REVIEW

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Association of BRCA1 Promoter Methylation with Breast Cancer in Asia: A Meta- Analysis

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Abstract

Objective: The aim of this study was to determine the degree of association of BRCA1 promoter methylation with breast cancer in Asia. **Methods:** The study sample for the present meta-analysis was provided by published research articles on associations of BRCA1 promoter methylation with breast cancer in Asia accessed through databases on PubMed, ProQuest and EBSCO published between 1997 and November 2017. Pooled odds ratios (OR) were calculated with fixed and random-effect models. Data were processed using Review Manager 5.3 (RevMan 5.3). **Results:** Of a total of 475 articles, 11 studies were included in our systematic review with meta-analysis of relevant data. The results showed a highly significant association between BRCA1 promoter methylation with breast cancer in Asia (OR = 8.78 [95% CI 4.15-18.56, p < 0.00001]). **Conclusion:** This analysis confirmed association between BRCA1 promoter methylation and breast cancer in Asia. BRCA1 promoter assessment might be a predictive or diagnostic aid for breast cancer prediction.

Keywords: BRCA1- methylation- breast cancer-Asia

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Introduction

Breast cancer ranks first among 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 end in death (Jemal et al., 2011).

Breast cancer in biomolecular level is a disease caused by gene mutations triggered by multifactor: dietary factors, environmental factors, and heredity. There are several risk factors such as age (over 50 years), reproductive factors (nullipara, early menarche, late menopause), family history, history of benign tumors. There are also some risk factors that can not be fully understood, such as malnutrition, alcohol consumption, no exercise, radiation and hormonal therapy (Harahap et al., 2017; Nindrea et al., 2017). In addition, there is also one factor that is suspected to be the cause of breast cancer is the influence of loss of expression of tumor suppressor gene.

One of the tumor suppressor genes that play an important role in carcinogenesis of breast cancer is BRCA1 (Breast Cancer gene 1). The BRCA 1 protein has a role to maintain genome stability through cellular function, such as gene transcription, response to DNA damage, cell cycle regulation, and ubiquitination. Inactivation of the BRCA1 gene interferes with gene stability, particularly in breast and ovarian cancers (Bar-Sade et al., 1998). The inactivation of this BRCA1 gene may occur in hereditary, the mutation of the gene sequence and can also be sporadic. The composition of the BRCA1 gene is substantially fixed, but there is a methylation on CpG Island at the location of the BRCA1 promoter. Focal hypermethylation at the tip regions of 5'CpG island causes the gene to not be transcribed. Changes in DNA methylation profiles can lead to sporadic breast cancer without alteration of the base order in the BRCA1 gene (Iwamoto et al., 2010).

Several previous studies have shown that BRCA1 promoter methylation is associated with an increased risk of breast cancer (Dobrovic and Simfendorfer, 1997; Iwamoto et al., 2011). However, these results also have differences that suggest BRCA1 promoter methylation has no effect on the occurrence of breast cancer in women (Cho et al., 2010). However, the research results are not always consistent. Therefore, this study aims to determine the relationship of BRCA1 promoter methylation with breast cancer in Asia with some research through the Meta-analysis study so that the conclusion drawn have 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

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out the association of BRCA1 promoter methylation with breast cancer in Asia. The research sample is a published research article on the internet through the database on PubMed, ProQuest and EBSCO published between 1997 and November 2017. The inclusion criteria of this study sample research with case-control and cohort study, research is in the region of Asia. Exclusion criterion is research which not available in full-text form.

Operational definitions

Variables in this study include independent variable is BRCA1 promoter methylation. While the dependent variable is breast cancer.

Research procedure

This study is conducted by collecting data through the identification of published research articles on association of BRCA1 promoter methylation with breast cancer in Asia on the internet on PubMed, ProQuest and EBSCO databases Figure 1.

Data collection technique

Search is limited only to English language articles. This article type is limited to journal articles. Research subjects are limited only to research with subjects of a human. The time of publication is limited from 1997 to November 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 Asia region, research variables (the independent variable is BRCA1 promoter methylation and the dependent variable is breast cancer) 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).

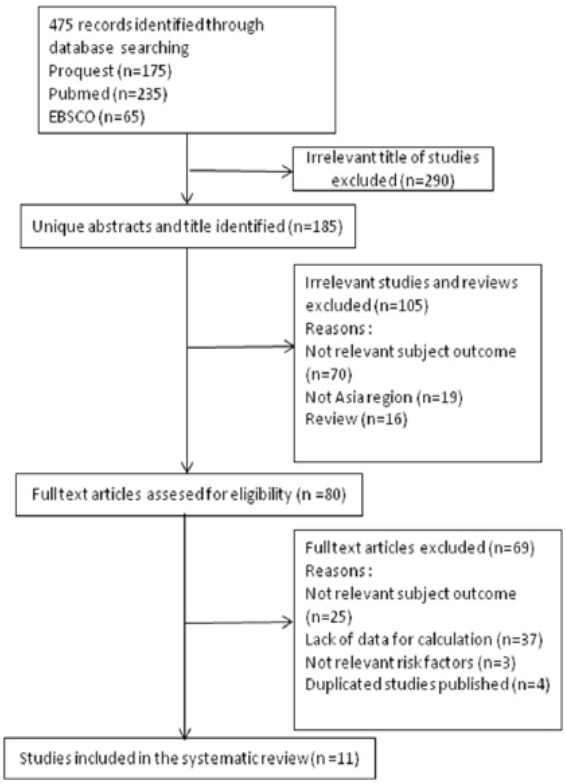

Figure 1. Flow Diagram Research Procedure

Results

Identification of 475 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 11 studies related to the association of BRCA1 promoter methylation with breast cancer in Asia Table 1.

