Relationship Between XRCC1 Arg399gln Polymorphism and Risk of Luminal Subtype Breast Cancer in Bali, Indonesia

I Wayan Gede Sutadarma[1,4,*], I Gede Putu Supadmanaba[1,4], Putu Anda Tusta Adiputra[2], Anggi Amanda Triana Devy[3], Anak Agung Bagus Putra Indrakusuma[3], I Gede Aswin Parisya Sasmana[3]

ABSTRACT

Background: Breast cancer is the second leading cause of cancer-related death and the most common type of cancer in women. Recent studies have shown that the development of carcinogenesis is influenced by impaired XRCC1 expression. Therefore, research on the relationship between the XRCC1 Arg399Gln polymorphism and the luminal subtype of breast cancer is important so that it can be used as a reference for further research development.

Methods: This study lasted for 12 months at the Integrated Biomedical Laboratory and Biochemistry Laboratory, Faculty of Medicine, Udayana University. The samples consisted of 30 samples of stored biological material from previous studies with a case-control study design. The status of the XRCC1 Arg399Gln polymorphism was determined by performing PCR on blood samples. Furthermore, the samples were analyzed with SPSS version 25.0.

Results: The number of samples in this study was 15 cases and 15 controls with the majority aged > 50 years. The results of the analysis showed that differences in age groups, menstrual status, and cancer grade were significantly associated with breast cancer subtypes ($p < 0.05$). Based on the results of sequencing and bivariate analysis, the XRCC1 Arg399Gln polymorphism acted as a protective risk factor for the development of luminal subtype breast cancer (OR = 0.182; $p = 0.028$).

Conclusion: XRCC1 Arg399Gln polymorphism is associated with the risk of luminal subtype breast cancer in Bali.

KEYWORDS

breast cancer; polymorphism; luminal subtype; XRCC1 Arg399Gln

AUTHOR AFFILIATIONS

[1] Department of Biochemistry, Faculty of Medicine, Udayana University, Indonesia
[2] Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Udayana University – Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia
[3] Faculty of Medicine, Udayana University, Indonesia
[4] Department of Clinical Nutrition, Faculty of Medicine, Udayana University – Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia
* Corresponding author: Department of Biochemistry, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Jl. Diponegoro, No. 45, Denpasar, Bali, Indonesia; sutadarma@yahoo.com

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INTRODUCTION

Breast cancer is one of the most common types of cancer found in women and is responsible for the second leading cause of death in women from cancer. In general, breast tissue consists of two types, namely glandular tissue and supporting tissue (stromal) (1). Breast glandular tissue includes the mammary glands and milk ducts. When neoplasms form, breast cells will grow and settle in the breast tissue as tumors that develop into malignant tumors and undergo metastasis (2, 3). A total of 627 thousand deaths were recorded in 2018 with 1.5 million women diagnosed with breast cancer each year. The incidence of breast cancer in Indonesia reaches 42.1 per 100 thousand population with an average mortality rate of 17 per 100 thousand population. In addition, as many as 80% of breast cancer cases are generally found at an advanced stage so treatment efforts are difficult (4–6).

The etiology of breast cancer is usually multifactorial and can interact with several risk factors such as age, gender, histology, genealogy, reproduction, hormonal, and genetic factors, such as mutations in the BRCA1, BRCA2, and TP53 genes (7). Breast cancer can be classified based on gene expression profiles (subtypes) consisting of Luminal A, Luminal B, and HER2, and basal-like (triple negative) (8). The luminal subtype is a subtype of breast cancer with the highest prevalence and diverse prognosis. Although the aggressiveness of this subtype tends to be lower when compared to TNBC, the high prevalence, and resistance to chemotherapy make research on luminal subtype breast cancer require more attention to be studied. The high prevalence of luminal subtype breast cancer and the many risk factors associated with breast cancer have led to the continued development of breast cancer prognostic markers, one of which is the XRCC1 (X-ray repair cross-complementing 1) gene polymorphism (9).

The XRCC1 gene is a gene that encodes a protein involved in base excision repair (10–12). The protein encoded by XRCC1 functions as a protein that interacts with 8-oxo guanine DNA glycoside, DNA ligase III, DNA polymerase β, and poly (ADP-ribose) polymerase at the site of damaged DNA. One study discussed the role of XRCC1 and showed that the XRCC1 Arg399Gln polymorphism is associated with the development of breast cancer (13). Other studies have also shown a relationship between the XRCC1 Arg399Gln polymorphism and the distribution of breast cancer subtypes. In this study, it was found that the dominant subtype distribution was the luminal subtype. The XRCC1 gene itself is located on chromosome 19q13.2 (13).

Based on this description, in-depth research is needed regarding the relationship between the XRCC1 Arg399Gln polymorphism and the luminal subtype in breast cancer cases, plus the very limited research in Indonesia that examines the relationship between the XRCC1 Arg399Gln gene polymorphism and the risk of luminal subtype breast cancer, especially in Bali. Therefore, research is needed to determine the relationship between the XRCC1 Arg399Gln gene polymorphism and its relationship with luminal subtype breast cancer at Prof. Dr. IGNG Ngoerah General Hospital, Bali, Indonesia.

