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RESEARCH

HLA-DRB1,-DQA1 and -DQB1 Allele and Haplotype Frequencies in Female Patients with Early Onset Breast Cancer

Majid Mahmoodi · Hedayat Nahvi · Mahdi Mahmoudi · Amir Kasaian · Mohammad-Ali Mohagheghi · Kouros Divsalar · Bijan Nahavandian · Abbas Jafari · Bita Ansarpour · Batoul Moradi · Asghar Aghamohammadi · Aliakbar Amirzargar

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Abstract Based on the reports, few HLA class II alleles are associated with susceptibility or protection in breast cancer. Here we investigate the association between HLA class II alleles and breast cancer in Iranian women. 100 patients with pathologically proven breast cancer who referred to Cancer Institute were randomly selected and compared with a group of 80 healthy blood donor subjects. The patients were studied in two groups, group 1 includes patients aging 40 years or younger and group 2 include patients aging over 40 years. HLA class II alleles were determined by amplification of DNA followed by HLA-typing using sequence-specific primer (SSP) for each allele. In group 1, the most frequent alleles were HLA-DQA1*0301 (P= 0.002, OR=3.3) and HLA-DQB1*0302 (P=0.04, OR= 2.8). In group 2, the following alleles increased significantly than those in controls including HLA-DQA1*0301 (P= 0.001, OR=3.4) and HLA-DRB1*0301 (P=0.04, OR= 2.3). In complete group of patients, the frequency of HLA-DQA1*0301 (P=0.001, OR=3.4) and HLA-DRB1*1303 (P=0.02, OR=2.3) increased significantly than those in control group. HLA-DQA1*0505, HLA-DQA1*0101, HLA-DRB1*1301and HLA-DRB1*0101 alleles showed negative association with breast cancer. Our findings suggest that HLA-DQA1*0301 allele is mainly associated with increased risk of breast cancer including early-onset of the disease. HLA-DQA1*0505 and HLA-DRB1*1301 are involved in protection. We conclude that specific alleles of HLA class II influence breast cancer risk.

Keywords Allele frequency · Breast cancer · Human leukocyte antigen (HLA) · HLA-DRB1 · -DQA1 · -DQB1

M. Mahmoodi · H. Nahvi · A. Kasaian · M.-A. Mohagheghi · B. Nahavandian · A. Jafari
Cancer Research Center, Tehran University of Medical Sciences, Tehran, Iran

M. Mahmoudi · B. Ansarpour · B. Moradi · A. Amirzargar
Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran

K. Divsalar
Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran

A. Aghamohammadi
Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

A. Amirzargar (✉)
Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
e-mail: amirzara@tums.ac.ir

Introduction

Breast cancer is the leading cause of cancer in women throughout the world and is the most prevalent cancer (4.4 million survivors up to 5 years following diagnosis); therefore, it is a major public health concern [1]. The incidence of breast cancer is increasing throughout the world for reasons not fully understood. Although higher age-specific incidence rates occur in developed countries, but nearly half of the cases of female breast cancer occur in developing countries [2]. In the development of breast cancer, age, hormonal disturbances, genetic and environment factors and even infectious agents could play a role

[3]. In inherited and familial breast cancer, mutation, deletions and other genetic alterations in the BRCA1 and BRCA2 genes have been proposed to be important genetic risk factors in the etiology of breast cancer [4]. The major histocompatibility complex (MHC) or more specifically the human leukocyte antigens (HLA) system is also considered to be important in tumor surveillance, since the function of the products of highly polymorphic MHC loci is to present peptide fragments including tumor antigens to the cells of immune system. Therefore this system modulates the efficacy of immune responses through the presentation of tumor antigens [5–7]. There are two types of HLA gene products, called HLA-class l molecules and HLA-class ll molecules which are structurally and functionally different [8]. HLA-class l molecules present peptide fragments (viral and self peptides) to the circulating cytotoxic $CD8^+$ T cells and HLA-class ll molecules present exogenously derived peptides such as bacteria and chemical toxins to circulating $CD4^+$ T cells. Previous studies have indicated that certain HLA-class ll alleles or haplotypes may be associated with the risk of certain cancers, such as cervical cancer [9, 10], gastric cancer [11, 12], ovarian cancer [13], malignant melanoma [14] and breast cancer [15–18]. The current study investigate positive or negative association of HLA-class II, HLA-DRB1,-DQA1,-DQB1, alleles and haplotype frequencies with breast cancer in two groups of female patients, including women with early-onset of the disease and patients diagnosed who are over 40 years old. The results of allele and haplotype frequency were compared with 80 healthy female subjects who were randomly selected from aged matched volunteer individuals.