Based on the results of systematic review there are 11 studies analyzed by meta-analysis Table 2. Meta-analysis of the association of BRCA1 promoter methylation with breast cancer in Asia Figure 2.

Figure 2 meta-analysis of BRCA1 promoter methylation with breast cancer in Asia (OR = 8.78 [95% CI 4.15-18.56, p <0.00001]). Funnel

Table 1. Systematic Review of Association of BRCA1 Promoter Methylation with Breast Cancer in Asia

First Author, Year	Region	Methods	Materials	Patients Characteristics	Number of Patients	
					Cases	Control
Chen et al., 2003	China	MSP	Tissue	Invasive ductal breast cancer	93	20
Bhavani et al., 2009	India	MSP	Tissue	Sporadic breast cancer	104	48
Jing et al., 2010	China	MSP	Blood	Sporadic breast cancer	50	50
Sharma et al., 2010	India	MSP	Tissue	Operable primary breast cancer	100	30
Al-moghrabi et al., 2011	Saudi Arabic	MSP	Blood	Sporadic breast cancer	7	73
Bal et al., 2012	India	MSP	Tissue	Sporadic breast cancer	74	21
Hsu et al., 2013	Taiwan	PCR	Tissue	Early-stage breast cancer	21	21
Hasan et al., 2013	India	MSP	Tissue	Sporadic breast cancer	29	26
Otani et al., 2014	Japan	PCR	Tissue	Primary breast cancer	15	15
Saelee et al., 2014	Thailand	MSP	Tissue	Invasive ductal breast cancer	38	7
Cai et al., 2016	China	Pyrosequencing	Tissue	Sporadic breast cancer	154	154

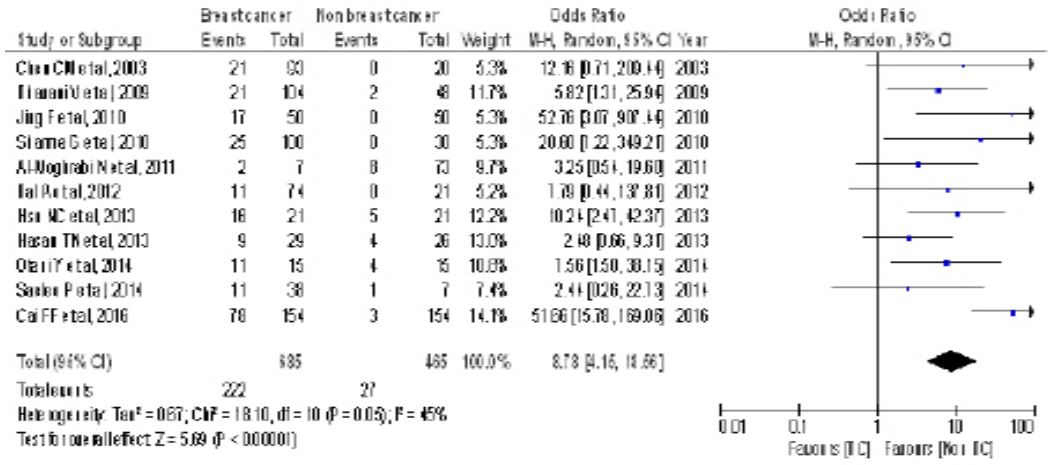

Figure 2. Forest Plots Association of BRCA1 Promoter Methylation with Breast Cancer in Asia

plot of association of BRCA1 promoter methylation with breast cancer in Asia Figure 3.

Figure 3 shows BRCA1 promoter methylation has a variation of homogeneous research for the occurrence of breast cancer, this is because the plot is symmetrical

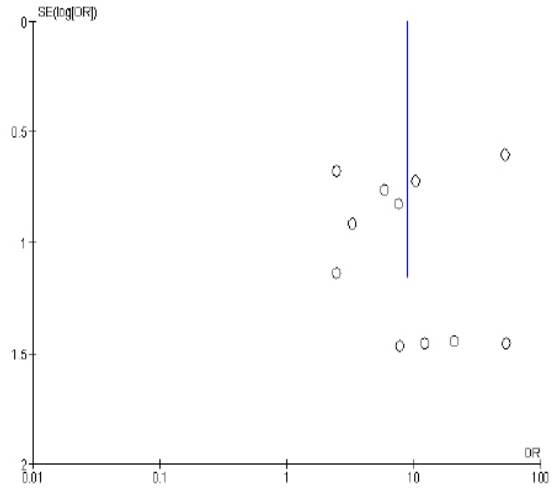

Figure 3. Funnel Plots Association of BRCA1 Promoter Methylation with Breast Cancer in Asia

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.