MATERIALS AND METHODS

STUDY DESIGN AND LOCATION

This study is an analytical study with a case-control study design to see the relationship between the XRCC1 Arg-399Gln polymorphism and the risk of luminal subtype breast cancer in Bali. The study was conducted at the Integrated Biomedical Laboratory and Biochemistry Laboratory, Faculty of Medicine, Udayana University. The study implementation period started from May 2023 to October 2023.

STUDY POPULATION

The accessible population is breast cancer patients who have had venous blood samples taken and stored as Stored Biological Material in the Department of Biochemistry, Faculty of Medicine, Udayana University, Bali, Indonesia. All participants have signed informed consent for the use of samples for research purposes following the Declaration of Helsinki. The sample size is calculated using the following sample size formula (14). The minimum sample size is 15 samples. Thus, the sample size for each group is 15 samples and the total sample size is 30 samples.

RESEARCH PROCEDURE

Subjects were collected using the purposive consecutive sampling method. The samples used in this study were stored biological materials obtained from cancer patients at the oncology polyclinic of Prof. Dr. Soetomo General Hospital IGNG Ngoerah. Basic characteristic data of the research sample were collected from medical record data. Since the accessible population was divided into two groups, the sample selection in this study was also divided into case and control groups. Sample selection with matching criteria according to the research design. Serum from blood samples will be subjected to a polymerase chain reaction to determine the XRCC1 Arg399Gln polymorphism. PCR results are continued with electrophoresis to provide an overview and interpretation of the polymorphism that occurs.

DATA ANALYSIS

The data obtained were then collected. After that, the data was analyzed with SPSS ver 25.

RESULTS

CHARACTERISTICS OF RESEARCH SUBJECTS

Based on the results of this study, it was found that the majority of the age of the research sample was >50 years (14 people; 93.3% for luminal, and 8 people; 53.3% for non-luminal). In the results of the bivariate analysis, the difference in age groups was significantly associated with breast cancer subtypes (p-value = 0.035). When viewed from the menstrual status, most of the research samples were post-menstrual patients as many as 12 people (80%) in the luminal subtype, but in non-luminal it was dominated by

Tab. 1 Characteristics of Research Subjects.

Variable	Luminal (n = 15)	Non-Luminal (n = 15)	OR	CI 95%	p-value
Age					
>50 years old	14 (93.3%)	8 (53.3%)	12.250	1.268–118.362	0.035*
≤50 years old	1 (6.7%)	7 (46.7%)			
Menstrual status					
Post-menopause	12 (80%)	6 (40%)	6.000	1.172–30.725	0.025*
Pre-menopause	3 (20%)	9 (60%)			
Stage					
Early Stage	5 (33.3%)	3 (20%)	2.000	0.381–10.511	0.682
Late Stage	10 (66.7%)	12 (80%)			
Grade					
I–II	14 (93.3%)	8 (53.3%)	12.250	1.268–118.362	0.035*
III	1 (6.7%)	7 (46.7%)			
T Stage					
T1–T2	5 (33.3%)	3 (20%)	2.000	0.381–10.511	0.682
T3–T4	10 (66.7%)	12 (80%)			
N Stage					
N0–N1	5 (33.3%)	3 (20%)	2.000	0.381–10.511	0.682
N2–N3	10 (66.7%)	12 (80%)			
M Stage					
M0	12 (80%)	11 (73.3%)	1.455	0.264–8.009	0.666
M1	3 (20%)	4 (26.7%)			

* The analysis was performed using the Chi-Square Test. The results were considered significant if p ≤ 0.05.

pre-menopausal women as many as 9 people (60%). In the bivariate analysis, a significant relationship was found between subtype and menstrual status (p-value = 0.025). Based on the stage, most patients were diagnosed at the final stage as many as 10 people (66.7%) in the luminal subtype, and 12 people (80%) in the non-luminal subtype. This proportion is then similar to the variables of tumor size and lymph node metastasis, although no statistically significant relationship was found in bivariate analysis. When evaluated on cancer grade, most of the study samples were found to have grade I–II, wherein the luminal group there were 14 people (93.3%), and in the non-luminal group, there were 8 people (53.3%), whereas in bivariate analysis this result was statistically significant with p-value = 0.035 (Tab. 1).

XRCC1 ARG399GLN POLYMORPHISM IN BREAST CANCER PATIENTS

Based on the results of this study which aims to evaluate the relationship between XRCC1 ARG399GLN gene polymorphism in breast cancer patients, it was found that there was a dominant proportion related to polymorphisms that occurred in the non-luminal subtype of 11 people (73.3%). On the other hand, only a small portion of the study samples had polymorphisms in the luminal subtype, namely 5 people (33.3%) of the total number of samples in the luminal subtype group (Tab. 2).

Tab. 2 Proportion of XRCC1 ARG399GLN Gene Polymorphism Occurrence in Breast Cancer Patients.

