohol consumption and breast cancer risk is that alcohol is thought to cause higher levels of estrogen and also that the alcohol consumption decreases the DNA repair effectiveness. Indeed, even low levels of alcohol intake (a little more than 1 drink for each day) can increase a woman's risk in breast cancer. The breast cancer risk increases with the amount of alcohol consumption.

Limitation

In preparing this systematic review, there is a possibility of error in determining the risk of bias from various studies. Some limitations such as small sample size, case and control selection can impact the interpretation of the findings. Although the findings cannot be generalized, the results indicate that certain established risk factors for breast cancer can vary in their relations. In addition, the risk of bias can also be found from the literature search due to the limited number of studies assessing the risk factors of breast cancer.

5. CONCLUSION

Based on the results and discussion that can be concluded in this systematic review, is that maximum breast cancer cases were in age group of 41 to 50 years. This study also shows that family history, age at menarche, age at menopause, age at first full term pregnancy, parity, usage of oral contraceptive, body mass index and alcohol are very much associated as risk factors of breast cancer. However, smoking is not significantly related to breast cancer.

6. RECOMMENDATION

In the future, there is a strong need for efficient and effective policy modification and health programs regarding the modifiable risk factors such as nulliparous, usage of oral contraceptives, breastfeed, obesity, alcohol consumption and smoking to prevent from developing breast cancer.

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