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Association Study of IL-17A Polymorphisms (rs8193036; rs3819024; rs2275913) with Lung, Breast and colorectal Cancer Risk in a Moroccan cohort

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Abstract

Cancer is among the main causes of morbidity and the second leading cause of mortality in the world. Genetic predisposition and environmental factors influence the development of several types of cancer. The aim of the present study is to ascertain whether common variants in IL17A gene are associated with the occurrence of lung, breast and colorectal cancers among Moroccan patients. A total of 553 subjects were enrolled, including 314 healthy controls, 100 lung cancer, 70 breast cancer and 69 colorectal cancer patients. Three single-nucleotide polymorphisms (SNPs) located within the IL17A gene were analyzed: rs8193036; rs3819024; rs2275913 and genotyped using TaqMan allelic discrimination assays. Our findings provide evidence that the functional polymorphism IL17A rs8193036 contributes to the risk of lung cancer. In contrast, the same SNP demonstrates a protective role for breast cancer in our study. Future larger studies with more rigorous study designs of other ethnic populations are required to confirm the current findings.

Keywords: IL17A polymorphisms, lung cancer, breast cancer, colorectal cancer

Full length article **Corresponding Author*, e-mail: y.zaid@um5r.ac.ma

1. Introduction

More than a quarter of people worldwide will ultimately be affected by cancer, it's responsible for 8.8 million deaths in 2015, cancer is among the main causes of morbidity and the second leading cause of mortality in the world. More than two-thirds of cancer deaths occur in low- and middle-income countries [1-4]. Fourteen million new cases were approximately reported in 2012 and the number of new cases is expected to increase by approximately 70% over the next two decades [5-6]. According to the World Health Organization, the main types of cancer responsible of death are: Lung cancer (1.69 million deaths), liver cancer (788,000 deaths), colorectal cancer (774,000 deaths), stomach cancer (754,000 deaths) and breast cancer (571,000 deaths) [7]. Although the underlying etiology and pathogenesis mechanisms of cancer have not yet been fully determined, complex interactions between an individual's genetic background and environmental factors have been suggested to be highly associated with cancer development [8]. Hereditary factors leading to cancer development of are not clearly elucidated, but the roles of genes encoding cytokines in carcinogenesis and tumor immunity have been well established [9]. Cytokines are important inflammatory mediators, as part of the regulatory network, they activate, directly or indirectly, downstream signaling pathways of malignancies development [10-11]. This may provide a new explanation of tumorigenesis in inflammatory-related malignancy. Accumulating data have demonstrated that a variety of inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukin- (IL-) 1, IL-6, IL-10, IL-17

are involved in the occurrence and development of cancer [2-12-13]. Interleukin-17 (IL-17) (also named as CTLA-8) is a proinflammatory cytokine that plays important functions in host defense against various microbial pathogens as well as tissue inflammation. Recently, several studies suggested a pathogenic role of IL-17A in autoimmune disorders and cancer [14-17]. In addition, IL-17 has been identified to facilitate the proliferation, migration, invasion, and drug resistance of cancer cells [18-19], thereby promoting tumor progression.

A lot of evidences from recent studies have shown increased IL- 17 expression in malignant tumors and an overexpression of IL-17 levels correlated with advanced cancer stage [18-22]. Numerous observational studies have revealed that people with a specific gene polymorphism may acquire increased susceptibility to many diseases. Therefore, identification of these risky gene polymorphisms would be beneficial for diagnosis and treatment. Single nucleotide polymorphisms (SNPs) can alter gene functions and therefore alter protein expression, which influence cell proliferation and increase cancer risk. Previous studies have shown that the functional IL-17A polymorphisms may contribute to the predisposition to several cancers, but the results were inconclusive [23-25]. Thus, the aim of the present study is to ascertain whether common variants in IL-17A gene inflammatory and immune responses are linked with the occurrence of lung, breast and colorectal cancers among Moroccan patients.

