BRCA1 GENE MUTATION SCREENING IN BREAST CANCER PATIENTS USING BOADICEA RISK PREDICTION MODEL AND HIGH RESOLUTION MELTING METHOD

SKRINING MUTASI GEN *BRCA1* PADA PASIEN KANKER PAYUDARA DENGAN MENGGUNAKAN MODEL PREDIKSI RISIKO BOADICEA DAN METODE *HIGH RESOLUTION MELTING*

THESIS

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Thesis

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DECLARATION

I hereby declare that this thesis is my own work and has not been submitted in any form for another degree or diploma at any university or other institution of tertiary education, there are no elements belonging Plagiarism forth in Decree No. 17 of 2010. Information derived from the published or unpublished work of others has been acknowledged in the text and a list of reference is given.

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ABBREVIATIONS

BARD1	: *BRCA1* associated RING domain 1
BOADICEA	: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BRCA1	: Breast cancer 1 gene
BRCA2	: Breast cancer 2 gene
DCIS	: Ductal Carcinoma in situ
DNA	: Deoxiribo Nucleic Acid
ER	: Estrogen Receptor
FDR	: Family Degree Relatives
FRR	: familial relative risk
GLOBOCAN	: Global Burden of Cancer Study
HBOC	: Hereditary Ovarian Breast Cancer Syndrome
HER2	: Human Epidermal Growth Factor
IBIS	: International Breast Cancer Intervention Study
IDC	: Invasive Ductal Carcinoma
ILC	: Invasive Lobular Carcinoma
NCCN	: National Comprehensive Cancer Network
PCR-HRMA	: Polymerase Chain Reaction-High Resolution Melting Analysis
PR	: Progestron Receptor
Rpm	: Rotate per minute
TNBC	: Triple negative breast cancer

BRCA1 GENE MUTATION SCREENING IN BREAST CANCER PATIENTS USING BOADICEA RISK PREDICTION MODEL AND HIGH RESOLUTION MELTING METHOD

ABSTRACT

Background: Hereditary Breast and Ovarian Cancer (HBOC) Syndrome is the most common hereditary cancer. Specific pattern of HBOC syndrome is related to specific mutation in the *BRCA1* gene. The aim of is this study was to identify patient who are predisposed to and to estimate the prevalence of *BRCA1*-related HBOC in Kariadi Hospital Semarang by using BOADICEA risk prediction model and Polymerase Chain Reaction-High Resolution Melting Analysis (PCR-HRMA) method.

Methods: One hundred unrelated patients from Oncology surgery and Chemotherapy Department of Dr. Kariadi Hospital were interviewed for clinical history, pedigree and familial history of HBOC syndrome related cancer. Data received, then were calculated using BOADICEA risk prediction tools. Patient with high score of BOADICEA were offered to perform genetic testing. In total, there were 11 patients with high score of BOADICEA, 2 patients with low score of BOADICEA, 2 patient's family members and 15 controls were performed genetic testing. Mutation screening using PCR-HRM was performed in exon 2-24 of *BRCA1* gene. Aberrant graphs were sequenced.

Results: There were 10 variants that had been found; 6 missense mutations (5 of them were polymorphism) and 3 synonymous mutations and one intronic mutation (novel). However, no pathogenic mutation was found in this study. One unclassified variant c.1480C>A/p.Gln494Lys was novel in this study.

Conclusion: The mutation found in breast cancer patients in our study classified to be polymorphism and unclassified variant. No known pathogenic mutation found. Further study with larger sample size is required to evaluate pathogenic mutation in breast cancer related HBOC syndrome in Indonesian population.

Keyword: HBOC syndrome, *BRCA1* gene, breast cancer, BOADICEA, PCR-HRM

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ABSTRAK

Latar Belakang: *Hereditary Breast and Ovarian Cancer* (HBOC) *Syndrome* merupakan bentuk kanker herediter terbanyak. *HBOC syndrome* memiliki keterkaitan spesifik dengan mutasi gen *BRCA1*. Tujuan dari penelitian ini adalah untuk mengidentifikasi pasien yang memiliki predisposisi dan untuk memperkirakan prevalensi *HBOC syndrome* terkait mutasi gen *BRCA1* di Rumah Sakit Dr. Kariadi Semarang dengan menggunakan BOADICEA *risk prediction model* dan metode *Polymerase Chain Reaction-High Resolution Melting Analysis* (PCR-HRMA).

Metode Penelitian: Sejumlah seratus pasien dari Bagian Bedah Onkologi dan Kemoterapi Rumah Sakit Dr. Kariadi Semarang dilakukan anamnesis mengenai riwayat perjalanan penyakit, pembuatan pedigree tiga generasi dan riwayat keluarga untuk kanker terkait *HBOC syndrome*. Data yang diperoleh selanjutya dihitung dengan menggunakan BOADICEA *risk prediction tool*. Pasien dengan skor BOADICEA tinggi selanjutnya dirujuk untuk menjalani pemeriksaan genetika. Dalam penelitian ini terdapat 11 pasien dengan skor BOADICEA tinggi, 2 pasien dengan skor BOADICEA rendah, 2 anggota keluarga pasien dengan skor BOADICEA tinggi dan 15 kontrol normal yang dilakukan pemeriksaan genetika. Skrining mutasi dilakukan dengan PCR-HRM pada exon 2-24 gen *BRCA1*. *Abberant graph* yang diperoleh selanjutnya dilakukan pemeriksaan sekuensing.

Hasil: Terdapat 10 varian yang ditemukan dalam penelitian ini, yaitu 6 *missense mutations* (5 di antaranya telah ditemukan sebagai polimorfisme), 3 *synonymous mutations* dan 1 *intronic mutation*. Akan tetapi tidak ditemukan adanya mutasi patogenik. Satu *unclassified variant* c.1480C>A/p.Gln494Lys baru ditemukan dalam penelitian ini.

Simpulan: Mutasi yang ditemukan pada pasien kanker payudara dalam penelitian ini cenderung merupakan polimorfisme dan *unclassified variant*. Tidak terdapat mutasi patogenik yang ditemukan. Penelitian lebih lanjut dengan jumlah sampel yang lebih besar diperlukan untuk mengevaluasi jenis mutasi pada kanker payudara terkait HBOC syndrome pada populasi Indonesia.

Kata kunci: *HBOC syndrome*, gen *BRCA1*, kanker payudara, BOADICEA, PCR-HRM