REVIEW

Breast Cancer Risk From Modifiable and Non-Modifiable Risk Factors among Women in Southeast Asia: A Meta-Analysis

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Abstract

Objective: The aim of this study was to determine breast cancer risk from modifiable and non-modifiable factors among women in Southeast Asia. **Methods:** This meta-analysis was performed on research articles on breast cancer risk factors in PubMed, ProQuest and EBSCO databases published between 1997 and October 2017. Pooled odds ratios (OR) are calculated using fixed and random-effect models. Data were processed using Review Manager 5.3 (RevMan 5.3). **Results:** From a total of 1,211 articles, 15 studies (1 cohort and 14 case control studies) met the criteria for systematic review. Meta-analysis results showed that of the known modifiable risk factors for breast cancer, parity (nulipara) had the highest odd ratio (OR = 1.85 [95% CI 1.47-2.32]) followed by body mass index (overweight) (OR = 1.61 [95% CI 1.43-1.80]) and use of oral contraceptives (OR = 1.27 [95% CI 1.07-1.51]). Of non-modifiable risk factors, family history of breast cancer had the highest odd ratio (OR = 2.53 [95% CI 1.25-5.09]), followed by age (≥ 40 years) (OR = 1.53 [95% CI 1.34-1.76]) and menopausal status (OR = 1.44 [95% CI 1.26-1.65]). **Conclusion:** This analysis confirmed associations between both modifiable risk factors (parity, body mass index and use of oral contraceptives) and non-modifiable risk factors (family history of breast cancer, age and menopausal status) with breast cancer.

Keywords: Breast cancer- risk factors- Southeast Asia

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Introduction

Breast cancer ranks first of all cancer diseases in women encountered worldwide (Torre et al., 2015). An estimated 23% or 1,383,500 new cases a year and 14% or 458,400 cases will be end in death (Jemal et al., 2011). The United States data in 2014 estimated 232,670 new cases of breast cancer (Siegel et al., 2014).

In Indonesia, there are 39,831 new cases of breast cancer every year. Hospital Information System in 2013 reports an incidence rate of 40/100,000 women. In 2009, breast cancer is the leading cause of death due to carcinoma disease hospitalized (Harahap et al., 2017).

Breast cancer is a heterogeneous tumor that has various subtypes with different biological behaviors and clinicopathological and molecular characteristics (Carey et al., 2006). In the last 20 years, there has been an increase in the understanding of multistep carcinogenesis and the leading role of genetic change in the diagnosis, treatment and prevention of breast cancer. This leads to an increase in prevention, detection and treatment strategies in breast cancer patients.

The cause of breast cancer is multifactorial. Several risk factors for breast cancer have been known nowadays. The risk factors are differentiated into non modifiable risk factors: age, sex, genetic factors (5-7%), family history of breast cancer, history of previous breast cancer and proliferative breast disease. Modifiable risk factors : menstrual and reproductive factors, radiation exposure, hormone replacement therapy, alcohol and high fat diet. Some environmental factors such as organochlorine chemicals, electromagnetic field and smoking (Clemons and Goss, 2001).

Breast cancer due to carcinogenesis is multifactorial, the occurrence of breast cancer in cancer patients in Southeast Asia has its own risk factors that could be different from breast cancer patients in western countries. Risk factors such as smoking, alcohol, obesity, nulliparas, early menarche, hormonal drug consumption are rare in patients with breast cancer in Southeast Asia (Harahap et al., 2017).

This study to determine breast cancer risk factors in Southeast Asian community with some research through a study Meta-analysis of risk factors for breast cancer so that the conclusions drawn have a stronger strength.

Materials and Methods

Study design and research sample

This research is a quantitative research with Meta-analysis study design. Meta Analysis is used to find out modifiable and non modifiable risk factors for breast cancer among women in the Southeast Asia. The research sample is a published research article about breast cancer

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risk factors on the internet through database on PubMed, ProQuest and EBSCO published between 1997 and October 2017. The inclusion criteria of this study sample is research on breast cancer risk factors with case control and cohort study, research is in the region of Southeast Asia. Exclusion criterion is research which not available in full text form.

Operational definitions

The variables in this study include independent variables is modifiable factors consists of marital status, parity, breastfeeding, hormonal contraceptive, physical activity, obesity, smoking, alcohol consumption, diet (carbohydrate, fat and protein), drug consumption >5 years, radiation on the chest and face and exposure to pesticides. While non modifiable risk factors including age, menarche age, menopause status, family history of breast cancer, previous cancer history and previous breast cancer history. Dependent variables of breast cancer.

