Penetrance of BRCA1/BRCA2 specific gene mutations in Iranian women with breast cancer

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ABSTRACT

Objectives: To estimate the penetrance of breast cancer genes 1 and 2 (BRCA1/BRCA2) specific gene mutations in Iranian women with breast cancer.

Methods: We conducted this study in the Department of Biostatistics, Tarbiat Modares University, Tehran, Iran between January and May 2008. The information was collected from the referral database of the Cancer Clinics, Day General Hospital, Tehran, Iran. We estimated the penetrance of breast cancer in carriers of BRCA1/2 specific gene mutations based on the modified kin-cohort method.

Results: Three hundred and forty-five probands were examined for specific mutations of BRCA1/2 genes.

The estimated penetrance for the age groups among BRCA1/2 carriers was 31.9% (<50 years) and 46.2% (≥50 years).

Conclusion: The reliable information of penetrance is considered important in genetic counseling. The low value of the estimated penetrance in this study might be attributed to the rare mutation in Iranian patients. Establishment and use of a kin-cohort gene databank is proposed as a solution for the preparation of the screening programs and the estimation of the penetrance to help reduce the risk of cancer.


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Cancer is regarded as a common, fatal disease in clinical medicine. Statistics show that cancer strikes more than one third of the general population, accounts for more than 20% of all deaths, and now is the second cause of mortality and morbidity after heart diseases and is expected to be the major cause of mortality and morbidity in the next decades. Despite the variation in the prevalence of cancer and number of patients in different countries, the World Health Organization (WHO) still considers cancer as a serious global problem. Cancer is one of the biggest threats to healthcare; according to the WHO's statistics, it accounts for 9% of all deaths worldwide. Approximately 5 million people die of cancer per year. Being diagnosed with cancer is an
The aim of this study is to estimate the penetrance of BRCA1/2 specific gene mutations in Iranian women with breast cancer.

**Methods.** Unrelated Iranian high risk breast cancer families were included in this study. The information database of the referral from Cancer-clinics, Day General Hospital was used; the BRCA1/2 mutation screening was performed by direct sequencing. The Local Research Ethics Committee approved the study. This study was conducted between January and May 2008, at the Department of Biostatistics, Tarbiat Modares University, Tehran, Iran. The whole and specific screening of BRCA1 and BRCA2 genes [pathogenic mutations in the BRCA2 (novel deletion c.4415_4418delAGAA) and one intronic variation in BRCA1 (intronic variation g.5075-53C>T)] was previously performed. The personal information for this research was collected with their informed consent.

The estimated penetrance was constructed from the cumulative risks by using the modified kin–cohort method described by Chatterjee et al. We used a modified rule by applying piecewise weibull model. The age of probands and their relatives were also summarized (mean±SD) separately for carriers and non-carriers groups.

**Results.** Three hundred and forty-five probands were examined for specific mutations of BRCA1/BRCA2 genes and 2.7% were carriers. The mean age value (±SD) of probands in carrier groups was 41.2 ± 13.9 years and non-carrier group was 49.2 ± 11 years and for their relatives were 52.9 ± 16.9 and 30.9 ± 19.1. Results showed that the proportions of age specific hazard value in carriers to non-carriers was 22.75 in <50 years and 78.2 in ≥50 years. The specific hazard values for breast cancer for non-carrier group were 0.4 (<50 years) and 1.7 (≥50 years) while in the carrier group the values were 9.1 (<50 years) and 13.3 (≥50 years). The estimated penetrance values for the BRCA1/2 non-carrier group were 0% (<50 years) and 1% (>50 years), and for carrier group were 31.9% (<50 years) and 46.2% (≥50 years).

**Discussion.** Detection of individuals susceptible to cancer and estimation of incidence probabilities for different age groups are of utmost importance. To date, some studies have found an increased risk of developing breast cancer in individuals who show homozygous genotypes for special variants. Warner et al estimated the breast cancer penetrance of 59.9% for the BRCA1 carriers and 28.3% for the BRCA2 carriers in 412 Jewish patients aged 70 years. They showed that...
approximately 12% of breast cancers in the Ashkenazi Jewish population are attributable to mutations in the BRCA1 or BRCA2 gene. Marroni et al.31 estimated the breast cancer penetrance was 27% at age 50 years, and 39% at age 70 in BRCA1 carriers, and 26% at age 50 and 44% at age 70 in BRCA2 carriers. Laloo et al.32 estimated the breast cancer penetrance was 58% at age 50 years in BRCA1-carriers and 84% in BRCA2-carriers. The range of estimated penetrance for BRCA1, BRCA2 carriers varied between 33% and 48%.33-35 Few studies concerning BRCA1 and BRCA2 penetrance in the Iranian population have been published: Yassaei et al.36 investigated 83 early-onset breast cancer patients from Tehran. Based on this study, the prevalence of BRCA1/2 mutations among early-onset breast cancer patients (<45 years) with or without a family history for the disease is thought to be approximately 6%. Ghaderi et al.37 performed BRCA1 mutation screening in a study comprising 80 patients with breast cancer with a median age of 42 years at onset of the disease from Shiraz, Iran. Only 2 of the patients had a family history of breast and/or ovarian cancer. In a study performed by Pietschman et al.,25 both BRCA1 and BRCA2 genes were screened in 10 high risk breast cancer families of non-Jewish origin. They found new specific gene mutations in Iranian women with breast cancer. Our results revealed lower penetrance (31.9% for ages ≤50). This might be due to the presence of a particular mutation spectrum found previously.26 Liede and Narod38 stated that penetrance or prevalence of BRCA1/2 mutations may be lower in Iran.

However, larger numbers of breast cancer patients, preferentially the young patients and family accumulation as a high risk population for the specific mutation(s) screening test, or for the penetrance analysis, is required in order to measure the impact of these genes on risk of hereditary breast cancer in unselected series, and to determine more precise conclusions in this regard. The patient's follow-up due to some social and family concerns was the major limitation of this study.

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References