2. Materials and methods

2.1. Study population

A total of 239 patients diagnosed with Cancer (100 lung cancer; 70 breast cancer; 69 colorectal cancer) at the Ibn Rochd Hospital (Casablanca, Morocco) were included. Samples from 314 blood donors were used as ethnically matched controls. A written consent was obtained from all participants and all the study was approved by the local ethics committee. The diagnosis of cancer was established according to conventional clinical and histological criteria. Clinical and demographic characteristics of patients were collected in a case report form. Genotyping Genomic DNA was isolated from peripheral blood, using standard procedures, and from Formalin Fixed Paraffin Embedded Tissues using the QIAamp® DNA FFPE Tissue Kit (Qiagen). Three single-nucleotide polymorphisms (SNPs) located within the IL17A gene were analyzed: rs8193036; rs3819024; rs2275913 and genotyped using TaqMan allelic discrimination assays on the 7500 Fast Real-Time PCR system (AB Applied Biosystems, USA).

2.2. Statistical analysis

The power calculation of the present study was carried out using Power Calculator of Genetic Studies 2006 software (http://www.sph.umich.edu/csg/abecasis/CaTS/).
Data were analyzed d using Plink software V1.07. The genotypes and alleles frequencies distribution were compared between patients and controls using the $\chi 2$ test or Fisher test. The strength of association was evaluated using the Odds ratios (ORs) with a confidence interval (CI) of 95%. For all SNPs, the Hardy-Weinberg equilibrium (HWE) was tested by the chi-square analysis. P value less than 0.05 was considered statistically significant. Bonferroni correction was applied to significant P values of IL17A polymorphisms to correct by the number of comparisons. Results The success rates of genotyping assays were (98-100%) for controls and (82-96%) for patients. In both groups, the genotype frequencies for all SNPs agree with those predicted under Hardy-Weinberg equilibrium. Frequency distribution of genotypes and variant alleles of IL17A polymorphisms (rs8193036, rs3819024, rs2275913) in patients and controls are shown in Tables 1 and 2.

3. Results and Discussions

3.1. Lung cancer

In the present study, the frequency of allele C for IL-17A rs8193036 was significantly higher in Lung Cancer patients compared with controls (32.92 vs. 25.32 %, P = 0.05, OR: 1.44, 95 % CI= 0.99-2.10). Regarding genotype frequencies, the homozygous variant genotype distribution was increased in LC group (13.41%) compared to controls (5.84%). Genotypic test disclosed a statistically significant difference between patients and controls (X2=5.69, P=0.05) (Table: 2). Concerning the effect of IL-17A SNP on disease risk, genetic model's assessment revealed a significant association under recessive genetic model CC vs. CT TT (OR = 2.49, 95% CI = 1.12 to 5.52; P=0.02). Furthermore, the analysis of both IL-17A (rs3819024) and IL-17A (rs2275913) polymorphisms distribution among LC patients and controls did not reveal any significant association, both in terms of allele and genotype frequencies. Similarly, any effect on disease risk when Genetic models were assessed.

3.2. Breast cancer

All the studied polymorphisms in IL-17A showed a lack of significant associations for BC when considering MAF and genotype distribution. Lower frequency of variant allele for the IL_17A rs8193036 was observed without being statistically significant (20.31 vs. 25.32%, P= 0.23, OR: 0.75, 95 % CI = 0.47-1.19). Taking into account these results, we performed genetic models' analysis to account for the variation of risk effect. A tendency of a protective effect was observed with BC patients under the dominant model CC CT vs. TT (OR: 0.60, 95% CI: 0.34-1.06, p =0.07). The genetic model analysis for the remaining SNPs disclosed no significant associations.

3.3. Colorectal cancer

We further analyzed the distribution of IL-17A polymorphisms in CC patients. In this regard, no statistically significant allele or genotype differences were observed between patients and controls. Similarly, no effect on disease risk was observed when Genetic models were assessed. With the prevalence of cancer increasing year to year, it is of utmost importance to bring to light new ways to withstand this disease. Inflammation is a prominent component of the tumor microenvironment; several studies have found high expression of IL-17 in various tumor tissues [26].

Table 1: Minor allele frequencies of *IL17A* genetic variants in Lung, breast and colorectal cancer patients and healthy controls from Morocco

*P = 0.05, OR (95%CI): 1.44 (0.99-2.10): Bonferroni's corrected Pc = 0.15.

