CHAPTER 1

INTRODUCTION

1.1 Background

Cancer is one of the main health problem in Indonesia and the second most common cause of mortality that contribute 13% of 22% mortality caused by noninfectious disease in the world.[1,2] In 2010, World Health Organization estimated that 12 million/year people worldwide suffering from cancer and 7.6 million of them are died. According to the International Union Against Cancer/UICC 2009, if cancer cannot be controlled, about 26 million people will suffering a cancer and approximately 17 million of those will die in 2030.[1] Ironically, it will worsen in developing country such as Indonesia with regard to the fact that almost 70% patients with cancer were diagnosed in the late stage.[2]

Theoretically, cancer occurs as a result of mutation in gene which plays a role in the cell proliferation.[3] In most cases, mutation is not inherited from the parents. However, there are about 5-10% family whose have the gene mutation which can be inherited from the parent to the next generation, called "Hereditary Cancer". Hereditary cancer characterized by mutation related to high penetrance of cancer development, transmission from mother or father, and related to other cancer. Hereditary cancer tends to have younger onset, and follows autosomal dominant inheritance pattern (i.e. it occur when individual only have one copy of the mutated gene).[4,5] One of the most common hereditary cancer is Hereditary

Breast and Ovarian Cancer (HBOC) Syndrome that has prevalence number in general population 1 in 400-500.[6,7,8]

Breast cancer is the most common cancer in Indonesian women (incidence 36.2 per 100,000) and include in top ten of mortality cause among the other diseases.[9,10] In general, the etiology of breast cancer is still poorly understood. Reproductive factors such as early menarche, older age at first pregnancy; hormonal factors such as oral contraceptive, and life style factors such as high fat intake, alcohol consumption, have been thought to be factors that increase risk of breast cancer.[11] However, approximatelly 5-10% of breast cancer cases related to HBOC syndrome.[5] Individuals with HBOC syndrome have significantly higher lifetime risk of breast cancer development than general population (life time risk to age 70 for breast cancer is 60-80%).[4] Specific pattern of HBOC syndrome is related to specific mutation in the *BRCA1* or *BRCA2* gene.[12,13]

BRCA1 and *BRCA2* are genes that encode protein which is play a role in tumor suppression. Both of them have autosomal dominant inherited pattern in which offspring from individual with these genes mutation have probability of 50% to get similar mutation.[14] Comparing with *BRCA2*, *BRCA1* has more prevalence related to HBOC; it is 1 in 300 per 100,000 population (while *BRCA2* gene only 1 in 800).[4] *BRCA1* gene is located in chromosome 17q21. Its main function is maintain chromosome stability by include in DNA damage repair process and in regulation process of cell cycle checkpoint as the response to DNA damage. Mutation in genomic region of *BRCA1* contributes to genetic instability.

Chromosomal instability caused by deficiency of *BRCA1* thought to be pathogenic basic in breast cancer development.[15]

According to several studies, *BRCA1*-related breast cancers tend to have high histological grade and lymph node positive.[16] Whereas, both of these points are significant prognostic indicator of breast cancer.[11] *BRCA1* related breast cancers also tends to have estrogen receptor (ER) negative, progesterone receptor (PgR) negative, HER2/neu negative (Triple-negative breast cancer/TNBC).[11,16] TNBC is an aggressive histological subtype with limited treatment options and very poor prognosis. Duration of response is usually short, with very common of rapid relapse and median survival of just 13 months.[17] Some finding also suggest that *BRCA1*-related breast cancers are less likely to be responsive to hormonal therapies such as tamoxifen.[18]

Based on these data, it can be concluded that individuals with *BRCA1*-related breast cancer have worse prognosis than breast cancer without *BRCA1* gene mutation, and carrier of *BRCA1* gene mutation has very high risk (70%-80%) to get breast cancer. Therefore, identification of individual who are predisposed to the hereditary breast cancer is very important. It will allows clinicians to assess early detection and intervention for *BRCA1*-related breast cancer patients, and determine the effective prevention for *BRCA1* gene mutation carrier (such as prophylactic mastectomy), in order to decrease mortality and morbidity rate related to hereditary breast cancer.

Identification of hereditary breast cancer by obtaining data from family history and pedigree construction are the most cost-effective method.[19] Several

models and scoring systems have been designed to assess the probability of the presence of a *BRCA1* mutation in an individual based on family history. However, among of these models, BOADICEA appeared to be the most accurate for assessing the risk of breast cancer.[20,21] Result data from BOADICEA provide risk estimation of *BRCA1* gene mutation for each individual which is included in pedigree construction. These data could direct clinicians to consider the highest risk-individual to undergo genetic testing for further assessment.[25]

In Indonesia, very few study that has been conducted to identify *BRCA1* gene mutation among breast cancer patients,[11] and none of them that use risk prediction tool to help determine which individual who should be offered for genetic testing.

