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

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ABSTRACT

الأهداف: تقدير اختراق تحولات الجين المحدد لسرطان الثدي BRCA1/BRAC2 للنساء الإيرانيات المصابات بسرطان الثدي.

الطريقة: أجريت هذه الدراسة خلال الفترة ما بين يناير 2008م وحتى مايو 2008م، في قسم الإحصاء ألإحيائي – جامعة تاربيات موداريس – طهران – إيران. تم استخدام قاعدة بيانات المعلومات للتحويل بما فيها عيادات السرطان، ومستشفى اليوم العام بطهران – إيران لهذا الغرض. قمنا بتقدير نفاذ سرطان الثدي لدى حاملات متحولات الجين المحدد BRCA1/2 بناء على طريقة كين–كوهورت.

النتائج: تم فحص عدد 345 للشواهد الأصلية أو الأولية للتحولات المحددة للجينات BRCA1/2. بلغ الاختراق المقدر لمجموعات العمر أقل وأكثر من 50 عاماً بين حاملات BRCA1/2 لسرطان الثدي 31.9% و 46.2% على التوالي.

خاتمة: تعتبر المعلومات المعتمدة للاختراق مهمة في الاستشارة الجينية. قد تكون القيمة المنخفضة للنفاذ المحدد في هذه الدراسة منسوبة إلى التحول النادر لدى المريضات الإيرانيات. تم اقتراح إنشاء واستعمال بنك بيانات كين– كوهورت للجينات كحل لإعداد برامج المسح (الفحص) وتقدير الاختراق وذلك للمساعدة في تقليل خطر السرطان.

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.[1] 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 the worldwide. Approximately 5 million people die of cancer per year.[2,3] Being diagnosed with cancer is an

extremely unpleasant ordeal for anyone. Cancer wreaks havoc on the patient's lifestyle.[4] Cancer is a prevalent disease in Iran and is the third cause of mortality and morbidity after cardiovascular and pulmonary diseases.[5] The number of afflicted with cancer in Iran increased from 5,979 in 1991 to 18,665 in 1994.[6] In Iran, the statistics revealed that the prevalence of cancer was 20/100,000 in men and 16.6/100,000 in women in 1998.[7] Cancer is fundamentally a genetic disease and is partially due to gene mutation. Many types of cancer have a higher incidence in the relatives of the patients than in the general population, and some of them exhibit the Mendelian inheritance.[1] For many diseases such as cancer; age is one of the primary risk factors. The risk of developing cancer increases with age; nonetheless, not everyone experiences the disease in his or her lifetime.[8] The risk of cancer increases up to 3-fold if one first-degree relative and up to 10-fold if more than one first-degree relative is affected. These familial risks tend to increase even further if the onset of the disease in the affected first-degree relative is at age ≤40.[1] Breast cancer is the most prevalent cancer in women in most countries;[9,10] and according to the WHO's data, the incidence rate of breast cancer increases by approximately 2% annually worldwide.[9] A woman has a 10% chance of developing breast cancer in her life.[11] The 2 breast cancer genes 1 and 2 (BRCA1 and BRCA2) are the most important predisposing genes in the causation of breast or ovarian cancer.[11,12] Mutations in the 2 genes BRCA1 and BRCA2 may be responsible for 5-10% of early-onset breast cancers,[13-15] and approximately 10% of all ovarian cancers.[16] Individuals who carry the mutation in BRCA1 are at increased risk of developing breast or ovarian cancer.[12] Easton et al[17] estimated the risk of breast or ovarian cancer in BRCA1 and BRCA2-mutation carriers at age 70 to be 94%. Hartge et al[18] found that 10% of 109 Jewish women who had been given a diagnosis of breast cancer in their forties carried one of the BRCA1 or BRCA2 mutations. With regard to the correlation between the genotype and phenotype of specific genes in individuals (penetrance), the breast cancer penetrance at age 70 for BRCA1 was estimated between 82% and 90%[19,20] and BRCA2 carriers at 84%.[19,21] Wacholder et al[22] estimated the cumulative probability of developing breast cancer, as a function of age, for carriers of mutations of BRCA1/BRCA2 in Ashkenazi Jews from the region surrounding Washington, DC. In this study, the penetrance for mutations in BRCA1/BRCA2 genes for the first occurrence of breast or ovarian cancer in 50-year old women was estimated at 37% and 70-year-old at 63%. Estimates of cancer risks among mutation carriers provide valuable opportunities to tailor cancer screening and prevention strategies and to refine clinical and behavioral interventions to reduce cancer risk.[23,24] 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.[25,26] 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.[25] 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.[27] 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.[1] To date, some studies have found an increased risk of developing breast cancer in individuals who show homozygous genotypes for special variants.[28,29] Warner et al[30] 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. Lallo 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: Yassaee 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 Narod[38] 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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