SNP ID	Subgroup	Number of Alleles	MAF %	Allele test	
				OR [95% CI]	P-value
***IL17A* rs8193036**	Controls; n=308	156/460	25.32		
	LC (n=82)	54/110	32.92	1.44 [0.99-2.10]	**0.05***
	BC (n=64)	26/102	20.31	0.75 [0.47-1.19]	0.23
	CC (n=65)	39/91	30	1.26 [0.83-1.91]	0.27
***IL17A* rs3819024**	Controls; n=310	136/484	21.93		
	LC (n=96)	41/151	21.35	0.96 [0.65-1.43]	0.86
	BC (n=64)	31/97	24.21	1.13 [0.72-1.77]	0.57
	CC (n=64)	32/96	25	1.18 [0.76-1.84]	0.44
***IL17A* rs2275913**	Controls; n=314	105/523	16.71		
	LC (n=100)	32/168	16	0.94 [0.61-1.46]	0.81
	BC (n=70)	29/111	20.71	1.30 [0.82-2.06]	0.26
	CC (n=69)	29/109	21.01	1.32 [0.83-2.10]	0.22

Table 2: Genetic models and genotypes distribution in patients and controls

Gene SNP	Group	1/2	Genotype, N (%)			Genotypic Test		Dominant model Genotype 11+12 vs. 22		Recessive model Genotype 11 vs. 12+22	
			CC	CT	TT	X^2	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
***IL17A* rs8193036**	Controls	**C/T**	18 (5.84)	120 (38.96)	170 (55.19)						
	LC		11 (13.41)	32 (39.02)	39 (47.56)	5.69	**0.05**	1.35 [0.83-2.21]	0.21	2.49 [1.12-5.52]	**0.02**
	BC		5 (7.81)	16 (25)	43 (67.18)	4.48	0.10	0.60 [0.34-1.06]	**0.07**	1.36 [0.48-3.82]	0.55
	CC		6 (9.23)	27 (41.53)	32 (49.23)	1.4	0.49	1.27 [0.74-2.17]	0.38	1.63 [0.62-4.30]	0.31
***IL17A* rs3819024**		**G/A**	GG	GA	AA						
	Controls		23 (7.41)	90 (29.03)	197 (63.54)						
	LC		5 (5.20)	31 (32.29)	60 (62.5)	0.79	0.67	1.04 [0.65-1.68]	0.85	0.68 [0.25-1.85]	0.45
	BC		3 (4.68)	25 (39.06)	36 (56.25)	NA	NA	1.35 [0.78-2.33]	0.27	0.61 [0.17-2.10]	0.43
	CC		6 (9.37)	20 (31.25)	38 (54.68)	0.49	0.77	1.19 [0.68-2.06]	0.52	1.29 [0.50-3.31]	0.59
***IL17A* rs2275913**		**G/A**	GG	GA	AA						
	Controls		10 (3.18)	85 (27.07)	219 (69.74)						
	LC		4 (4)	24 (24)	72 (72)	NA	NA	0.89 [0.54-1.47]	0.66	1.26 [0.38-4.13]	0.69
	BC		2 (2.85)	25 (35.71)	43 (61.42)	NA	NA	1.44 [0.84-2.47]	0.17	0.89 [0.19-4.17]	0.88
	CC		3 (4.34)	23 (33.33)	43 (62.31)	NA	NA	1.39 [0.80-2.40]	0.23	1.38 [0.37-5.15]	0.63

Arguably, the last decades have witnessed conflicting approaches to the dual role of IL-17, providing an almost paradoxical pro- and antiangiogenesis pathway on the association between IL-17 and the pathophysiology of cancer [18]. Currently, six IL-17 family members have been classified, IL-17A through to F. The prototypic family member has been identified as IL-17A [27].

Latterly, studies investigating the role of IL-17 in carcinogenesis and tumor progression show that IL17-A as well as IL-17F polymorphisms are highly associated with increased risk of development for multiple forms of cancer [28]. Another recent meta-analysis reported that IL-17A rs2275913 polymorphism was found to be significantly associated with the risk of gastric cancer but not with hepatocellular carcinoma or colorectal cancer [29]. Furthermore, Lu Y *et al.* addressed the IL-17 gene polymorphism and cancer controversy, they reported the positive association of IL-17A with an increased risk of numerous cancers, such as gastric cancer, cervical cancer, breast cancer, and ovarian cancer [30]. Interestingly, current evidence suggests that 197A allele of IL-17A rs2275913 when stimulated from peripheral blood mononuclear cells of healthy individuals in vitro transcribed higher levels of mRNA, also, significantly more IL-17 protein was produced in comparison to those not having the 197A allele. Moreover, higher luciferase activity was reported with the 197A allele than the 197G allele of IL-17A rs2275913 [31]. Meanwhile, Yi Quan *et al*. reported that IL17A had significantly increased peripheral blood and tissues levels from a variety of cancer patients. Conjointly, the overexpression of IL-17 was associated with increased malignancy [32-33]. Therefore, in the present case-control study, we investigated the potential influence of three IL-17A polymorphisms on the risk of LC, BC and CC in a Moroccan population. In fact, we evaluated three SNPs (rs8193036, rs2275913, rs3819024) whose MAFs were all >5 % and were within the ranges reported in African populations (HapMap database). We compared the allele frequencies and genotype frequencies under dominant and recessive inheritance models between LC, BC, CC and the control group.

