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Breast cancer is protected by the KIR gene *2DL1* and affected by *2DL2*: A systematic review

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ABSTRACT

Breast cancer has been known as the most common cancer and the most common malignancy among women and also has been proven as the first cancer-related cause of death among them. Genetic diversity of several genes is related to breast cancer. Since this molecular approach is mainly limited to cell cycle genes, we intend to evaluate statistically the relation of the genes killer-cell immunoglobulin-like receptors (KIRs) as a systematic review. Through our re-analysis on the new hypothetical population made up of previous studies, we conclude that breast cancer is protected by KIR2DL1 and affected by KIR2DL2.

Key words: breast cancer, immunology, molecular biology, genetics, KIR.

INTRODUCTION

Breast cancer has been known as the most common cancer and the most common malignancy among women and also has been proven as the first cancer-related cause of death among them [1-7]. Most breast cancer mortalities occur in developing countries and a lot of cases of this type of cancer can be treated by early diagnosis [8-10]. However, there are some barriers impeding women from its screening methods such as mammography, breast self-examination and clinical examination[11-13]. Other than clinical screening actions, there are some molecular technics including cancerous antigen (CA) biomarkers assaying like CA 15-3 [14].

There are many factors including familial history, age, the age of the first pregnancy, the age of menarche and menopause, radiation, previous benign disease, oral contraceptives, hormone replacement therapies and life style which are known as the risk factors of breast cancer [15]. Of the protective factors, pregnancy could be named [16] because of the protective effect of the hormone human chorionic gonadotropin (HCG)[17, 18]. The treatment is conducted usually by chemotherapeutic medicines such as exemestane[8] and other platinum based compounds [19, 20], traditional radiation therapy [21] and immunoradiotherapy based on monoclonal antibodies [22].

Proto-oncogenes and tumor suppressor genes are factors which can be associated with breast cancer as the tumor suppressor gene *TP53* is mutated in about 30% of cases [23].The proto-oncogene *ERBB2* is also associated with breast cancer which is over-expressed in about 30% of the patients. Such patients do not respond to endocrine and chemotherapy who can be treated by the mentioned monoclonal antibodies [22].Since this molecular approach in mainly limited to cell cycle genes, we intend to evaluate statistically the relation of the genes *killer-cell immunoglobulin-like receptors* (*KIRs*) as a systematic review.

MATERIALS AND METHODS

Present systematic review consists of searching in Pubmed and google scholar without regarding the time period. Only 2 articles with the same protocol were found which has both KIR and "breast cancer" word in their titles. Because of this number was not enough to perform meta-analysis, we made up a new hypothetical population of the both articles including 263 patients with breast cancer and 355 individuals as a control.

In order to re-analyze the new population, we used chi-squared test with Yate's correction through Graph pad prism software for each gene separately. The significance par were considered as p = 0.05. The 5 genes *2DL4*, *3DL2*, *3DL3*, *2DP1* and *3DP1* were excluded from test because of their persistence in all participants of the both groups and from the mathematical points of view it made denominator of the fraction zero.

ABOUT KIR

There are some polymorphic glycoproteins, such as KIRs (also called as CD158), that are appeared on cell surface of natural killer cells (NKs) and T cell subsets [24]. Types of KIR gene family arepolymorphic as well as allelic polymorphisms make the genomic diversity[25]. It is important that the human leukocyte antigen (HLA) [26]can be considered as the most polymorphic loci in human genome which makes a direct contact between its molecules and the KIR's. KIR genes can be divided into two distinct groups (2D or 3D) but it depends on the number of extracellular immunoglobulin domains. KIR molecules are categorized in two types based on length of intracellular area; inhibitory and activating. While the inhibitory KIRs (iKIRs) are demonstrated by a long intra-cytoplasmic sequence with at least one immunoreceptor tyrosine-based inhibitory motif (ITIM), the activating KIRs (aKIRs) are equipped to a short intra-cytoplasmic sequence without ITIM [25].

By far, several kinds of KIR receptors in human genome are recognized [27].A small portion of total lymphocytes, approximately 10-15%, in peripheral blood includes NKs which are a subsets of lymphocytes [28]. Generally, NKs are able to kill the targeted cells of theirs and production of a variety of cytokines and chemokines in order to provide innate immunity and adaptive immune responses [29]. In order to pathogenesis of diverse kinds of diseases, the activity of NKs based on interaction with HLA class I as their ligands is regulated by inhibitory or activates signals generated by KIR. [30]. To obtain different thresholds of activation in NK family, different combinations of KIR-HLA genotypes are identified in which it is proved that such combinations are related to a number of human diseases and complications such as viral infections, autoimmune disorders and cancers [31] as well as reproduction abnormalities [32, 33]. Note that a centromeric and telomeric region is appeared in KIR gene cluster on chromosome 19q13.4 within the leukocyte receptor complex (LRC) [34]. Table 1 shows the detail of the fourteen identified KIR genes and two pseudogenes. [35].