Discussion

The result of a meta-analysis of BRCA1 promoter methylation with breast cancer in Asia (OR = 8.78 [95% CI 4.15-18.56, p <0.00001]). BRCA1 promoter methylation has a variation of homogeneous research or no heterogeneity between studies for the occurrence of breast cancer.

Several studies have suggested the role of BRCA1 methylation in the aggressiveness of breast cancer, and BRCA1 tumor methylation is found primarily in tumors of grade III rather than grade I and II (Wei at al., 2005; Birgisdottir et al., 2006; BenGacem et al., 2012). In previous studies, loss of gene expression in breast cancer, often associated with BRCA1 promoter hypermethylation. For example, several studies have shown that BRCA1 promoter methylation is associated with a decrease in mRNA BRCA1 levels in clinical breast cancer specimens, and also with decreased levels of breast cancer cell protein and sporadic breast cancer (Baldwin et

Table 2. Meta-analysis Association of BRCA1 Promoter Methylation with Breast Cancer in Asia

First Author, Year	Weight (%)	Pooled Odds Ratio (95% CI)	p-value	Heterogeneity Test		
				χ^2	p value	I^2 (%)
Study data (BRCA1 promoter methylation)		8.78 (4.15-18.56)	<0.0001	18.10	0.05	45
Chen et al., 2003	5.3					
Bhavani et al., 2009	11.7					
Jing et al., 2010	5.3					
Sharma et al., 2010	5.3					
Al-moghrabi et al., 2011	9.7					
Bal et al., 2012	5.2					
Hsu et al., 2013	12.2					
Hasan et al., 2013	13.0					
Otani et al., 2014	10.8					
Saelee et al., 2014	7.4					
Cai et al., 2016	14.1					

al., 2000; Mirza et al., 2007; Bal et al., 2012).

Methylation is not the only mechanism to reduce BRCA1 protein expression (Sharma et al., 2010). Therefore, some mechanisms affect the inactivation of BRCA1 function in breast cancer (Rice et al., 2000). Several studies have shown that mutations, loss of heterozygosity, and deletion may also suppress BRCA1 expression in invasive sporadic breast tumors (Birgisdottir et al., 2006)

BRCA1 promoter methylation is common in sporadic breast cancer. BRCA1 promoter methylation measurements can actually be a new diagnostic tool (Jemal et al., 2011; Li et al., 2013; Pace and Keating, 2014). Previous research has shown that CpG island hypermethylation promoters to tumor suppressor genes may occur earlier in tumor development, which has implications for early detection of cancer, especially in people with breast cancer risk with a family history of previous breast cancer (Stefansson et al., 2011; Wong et al., 2011). Patients who had BRCA1 promoter methylation had significantly worse disease-free survival than patients with non-methylated BRCA1 promoters (Xu et al., 2011). Attempts to perform BRCA1 promoter methylation detection will enable adjustment of antitumor therapy and apply the appropriate treatment and care protocols to patients.

Methylation status in cancer tissue can be used as a tool to understand the gradual molecular changes in the phase of carcinogenesis. Breast cancer shows a drastic change in the status of DNA methylation which further leads to chromosomal instability and suppressor tumor silencing gene. From the epigenetic analysis of cancer tissue found an association between epigenetic and cancer histopathologic types (Kanal, 2008). Methylation of BRCA1 promoters can be used as a treatment guide, breast cancer cell cultures with BRCA1 promoter hypermethylation (UACC3199 and HCC-38 cell culture) are equally as good as cisplatin chemotherapy, such as culture cells with BRCA1 mutation (MDA-MB-436 cell culture) (Stefansson et al., 2011). In addition, Triple Negative Breast Cancer (TNBC) has a poor prognosis and response. TNBC by methylation of BRCA1 promoters has a good response to chemotherapy on the basis of Anthraxline in sporadic breast cancer (Ignatov et al., 2013). Likewise, the use of anti-methylation drugs, such as 5 Aza and hydralazine which can relinquish methyl groups binding to CpG Island can provide new hope in breast cancer patients, especially with advanced stages.

However, certain limitations of the study should be considered. First, the number of studies contained in the present meta-analysis is relatively small, particularly in Asia populations, and the results should be confirmed in large samples. Second, the associations among BRCA1 promoter methylation, the prognosis of patients and the negative status of the breast cancer-related therapeutic target receptors should be further investigated.

In conclusion, the results of this meta-analysis show that BRCA1 promoter methylation was associated with an increased risk of breast cancer. The results of this study recommend the need for large-scale studies that use uniform criteria on detection methods for methylation and sample materials before the BRCA1 promoter method can be a predictive or diagnostic biomarker useful for breast cancer patients and applied to future therapeutic strategies.

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