In the analysis of IL-17A rs8193036 (Table 1), our data showed that the frequencies of rs3819024 CC homozygote and C allele were significantly higher in lung cancer patients than in controls. Individuals carrying the C allele had a significantly increased risk of lung cancer (32.92 vs. 25.32 %, P = 0.05, OR: 1.44, 95 % CI= 0.99-2.10). Additionally, the association between rs8193036 and LC risk remained significant under the recessive model CC vs. CT+TT (OR = 2.49, 95% CI = 1.12 to 5.52; P=0.02) as shown in (Table 2). Our findings demonstrate a protective role for BC under the dominant model CC+CT *vs.* TT (OR: 0.60, 95% CI: 0.34-1.06, P=0.07). Notwithstanding, Slattery ML *et al*. revealed in one study that carriers with the rs8193036 CC genotype had higher breast cancer mortality [34]. Further, no significant association between rs8193036 of IL-17A gene polymorphism and risk of colorectal cancer was observed. While no studies were found regarding rs8193036 for its association with cancer risk, a few studies have investigated the role of IL-17 rs3819024 in cancers occurrence. Fei Zhou *et al*. reported that a decreased gastric cancer risk was independently associated with rs3819024 [35]. Another study also showed, that women with an A allele of rs3819024 were at reduced risk of breast cancer if they consumed a diet high in folate [34]. In addition, Ren et al. provides evidence that the functional polymorphism IL17A rs3819024 A>G may be involved in the risk of gastric cardia adenocarcinoma [36]. It is interesting to note that the SNP in IL-17A (rs2275913), which was not significant in this study, was strongly associated with cancer colorectal risk in a recent report in a Middle Eastern population [37]. In addition, Omrane I *et al.* showed that IL17A GG genotype could protect against colon cancer unlike AA genotype that could further the susceptibility of colon cancer in a Tunisian cohort [38]. A Chinese study revealed that rs2275913 enhanced the risk of lung cancer and is correlated with subtypes of clinical pathology and tobacco smoking status. Moreover, they suggested that SNPs of IL-17A may play a critical role for predicting the risk of lung cancer [24]. Recently, Zhou F *et al*. demonstrated that the rs2275913 (GA + AA) genotypes were independently associated with an increased gastric cancer risk in a dominant genetic model [35]. Lastly, Wang *et al*. established that IL17A rs2275913 polymorphism is highly correlated with occurrence and progression of breast cancer taking into consideration tumor suppressor protein 53 (P53) and progesterone receptor (PR) status [39].

4. Conclusions

Throughout the years, conflicting reports have arisen from IL-17's role in cancer risk and metastasis. Lessons are learned and paradigms are changing, IL-17 and its role in cancer pathophysiology do offer impressive new options for potential therapeutic and diagnostic targets, which in time will hopefully unfold into novel therapies in the battle against cancer. Our findings provide evidence that the functional polymorphism IL17A rs8193036 contribute to the risk of lung cancer. In contrast, the same SNP demonstrates in our study a protective role for breast cancer. With assumptions still divided on IL-17, it clearly demonstrates a need for more investigation in this area. Our study was a preliminary investigation and future larger studies with more rigorous study designs of other ethnic populations are required to confirm the current findings.

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Conflicts of interest/Competing interests

The authors declare that the research was conducted in the absence of any competing interests.

Ethics approval

All the study was approved by the local ethics committee of Hassan II University.

Consent to participate

A written consent was obtained from all participants.

Consent for publication

The contents and publication of the manuscript have been approved by all coauthors.

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