Research procedure

This study is conducted by collecting data through the identification of published research articles on breast cancer risk factors on the internet on PubMed, ProQuest and EBSCO databases (Figure 1).

Data collection technique

Search done by entering keywords as follows: ((breast cancer) AND (age OR age of menarche OR age of menopause OR menopausal status OR parity OR family history of breast cancer OR homonal contraceptive OR breastfeeding OR marital status OR previous cancer history OR physical activity OR activity OR body mass index OR obesity OR smoking OR tobacco use OR cigarette OR alcohol consumption OR unhealthy diet OR diet OR trans fat OR saturated fat OR drugs consumption OR radiation of the chest OR radiation of the face OR pesticides exposure) AND (South East Asia OR Indonesia OR Malaysia OR Singapore OR Brunei OR Thailand OR Myanmar OR Vietnam OR Philippine OR Cambodia OR Laos OR East Timor)).

Search is limited only for english language articles. This article type is limited to journal articles. Research subjects are limited only to research with subjects of human. The time of publication is limited from 1997 to October 2017. Articles with potentially relevant titles are reviewed abstract, while irrelevant articles are excluded. Furthermore, the article is reviewed abstract. Articles that have potentially relevant abstracts will then be reviewed in full-text. While irrelevant articles are excluded. Furthermore, the article is excluded based on the location of the study that is not specific or outside the Southeast Asian region, outcome (breast cancer disease) and the design of the study (case control or cohort study).

Data analysis

The analysis held to get the value of pooled odds ratio which is the combined odds ratio value from the research. Data analysis by Mantel-Haenszel method using fixed effect model and DerSimonian-Laird random-effect model. Data is analyzed by using Review Manager 5.3 (RevMan 5.3).

Results

Identification on 1,211 articles, done by review through the title of the articles, then reviewed abstract, then reviewed in full text form. Irrelevant articles are excluded. Selection of studies conducted to obtain 15 studies related to breast cancer risk from modifiable and non-modifiable risk factors among women in the Southeast Asia (Table 1).

Based on the results of systematic review there are 15 studies (1 study with cohort study and 14 research with case control study) analyzed by meta-analysis. The research variables analyzed based on the systematic review that has been done are modifiable risk factors including oral contraceptives, breastfeeding, parity, body mass index and marital status. Non-modifiable risk factors including age, family history of breast cancer and menopausal status.

Meta analysis study of modifiable risk factors including oral contraceptives, breastfeeding, parity, body mass index and marital status (Figure 2).

Figure 2 on the basis of modifiable breast cancer risk factors known parity (nulipara) has the highest odd ratio (OR = 1.85 [95% CI 1.47-2.32]) followed by Body Mass Index (overweight) (OR = 1, 61 [95% CI 1.43-1.80]) and oral contraceptives (OR = 1.27 [95% CI 1.07-1.51]). While breastfeeding and marital status are not associated with breast cancer. Funnel plot modifiable breast cancer risk factors in the Southeast Asia (Figure 3).

Figure 3 shows parity (nullipara), body mass index (overweight) and oral contraceptive have variation of homogeneous research for breast cancer, it is caused by the plot is symmetrical based on the vertical line meaning when the analysis is taken on the population, time and

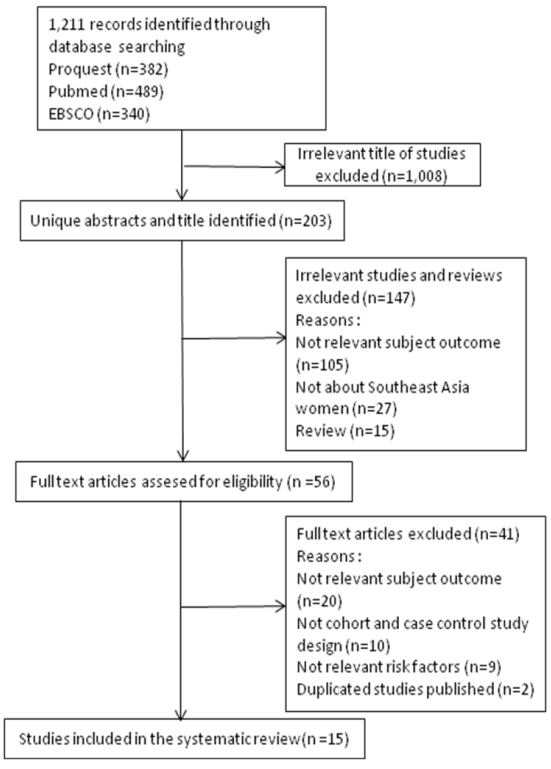

Figure 1. Flow Diagram Research Procedure

Table 1. Systematic Review of Breast Cancer Risk From Modifiable and Non Modifiable Risk Factors Among Women in the Southeast Asia