Patients and Methods

Patients and Control Group

Between March 2007 and June 2009, a total of 100 female patients with breast cancer were randomly selected from pathologically proven cases referred to Cancer Institute, Tehran University of Medical Sciences, Tehran-Iran. The patients were studied in two groups, group 1 includes 49, 40 years old or younger, patients and group 2 includes 51 patients aging over 40 years. Diagnosis of breast cancer was based on pathological examination of the tissue or biopsies of the tumor. Patients who suffered diseases associated with specific MHC alleles such as diabetes mellitus or thyroid disorders or autoimmune diseases were not included in this study. The control group includes 80 healthy female subjects who were also randomly selected from aged matched volunteer individuals. In controls, individuals who had history of any type of cancer or autoimmune diseases or family history of such disorders in first-degree relatives or being affected by any other systemic diseases were excluded from this study. This project was approved by the Ethical Committee of Tehran University of Medical Sciences, and written informed consent was obtained from the subjects for blood sampling.

DNA Extraction and HLA Typing

Genomic DNA was extracted from peripheral blood leukocytes by modified salting out method [19]. HLA-DRB, -DQA1, and -DQB1 typing was performed by polymerase chain reaction based on sequence-specific primers (PCR-SSP) [20], following Olerup O, Zetterquist method [21]. HLA-DRB, -DQA1, and -DQB1 PCR-SSP kits were supplied by Biotest (Germany). Taq DNA polymerase was from Roche (Basel, Switzerland). The PCR reactions were carried out in 10 µl volumes. Samples were amplified in Techne genius thermal cyclers, after initial denaturation at 94°C for 2 min, followed by 10 cycles of 94°C denaturation for 10 s, 65°C annealing and extension for 60 s, and finally, 20 cycles of 94°C denaturation for 10 s, 61°C annealing for 50 s, and 72°C extension for 30 s. After amplification, PCR products were run on an agarose gel, and then gel was interpreted for specific bands using a UV trans-illuminator. The haplotypes were calculated according to Iranian populations specific linkage disequilibrium pattern among HLA-DRB1, -DQA1, and –DQB1 alleles [22].

Statistical Analysis

Differences in the frequencies of HLA-DRB,-DQA1 and -DQB1 alleles and haplotype frequencies among studied groups were analyzed using the chi-square test after Yates' correction. Fisher's exact 2-tailed correction test was used when necessary. Frequency of each allele in breast cancer patients was compared with the frequency of the same allele in controls. The odds ratio (OR) and its 95% confidence intervals (CI) were calculated using SPSS version 16 and a P value of 0.05 or less was considered to be significant.

Results

Demographic and clinical characteristics of two groups of female patients with breast cancer are shown in Table 1. The HLA-DRB1, -DQA1, and –DQB1 allele frequencies of these two groups of patients and controls are presented in Table 2. In group 1 (younger patients), the most frequent alleles in the DQ region were HLA-DQA1*0301 ($p = 0.002$,

Table 1 Demographic and clinical characteristics of breast cancer female patients investigated in this study

Parameter	Group 1	Group 2	Total patients
Total number of subjects	49	51	100
Age mean (years) at the time of study (range)	35.5 (26–40)	53.1 (41–75)	44.3 (26–75)
Tumor site, N (%)			
Left breast	19	27	46
Right breast	30	24	54
Pathological diagnosis. N (%)			
Ductal carcinoma	41	45	86
Lobular carcinoma	8	6	14
Pathological TNM stage, N (%)			
Stage I	3 (6)	9 (18)	12
Stage II	20 (41)	17 (33)	37
Stage III	26 (53)	25 (49)	51

OR=3.3, 95% CI: 1.5–7.1) and HLA-DQB1*0302 (p= 0.04, OR=2.8, 95% CI: 1–7.3). In group 2, the following alleles increased significantly than those in controls including HLA-DQA1*0301 (P=0.001, OR=3.4, 95% CI: 1.6–7.2), HLA-DRB1*1303 (3.9% vs. 0.0%, P=0.02), HLA-DRB1*0301 (P=0.04, OR=2.3, 95% CI:1.03–5.07) and HLA-DRB5 (P= 0.005, OR=2.3, 95% CI:1.3–4.3). In entire patients, the frequency of alleles HLA-DQA1*0301 (P=0.0001, OR=3.3, 95% CI: 1.7–6.6) and HLA-DRB1*1303 (3% vs. 0%, P= 0.03) were appeared to be significantly higher than those in control group (Table 3).