This study is designed to identify patient who are predisposed to and to estimate the prevalence of *BRCA1*-related HBOC in Kariadi Hospital Semarang. Subjects are patient who diagnosed histopathologically with breast cancer. Family history of cancer and pedigree construction, onset of the first cancer diagnosed, result of histopathological finding and genetic testing (if available) according to criteria from National Comprehensive Cancer Network/ NCCN Guideline will be collected. The received data, then will be analyzed by using BOADICEA risk prediction model for HBOC syndrome. Genetic testing will be performed in individual with prediction result suspected to mutation of *BRCA1* gene (BOADICEA score $\geq$ 1.5) by using Polymerase Chain Reaction-High Resolution Melting Analysis (PCR-HRMA) method to prove the presence of gene mutation and determining location of gene mutation using sequencing technique.

PCR-HRMA is used as method in this study because it has many advantage. Unlike other scanning methods, mutation analysis by PCR-HRMA provides a closed-tube system that reduces the risk of contamination, decreases analytical time and requires no sample processing or separation after PCR.[22] PCR-HRMA also allows to analyze all exon that will enable clinicians to find novel gene mutation based on analysis of variant differentiation in curve as the result of PCR-HRMA.[23]

BRCA1-hereditary breast cancer identification was designed to identify, patient who are at risk of it, will get proper genetic counseling session and offer screening to the family member and intervention in early stage, in order to achieve better prognosis and to prevent mortality rate.

1.2 Research Question

What is the percentage of individual suspected to Hereditary Breast Ovarian Cancer (HBOC) Syndrome related to *BRCA1* gene mutation among breast cancer patients in Kariadi Hospital Semarang?

1.3 Aim of Study

1. General aim

   To determine the prevalence of HBOC syndrome related to *BRCA1* gene mutation among breast cancer patients in Kariadi Hospital Semarang.

2. Specific aim

   a. To determine the estimation risk of breast cancer patients and their family for HBOC syndrome based on BOADICEA risk prediction model analysis in Kariadi Hospital Semarang.

   b. To prove the presence of *BRCA1* mutation in suspected individual (breast cancer patient and family with positive result of BOADICEA) by using PCR-HRM analysis.

1.4 Benefit of Study

1. The result of this study can be used as consideration to perform genetic counseling session in patient and family who are predisposed to hereditary cancer in order to do prevention and early intervention.
2. The prevalence data can be used for future study.

1.5 Originality

This following table summarizes several studies which is similar with this current study.

No	Research title	Researcher	Time and Location	Methods
1	Prevalence of Family History of Breast, Colorectal, Prostate, and Lung Cancer in a Population-Based Study[24]	P.L.Mai, L.Wideroff, M.H.Greene, B.I.Graubard	2001 Connecticut, USA	Sample: 1019 with demografic information and family cancer history. Data collection: by interviewing family history of cancer and logistic regression was used to compare prevalence by demographic factors.
2	Population Prevalence of First-Degree Family	Ingrid J. Hall, Andrea	2005 USA	31,428 adults from general population were

	History of Breast and Ovarian Cancer in the United States: Implications for Genetic Testing[25]	Middlebrooks and Steven S. Coughlin		asked if any first-degree relatives had breast or ovarian cancer and if the relative with cancer was younger than age 50 when diagnosed, and SUDAAN 9 was used to estimate proportion of general population.
3	Identification of *BRCA1/2* Founder Mutations in Southern Chinese Breast Cancer Patients Using Gene Sequencing and High Resolution DNA Melting Analysis[26]	Ava Kwong, Enders Kai On Ng, Chris Lei Po Wong, Fian Bic Fai Law, Tommy Au, Hong Nei Wong, Allison W. Kurian, Dee W. West, James M. Ford, Edmond Siu Kwan Ma	2007-2011 In southern China.	Sample: 651 clinically high-risk breast and/or ovarian cancer patients Method: *BRCA1* and *BRCA2* mutation screening was performed using bi-directional sequencing and confirmed by HRM analysis.
4	*BRCA1* and *BRCA2* germline mutation analysis in the Indonesian population.[11]	Purnomosari D, Pals G, Wahyono A, Aryandono T, Manuaba T, Haryono S, Diest	2007 In Jakarta, Bandung, Yogyakarta Indonesia	Sample: 136 breast cancer patient Method: MLPA

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