First Author, Year	Region	Type of Study	Exposure	Number of Sample	
				Cases	Control
Nguyen et al., 2016	Vietnam	Case Control	Oral contraceptive	294	294
Yen et al., 2016	Malaysia	Case Control	Breesfeeding	122	121
Sulaiman et al., 2014	Malaysia	Case Control	Family history of breast cancer	382	382
Pimhanam et al., 2014	Thailand	Case Control	Oral contraceptive, breastfeeding	444	444
Lee et al., 2014	Singapore	Case Control	Parity	411	1,212
Sangrajrang et al., 2013	Thailand	Case Control	Breastfeeding, Family history of breast cancer, Age, menopausal status, body mass index	1,130	1,142
Gao et al., 2012	South-east Asia	Case Control	Parity, body mass index	439	1,198
Sulaiman et al., 2011	Malaysia	Case Control	Family history of breast cancer, marital status	382	382
Razif et al., 2011	Malaysia	Case Control	Family history of breast cancer, marital status	216	216
Ekpanyaskul et al., 2010	Thailand	Case Control	Oral contraceptive, breastfeeding, Family history of breast cancer, age, body mass index, marital status	516	516
Sangrajrang et al., 2010	Thailand	Case Control	Breastfeeding, Family history of breast cancer, age, menopausal status, smoking, body mass index	570	497
Jordan et al., 2009	Thailand	Case Control	Body mass index	43	860
Gibson et al., 2010	Phillipine	Cohort	Parity	123	978
Yip et al., 2008	Malaysia	Case Control	Age	252	1,301
Suzana et al., 2008	Malaysia	Case Control	Breastfeeding	57	139

place as well different conditions then the results will be consistent. This is different from breastfeeding and marital status.

Based on the results of meta analysis study of non modifiable risk factor analysis including age, family history of breast cancer and menopausal status (Figure 4).

Figure 4 on non-modifiable risk factors for breast cancer family history of breast cancer has the highest odd ratio (OR = 2.53 [95% CI 1.25-5.09]) followed by age (≥ 40 years) (OR = 1.53 [95% CI 1.34-1.76]) and menopausal status (OR = 1.44 [95% CI 1.26-1.65]). Funnel plot non modifiable breast cancer risk factors in the Southeast Asia (Figure 5).

Figure 5 shows the family history of breast cancer has a variation of homogeneous research for the occurrence of breast cancer, this is because the plot is symmetrical based on the vertical line means that if the analysis is done on the population, time and place and different conditions then the results will be consistent. This is different from age and menopausal status.

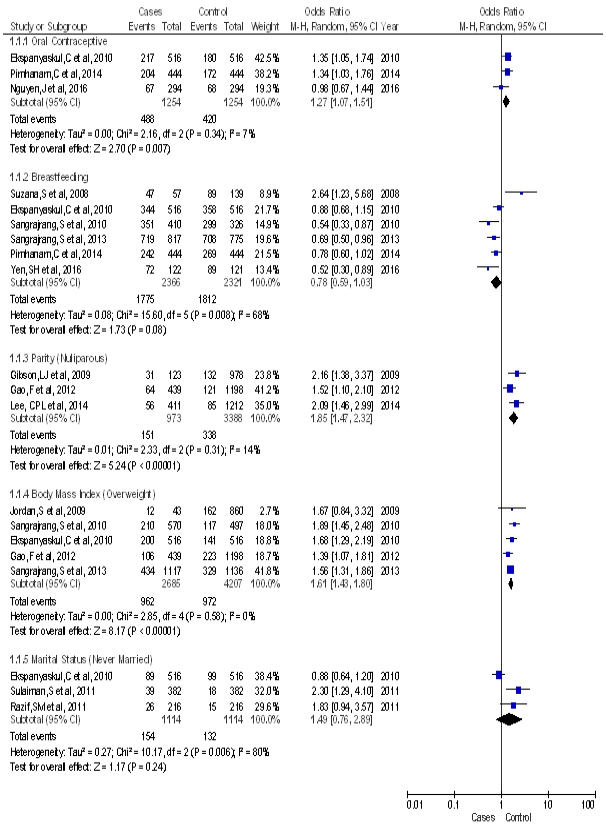

Figure 2. Forest Plots Modifiable Breast Cancer Risk Factors in the Southeast Asia