The alleles which showed a tendency to protection against breast cancer were as follows; in group 1, the frequency of HLA-DQA1*0505 (P=0.004, OR=0.3, 95% CI:0.15–0.7), HLA-DQB1*0602 (P=0.02, OR=0.3, 95% CI:0.09–0.9) and HLA-DRB1*0101 (P=0.05, OR=0.23, 95% CI:0.05–1) decreased significantly compared with that in control group. In group 2, the frequency of HLA-DRB1*1301 (0%, vs. 7.5%, P=0.004, OR=0.12,) and HLA-DQA1*0101 (0% vs. 8.1%, P=0.002, OR=0.3) was significantly lower than the frequency of those in control group. In entire group of patients, the following alleles appeared to be significantly lower than those in controls including HLA-DQA1*0505 (P=0.003, OR=0.4, 95% CI:0.2–0.7), HLA-DRB1*1301 (P=0.002, OR=0.12, 95% CI:0.02–0.5), HLA-DQA1*0101 (P=0.01, OR=0.21, 95% CI:0.07–0.7), HLA-DRB1*0101 (P=0.02, OR=0.29, 95% CI:0.1–0.8) and HLA-DQB1*0602 (P=0.02, OR=0.4, 95% CI:0.18-0.87) (Table 3). The data of haplotype frequencies is presented is Table 4, the more frequent Haplotype in patients of group 1 than in controls is DRB1*07- DQA1*0201- DQB1*0201 (OR=3, P=0.04) and the most frequent haplotypes in patients of group 2 are DRB1*15- DQA1*0103- DQB1*0601 (OR= 5.4, P=0.03) and DRB1*1301- DQA1*0103- DQB1*0602 (OR=0.08, P=0.05).

No significant relationship was found between the HLA-DRB1, -DQA1, and–DQB1 allele frequencies and clinicopathological parameters such as marital status (single/married), tumor site (left or right breast), histological type (ductal or lobular carcinoma) and Pathological tumor stage.

Discussion

The origin of malignant neoplasm is unknown and multifactorial [23]. Certain factors can cause the appearance of the disease and also they often are able to help the tumor to continue its growth and would result in metastasis. By accepting the immunological surveillance as an important mechanism in tumor gene process, inheriting HLA class II alleles can make an individual resistant or susceptible to tumor presentation [15–18]. Beside that, the dominant pathogen of a geographical area, could affect the frequency of presentation of different HLA alleles [18].

Breast cancer is the most frequent cancer in women [24] and the second fatal form of malignancy among female worldwide [25, 26], accounting for 16% of cancer deaths [27]. Female breast cancer is ranked first among malignancies in Iran [28, 29], consequently, studying the disease and the factors predisposing its presentation is of prime importance to identify at-risk group.

The results of the present study indicate that there is a strong positive association of HLA-DQA1*0301 allele with breast cancer including early-onset of the disease (21.5% vs. 7.5%, p= 0.0001, OR=3.3). Besides that, the results reveals the significant association of HLA-DRB1*1303 allele with susceptibility and the significant participation of HLA-DQA1*0505, HLA-DQB1*0602, HLA-DQA1*0101, HLA-DRB1*1301 as well as HLA-DRB1*0101 alleles in protection in entire patients.