NK has two subsets of $CD16^{+}CD56^{dim}$ and $CD16^{-}CD56^{bright}$where the type of dim benefits from more cytotoxic capacity called as "cytotoxic NK" while the bright one is utilized in secretion of inflammatory cytokines called as "immune-regulatory NK". By comparing them, the dim form shows more expression of KIR [24, 29, 32, 34, 36-40].

Table 1KIR has 14 discovered genes and 2 discovered pseudo-genes. Seven number of them are inhibitory, 1 of them is both inhibitory and activating and 6 number them are activating. Each gene has different alleles; So KIR is highly polymorphic like HLA

KIR genes															
Inhibitory KIRs								Activating KIRs						Pseudo genes	
2DL1	2DL2	2DL3	2DL4	2DL5	3DL1	3DL2	3DL3	2DS1	2DS2	2DS3	2DS4	2DS5	3DS1	2DP1	3DP1

The KIR gene cluster is a type of gene where the flanking of this gene is performed by KIR3DL3 and KIR3DL2 at the centromeric end and the telomeric end, respectively. Note that both of them are presented on virtually all haplotypes. The two groups of KIR haplotypes which are named as haplotypes “A” and “B” are described based on the gene content. The most prevalent form of A haplotypes is the combination of five inhibitory genes (KIR2DL1, 2DL3, 3DL1, 3DL2 and 3DL3), one activating gene (KIR2DS4), and the KIR2DL4 as the common gene between the inhibitory and activating capacity. In this regard, the null variants of both KIR2DS4 and KIR2DL4 that are not expressed on the cell surface are possessed by A haplotypes which are technically free of functional aKIR gene. Variable numbers of activating and inhibitory genes are possessed by B haplotypes which can be considered as the main contributors to the extraordinary differences in KIR gene profiles observed in isolated ethnic populations across the world. To trigger the signal which turns off the NKs, interaction of inhibitory KIR with HLA class I as their ligands is employed. Thus, the healthy cell can be protected from NK lysis by expressing HLA-A, -B or -C molecules. Note that tumor transformation or viral infection results down-regulation of HLA class I expression which makes NKs to lyse these unhealthy targeted cells of theirs, a phenomenon first described as"missing-self"hypothesis. In such cases, since the combined KIR-HLA genotypes results the lower inhibition and higher

activation, it is capable to resist against the viral infections and cancers. On the other hand, risk of susceptibility to autoimmune and inflammatory disease can be increased by these dominant activating genotypes [31].

KIR AND BREAST CANCER

In study of Ozturk et al [41] the framework genes *2DL4*, *3DL2*, *3DL3*, and *3DP1* were present in all the samples and alsothepseudogene*2DP1* was present in most samples (in 99/6% of patient group and 100% of control group). A tendency was found that inhibitory KIR genes having a higher expression compared with activating KIR genes in all study samples. Among them, inhibitory the KIR genes *2DL1*, *2DL3*, and *3DL1* had higher frequencies in all samples, which were more than 85%.With the exception of *KIR2DS4*, frequencies of the remaining activating genes were all lower than 58%.In addition, in the study of Ozturk's et al, the frequencies of inhibitory *KIR2DL1* genes in the control group were higher rather than in the patient group. There was a significant negative correlation between *2DL1* genes and breast cancer development (P = 0.03) which shows expression of this inhibitory gene can be protective against breast cancer, in contrast to the other inhibitory genes. In that study of Ozturk's et al, *KIR2DS1* genes were more common in patients rather than in the controls, but not statistically significant (P = 0.16) (table 2).
The proportion of breast cancer patients with the inhibitory *KIR2DL2* in study of Jobim et al [42]was significantly higher than the healthy controls (71.5% vs 55.5%; P = 0.0001).

CONCLUSION

In one of the studies, only *KIR2DL1* was statistically related to breast cancer and this correlation was protective; in the other one, only *KIR2DL2* was statistically related to breast cancer and this correlation was being as a risk factor. Through our re-analysis, we conclude that breast cancer is protected by *KIR2DL1* and affected by *KIR2DL2*, but the odds ratio of the second's was higher.

Table 2 Distribution of KIR genes in breast cancer and control groups

Gene	Ozturk et al, 2012		Jobim et al, 2013		Total (Ozturk and Jobim)		P value
	Breast N= 33	Control N= 77	Breast N= 230	Control N= 278	Breast N= 263	Control N= 355	
2DL1	30*	77	221	273	251	350	0.03*
2DL2	18	40	170**	157	188	197	0.0001***
2DL3	25	65	212	240	237	305	0.14
2DL4	33	77	230	278	263	355	NS
2DL5	22	45	129	157	151	202	0.96
3DL1	29	68	222	257	251	325	0.08
3DL2	33	77	230	278	263	355	NS
3DL3	33	77	230	278	263	355	NS
2DS1	18	24	94	101	112	125	0.16
2DS2	18	40	133	149	151	189	0.34
2DS3	9	28	69	85	78	113	0.62
2DS4	30	68	211	269	241	337	0.13
2DS5	17	28	86	109	103	137	0.95
3DS1	16	29	88	107	104	136	0.81
2DP1	32	77	230	278	262	355	NS
3DP1	33	77	230	278	263	355	NS

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