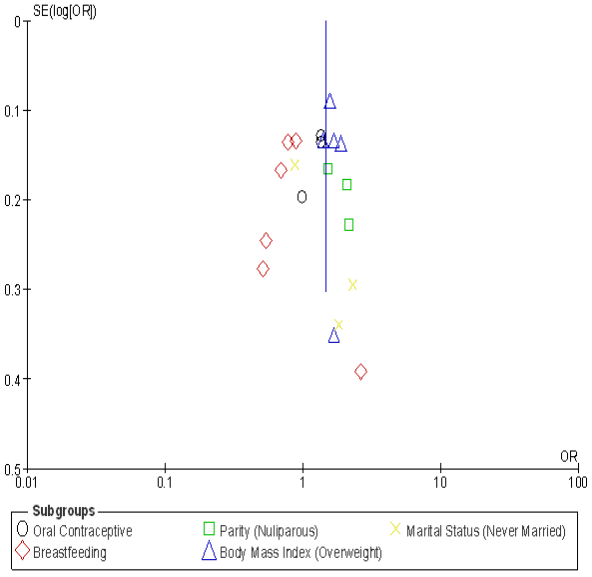

Figure 3. Funnel Plots Modifiable Breast Cancer Risk Factors in the Southeast Asia

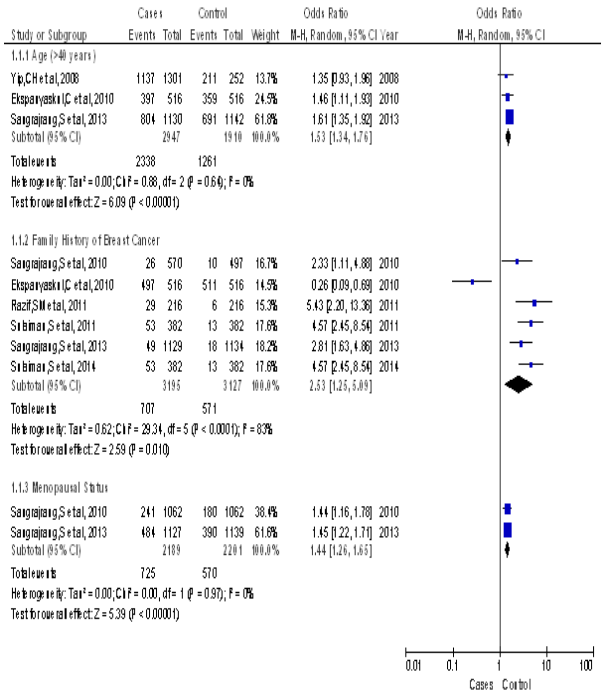

Figure 4. Forest Plots non Modifiable Breast Cancer Risk Factors in the Southeast Asia

Discussion

The result of meta-analysis of modifiable risk factors of breast cancer is known parity (nulipara) has the highest odd ratio (OR = 1,85 [95% CI 1,47-2,32]) followed by Body Mass Index (overweight) (OR = 1.61 [95% CI 1.43-1.80]) and oral contraceptives (OR = 1.27 [95% CI 1.07-1.51]) with breast cancer. Parity (nullipara), body mass index (overweight) and oral contraceptives have a variation of homogeneous research for the occurrence of breast cancer.

Based on the research, women nulipara have 30% breast cancer risk compared to multiparous women. It is caused by nulliparous women never breastfeed. This is related to women who breastfeed estrogen and progesterone levels will remain low during breastfeeding thus reducing the influence of these hormones on the proliferation of tissues including breast tissue (Redondo et al., 2012). Some studies have found nulliparous women have risk factors for breast cancer compared to women with multiparous (Lambe et al., 1996; Redondo et al., 2012).