Associations between HLA class II genes and breast cancer have been examined by few investigators in other

Table 2 Frequencies of HLA-DRB1,-DQA1 and -DQB1 alleles in female patients with early-onset of breast cancer (group I) and patients aging over 40 years (group II) in comparison with healthy controls (group III)

	Patients≤40 (I) (*N*=49)		Patients>40 (II) (*N*=51)		Controls (III) (*N*=80)		OR (I vs. III)	*P*(I vs. III)	OR (II vs. III)	*P*(II vs. III)
	N	%	n	%	n	%				
DQA1-*0101	4	4.1	0	0	13	8.1	0.48	0.30	–	0.002
DQA1-*01021	10	10.2	11	10.7	20	12.5	0.79	0.69	0.84	0.70
DQA1-*0103	9	9.2	17	16.6	22	13.7	0.63	0.32	1.25	0.59
DQA1-*0104	8	8.2	9	8.8	15	9.3	0.85	0.82	0.93	1.0
DQA1-*0201	19	19.4	13	12.7	21	13.1	1.59	0.21	0.96	1.0
DQA1-*0301	21	21.4	22	21.6	12	7.5	3.36	0.002	3.4	0.001
DQA1-*0401	2	2	1	0.98	5	3.1	0.64	0.71	0.3	0.40
DQA1-*0501	14	14.3	15	14.7	15	9.3	1.61	0.31	1.7	0.23
DQA1-*0505	9	9.2	13	12.7	37	23.1	0.33	0.004	0.48	0.03
DQB1-*0201	25	25.5	24	18.7	30	18.7	1.48	0.213	1.3	0.43
DQB1-*0301	23	23.5	22	23.1	37	23.1	1.02	1.000	0.9	0.9
DQB1-*0302	11	11.2	8	4.4	7	4.4	2.76	0.045	1.9	0.3
DQB1-*0303	1	1	1	4.4	7	4.4	0.22	0.161	0.2	0.15
DQB1-*0401	3	3.1	1	2.5	4	2.5	1.23)	1.00	0.4	0.7
DQB1-*0501	12	12.2	13	13.7	22	13.7	0.87	0.85	0.9	0.9
DQB1-*0502	3	3	9	5.6	9	5.6	0.53	0.38	1.6	0.5
DQB1-*0601	7	7.1	13	6.9	11	6.9	1.04	1.00	1.9	0.1
DQB1-*0602	4	4.1	7	12.5	20	12.5	.29	0.027	0.5	0.1
DQB1-*0603	3	3	1	0	0	0	–	0.054	–	0.4
DQB1-*0604	5	5.1	2	3.8	6	3.8	1.38	0.75	0.5	0.48
DRB1*0101	2	2	3	2.9	13	8.1	0.23	0.05	0.3	0.1
DRB1*15	13	13.3	21	20.5	23	14.3	0.91	0.85	1.5	0.2
DRB1*16	2	2	4	3.9	3	1.8	1.09	1.00	2.1	0.4
DRB1*0301	8	8.2	16	15.6	12	7.5	1.09	1.00	2.3	0.04
DRB1*0401	15	15.3	11	10.7	12	7.5	2.23	0.049	1.5	0.4
DRB1*07	16	16.3	12	11.7	23	14.3	1.16	0.7	0.8	0.6
DRB1*08	5	5.1	2	1.96	5	3.1	1.64	0.5	0.6	0.7
DRB1*1001	3	3.1	7	6.8	4	2.5	1.23	1.00	2.9	0.1
DRB1*11	17	17.3	17	16.6	39	24.3	0.65	0.21	0.6	0.2
DRB1*12	1	1	0	0	0	0	–	0.38	–	–
DRB1*1301	2	2	0	0	12	7.5	0.26	0.08	–	0.004
DRB1*1302	5	5.1	2	1.96	6	3.8	1.38	0.75	0.5	0.48
DRB1*1303	2	2	4	3.9	0	0	–	0.14	–	0.02
DRB1*1401	7	7.1	3	2.9	7	4.5	1.68	0.40	0.7	0.7
DRB3	49	50	47	46	76	47.5	1.1	0.7	0.9	0.8
DRB4	32	32.6	24	23.5	36	22.5	1.7	0.08	1.1	0.9
DRB5	13	13.3	31	30.4	25	16	0.82	0.71	2.4	0.005

N number of donors, *n* number of alleles, *OR* odds ratio, *P* probability

regions of the world. In 2000, Chaudhuri et al. [15], in a group of 173 patients with breast cancer and 215 ethnically matched Caucasian-origin controls, reported that DQB*03032 and DRB1*11 alleles represent protective factors toward early-age of the disease. In our female population, DQB*0303 was appeared to be protective allele in early-onset of the disease or in entire patients, but the decreased frequency of that in compare with control group was not significant. In an earlier study, conducted in southern province of Iran, Ghaderi et al. [16] examined the association between HLA-DRB1 alleles and breast cancer in 36 women in comparison with the same number of