Variable	Luminal (n = 15)	Non-Luminal (n = 15)
Polymorphism status		
Polymorphism	5 (33,3%)	11 (73.3%)
Non-Polymorphism	10 (66.7%)	4 (26.7%)

RELATIONSHIP OF XRCC1 ARG399GLN POLYMORPHISM WITH LUMINAL SUBTYPE BREAST CANCER RISK

When reviewed regarding the relationship of XRCC1 ARG399GLN gene polymorphism with the risk of luminal subtype breast cancer, this study found that XRCC1 ARG399GLN gene polymorphism acts as a protective risk factor for the development of luminal subtype breast cancer with an OR value of 0.182; 95% CI 0.038–0.873 (Tab. 3).

Tab. 3 Relationship of XRCC1 ARG399GLN Polymorphism with Luminal Subtype Breast Cancer Risk.

Variable	Polymorphism status		OR	CI 95%	p-value
	Polymorphism	Non-Polymorphism			
Luminal	5 (33.3%)	10 (66.7%)	0.182	0.038–0.873	0.028*
Non-Luminal	11 (73.3%)	4 (26.7%)			

DISCUSSION

Base excision repair (BER) is a process of repairing localized DNA damage due to oxidative stress and ionizing radiation. The XRCC1 gene (X-ray repair cross-complementing group 1) is one of the genes involved in the DNA base excision repair process and maintaining genetic stability. XRCC1 has three different domains that interact with poly (ADP-ribose) polymerase, DNA polymerase b, and DNA ligase III. Recent studies have shown that XRCC1 polymorphisms affect the risk of breast cancer. Commonly studied polymorphisms are Arg194Trp, Arg399Gln, and Arg280His. Women will have a high risk of breast cancer when there are XRCC1 gene polymorphisms, including Arg399Gln which have been reported by various previous studies with some similarities in demographic characteristics in this study (15, 16).

Women aged >50 years and postmenopausal tend to have luminal breast cancer in this study. In addition, the luminal subtype was found more in grades I–II. These results follow the study by Mills et al (2020) that women with ER+/HER2– breast cancer aged ≥75 years have a more aggressive incidence of luminal type B cancer. It was also found that the luminal A and B subtypes were found most in grade II, with tumor size >2 cm for luminal B, and no lymph node metastasis in luminal A, but there was in luminal B (17). However, Zhang et al (2019) found that postmenopausal women experienced HER2 and basal-like subtypes more often than luminal subtypes. Other studies have suggested that delayed menopause is associated with an increased risk of basal and luminal tumors (18).

A study by Akhzari et al (2018) showed that XRCC1 gene polymorphism in 150 breast cancer patients had 76.67% heterozygosity and 27.87% homozygosity. Meanwhile, the probability of the patient group with heterozygous genotype (Arg/Gln) was higher compared to homozygosity (19). Luminal breast cancer is clinically low-stage, slow-growing, and has a good prognosis with a lower incidence of recurrence and a higher survival rate. This carcinoma has a high response rate to hormone therapy (tamoxifen or aromatase inhibitors), and the benefits of chemotherapy are more limited. Luminal B breast cancer has a higher grade and worse prognosis compared to luminal A. This tumor is ER positive and PR negative and has high Ki67 expression (more than 20%) (20).

XRCC1 polymorphisms were significantly associated with breast cancer subtypes ($p<0.05$). XRCC1 polymorphisms showed high frequencies in luminal A, HER2-positive, and TNBC breast cancers (21). Meta-analysis showed a significant association between XRCC1 Arg399Gln polymorphism and breast cancer risk (OR for dominant model = 1.12, 95%CI: 1.02–1.24, $P_{herogeneity}$ = 0.003; OR for additive model = 1.07, 95%CI: 1.01–1.14, $P_{heterogeneity}$ = 0.017) (22). Non-luminal breast cancer subtypes such as TNBC are highly aggressive phenotypes associated with poor prognosis. This condition is characterized by a lack of expression of estrogen receptors (ER), progesterone receptors (PR), and epidermal growth factor receptor-2 (HER2) (23, 24). The absence of these markers leads to rapid metastasis, treatment resistance, and high recurrence rates. Breast cancer cells with higher-than-normal HER2 levels are called HER2-positive. These cancers tend to grow and spread faster than HER2-negative breast cancers but are more likely to respond to treatment with drugs that target the HER2 protein (25).

CONCLUSION

Based on the results of the study on the analysis of the relationship between the XRCC1 Arg399Gln polymorphism and the risk of luminal subtype breast cancer in the oncology polyclinic of Prof. Dr. IGNG Ngoerah Hospital, Denpasar, Bali, it was found that individuals who have the XRCC1 Arg399Gln polymorphism have a lower risk of developing luminal subtype breast cancer compared to non-luminal subtypes. Therefore, it can be concluded that the XRCC1 Arg399Gln polymorphism has a protective effect on the development of luminal subtype breast cancer.

CONFLICT OF INTEREST

None.

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