Body mass index was positively correlated with breast cancer in this study. Obesity is a known risk factor for breast cancer in both pre and post menopausal women (Cecchini et al., 2012; Tamaki et al., 2014). In general, women with overweight have an increased breast cancer risk after post-menopausal (Garrisi et al., 2012). However, there is a decreased risk of breast cancer at the time of premenopause (John et al., 2015). Several previous studies have shown an increased risk of breast cancer at the time of premenopause (Amadou et al., 2013; Bandera et al., 2013). In addition, it is also known a positive relationship between obesity and breast cancer development. Obesity can disrupt some biological pathways, including swelling,

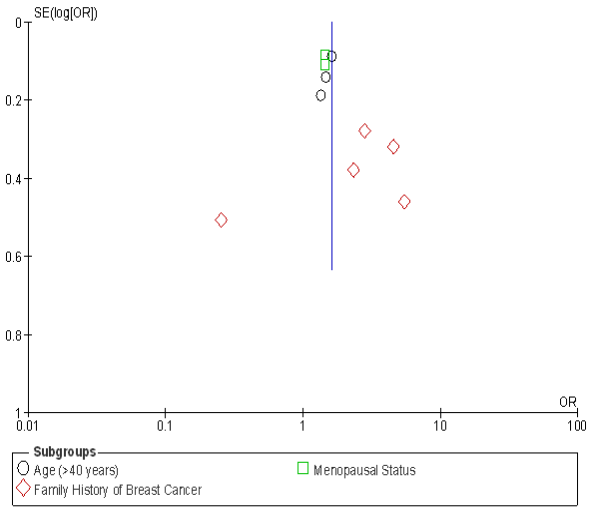

Figure 5. Funnel Plots non Modifiable Breast Cancer Risk Factors in the Southeast Asia

insulin resistance, and synthesis of endogenous sex hormones (Ray et al., 2012).

The results of this study have a significant relationship between oral contraceptives and breast cancer, which is consistent with several other studies (Brinton et al., 1997; Norsa'adah et al., 2005). The association of oral contraceptive with breast cancer is associated with duration, dose, usage pattern, type of oral contraceptive and age of first use (McPherson et al., 2000). Following national family planning programs in Indonesia and Malaysia, oral contraceptive have been widely used by women in reproductive ages (Norsa'adah et al., 2005; Harahap et al., 2017).

Several assumptions about the relationship between the use of oral contraceptives and breast cancer have been proposed. The first assumption is that breast cancer is caused by the increase of estrogen in the body, which is caused by two factors. One is that oral contraceptives are mainly composed of estrogen and progesterone, another factor is numerous pregnancies for more exposure with female hormones. Hence, these pills are likely to increase estrogen levels and then enhance the risk of breast cancer. Another mechanism justifies the impact of high levels of estrogen on the incidence of breast cancer after using pills; reduction and control of estrogen levels is possible by doing physical activities. Those who exercise while using these pills are less exposed to the increase of the level of estrogen and also incidence of breast cancer (Marchbanks et al., 2002; Coyle, 2008).

This study suggests the need for education and counseling about eating habits and the importance of avoiding foods with high fat content, especially those who already have other risk factors such as family history of breast cancer. In addition, it also needs a campaign revealing a direct relationship between oral contraceptive use and breast cancer risk.

The findings of the research which non modifiable risk factors for breast cancer family history has the highest odd ratio (OR = 2.53 [95% CI 1.25-5.09]) followed by age (≥ 40 years) (OR = 1.53 [95% CI 1.34-1.76]) and menopausal status (OR = 1.44 [95% CI 1.26-1.65]).

Family history of breast cancer has a variation of homogeneous research for the occurrence of breast cancer, if the analysis is done on the population, time and place and different conditions then the results will be consistent.

This study revealed the similarity that subjects with a family history of breast cancer had a significantly higher risk of breast cancer than those who did not have a family history, consistent with other studies (Duffy et al., 1997; Pharoah et al., 1997). Subjects with a family history of first-degree relatives including sisters, mothers or children with breast cancer or distant relatives, grandmothers, grandchildren, aunts or nephews, who had breast cancer showed higher risk (OR = 2.95 and OR = 2.84) compared with the results of the meta-analysis of OR = 1.5-2.1 (Pharoah et al., 1997). These results suggest that women with a family history of breast cancer have a higher risk of developing breast cancer than those who do not. Women with a family history of breast cancer should be counseled and educated about the risk of breast cancer, and it is recommended to make early detection of breast cancer.

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