Table 3 Frequencies of HLA-DRB1,-DQA1 and -DQB1 alleles in 100 female patients with breast cancer (age range: 26–75 years) in comparison with healthy controls

	Patients (*N*=100)		Controls (*N*=80)		OR	95% CI	*P*
	n	%	N	%			
DQA1-*0101	4	2	13	8.1	0.21	0.07–0.72	0.010
DQA1-*01021	21	10.5	20	12.5	0.82	0.42–1.57	0.6
DQA1-*0103	26	13	22	13.7	0.93	0.51–1.72	0.9
DQA1-*0104	17	8.5	15	9.3	0.89	0.43–1.85)	0.8
DQA1-*0201	32	16	21	13.1	1.26	0.69–2.28	0.4
DQA1-*0301	43	21.5	12	7.5	3.37	1.71–6.65	0.0001
DQA1-*0401	3	1.5	5	3.1	0.5	0.11–2.01)	0.5
DQA1-*0501	29	14.5	15	9.3	1.6	0.84–3.17	0.1
DQA1-*0505	22	11	37	23.1	0.4	0.23–0.73	0.003
DQB1-*0201	49	24.5	30	18.7	1.41	0.84–2.3	0.2
DQB1-*0301	45	22.5	37	23.1	0.96	0.58–1.58	0.9
DQB1-*0302	19	9.5	7	4.4	2.3	0.93–5.60	0.06
DQB1-*0303	2	1	7	4.4	0.2	0.04–1.07)	0.08
DQB1-*0401	4	2	4	2.5	0.8	0.19–3.23	1.0
DQB1-*0501	25	12.5	22	13.7	0.9	0.48–1.65	0.7
DQB1-*0502	12	6	9	5.6	1.1	0.44–2.61	1.0
DQB1-*0601	20	10	11	6.9	1.5	0.69–3.24	0.3
DQB1-*0602	11	5.5	20	12.5	0.4	0.18–0.87	0.02
DQB1-*0603	4	2	0	0	–	–	0.1
DQB1-*0604	7	3.5	6	3.8	0.9	0.30–2.82	1.0
DRB1*0101	5	2.5	13	8.1	0.3	0.10–0.83	0.02
DRB1*15	34	17	23	14.3	1.2	0.68–2.16	0.6
DRB1*16	6	3	3	1.8	1.6	0.39–6.57	0.7
DRB1*0301	24	12	12	7.5	1.7	0.81–3.47	0.2
DRB1*0401	26	13	12	7.5	1.8	0.89–3.78	0.1
DRB1*07	28	14	23	14.3	0.97	0.53–1.76	1.0
DRB1*08	7	3.5	5	3.1	1.1	0.35–3.61	1.0
DRB1*1001	10	5	4	2.5	2.05	0.63–6.67	0.3
DRB1*11	34	17	39	24.3	0.6	0.37–1.06	0.08
DRB1*12	1	0.5	0	0	–	–	1.0
DRB1*1301	2	1	12	7.5	0.1	0.02–0.56	0.002
DRB1*1302	7	3.5	6	3.8	0.9	0.31–2.82	1.0
DRB1*1303	6	3	0	0	–	–	0.03
DRB1*1401	10	5	7	4.5	1.1	0.42–3.09	0.8
Total number of alleles	200		160				

N number of donors, *n* number of alleles, *OR* odds ratio, *P* probability

healthy individuals. They found that the cancer patients had significant increased frequency of HLA-DRB1*12 allele and decreased frequency of HLA-DRB1*11 allele. In the current study, the frequency of HLA-DRB1*12 was quite low among patients or controls, meanwhile HLADRB1*11 showed no association with the disease. These disparate findings, which focused on HLA-DRB1 alleles, may in part be explained by ethnic differences and also the influence of low sample size of the study of Ghaderi et al. should be considered.

In a different ethnic group, Tunisian patients, Baccar Harrath et al. [30] by molecular typing of HLA-DRB1 and -DQB1 loci in 70 female patients and 70 female control subjects reported a negative association between HLA-DRB1* 07-DQB1*02 haplotype and the incidence of breast cancer (6.42% haplotypes in patients versus

Table 4 Frequencies of HLA-DRB1,-DQA1 and -DQB1 haplotypes in female patients with early-onset of breast cancer (group I) and patients aging over 40 years (group II) in comparison with healthy controls (group III)

DRB1- DQA1- DQB1 Haplotypes	Group I (*N*=49) %	Group II (*N*=51) %	Controls (III) (*N*=80) %	OR (I vs. III)	*P*(I vs. III)	OR (II vs. III)	*P*(II vs. III)
DRB1*0101DQA1*0101- DQB1*0501	2.04	2.9	5.5	0.3	0.2	0.5	0.5
DRB1*15- DQA1*0102- DQB*0602	7	2	2.5	2.4	0.3	0.6	1
DRB1*15- DQA1*0103- DQB*0601	3	10	1.5	1.5	1	5.4	0.03
DRB1*15- DQA1*0103- DQB*0602	1	4	0	–	–	9	0.1
DRB1*16- DQA1*0102- DQB*0502	2	4	6.5	0.2	0.1	0.5	0.5
DRB1*0301- DQA1*0501- DQB*0201	8	16	10	0.7	0.8	1.7	0.3
DRB1*04- DQA1*0301- DQB*0302	8	7	3.5	2.8	0.2	2.4	0.3
DRB1*07- DQA1*0201- DQB*0201	16	12	6.5	3	0.04	2	0.2
DRB1*1001- DQA1*0104- DQB*0501	3	7	4	0.7	1	1.8	0.5
DRB1*1101- DQA1*0501- DQB*0301	17	17	25	–	–	0.6	0.25
DRB1*1301- DQA1*0103- DQB*0602	2	0	4.5	0.4	0.4	0.08	0.05
DRB1*1302- DQA1*0103- DQB*0301	5	2	2	2.6	0.4	–	–
DRB1*1303- DQA1*0301- DQB*0604	2	4	1	2	1	4	0.3
DRB1*1401-QA1*0104- DQB1*0502	1	2	5.5	0.1	0.1	0.3	0.2

N number of donors,% percent of haplotypes, *OR* odds ratio, *P* probability

15.71% in control group, *P*=0.013). In our study, we found that the haplotype DRB1*07- DQA1*0201-DQB1*0201 is more frequent in patients with early-onset of the disease (*P*= 0.04). This difference might partially be due to differences in ethnicity.

In a more recent study, Cantú de León et al. [17] used high-resolution HLA class I and class II allele typing in a group of 100 Mexican mestizo breast cancer patients and 99 matched healthy controls. They found that DRB1*1301 is presented in seven cases but in only one control, and also they report a negative association of DQB1*0301 allele with the disease (OR=0.078, p=0.00001). In contrast, in the current study, the frequency of DRB1*1301 is significantly lower in patient group than controls (1% vs. 7.5%, *P*=0.002, OR=0.12) and HLA-DQB1*0301 has the same frequency in patient and control groups. This inconsistency may represent population-specific of HLA class II alleles.

In the current study, HLA-DQA1*0301 allele is found to be associated with the development of breast cancer in entire patients and HLA-DQB1*0602 appears to protect against the early-onset of the disease, these finding are consistent with the finding of Ferrera et al. [31] who looked for the possible association of HLA-DQA1 and - DQB1 alleles in the development of dysplasia and carcinoma of the cervix in Honduran female patients compared with that in the general population, they revealed that a predominance of HLA-DQA1*0301 allele among severe-case patients [relative risk (RR)=3.45, p= 0.008], whereas a negative correlation was observed between DQB1*0602 and the presence of human papillomavirus (HPV-16 or HPV-18) associated tumors. These correlations suggest that specific alleles of HLA class II are most probably involved in progression toward and protection from the development of cancer.

Overall, we identified HLA-DQA1*0301 allele is mainly associated with increased risk of breast cancer development including early-age of the disease in Iranian women. Besides that, we found the involvement of HLA-DQA1*0505 and HLA-DQB1*0602 alleles in protection against the disease in our female younger population. This study also revealed that the haplotype DRB1*07-DQA1*0201-DQB1*0201 is more frequent in patients with early-onset of the disease. We conclude that HLA class II polymorphism influences breast cancer risk. Clearly more extensive studies need to be conducted.

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