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ORIGINAL ARTICLE

Association of Genetic Variants in NF-kB with Susceptibility to Breast Cancer: a Case Control Study

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Abstract

Insofar as altered NF-κB signaling stemming from the presence of specific genetic variants in *NF-κB* gene contribute to cancer pathogenesis, this study evaluated the association between *NF-κB* rs147574894/I552V, rs148626207/M860T rs3774937 and rs1598859 variants and breast cancer and associated features and complications. This was a retrospective case-control study, which involved 207 women with breast cancer, and 214 cancer-free women who served as controls. *NF-κB* genotyping was done by real-time PCR. Significantly higher rs3774937 minor allele frequencies (MAF), and lower rs147574894 MAF were seen among breast cancer patients, thereby imparting disease susceptibility and protective nature to these variants, respectively. Significant association of rs3774937 and rs147574894 genotypes with breast cancer was seen under the dominant model. Histological type and grade, molecular type, Her2 positivity and ER+/Her2- correlated positively, while distant metastasis negatively correlated with rs3774937. On the other hand, rs147574894 negatively correlated with histological type and grade, tumor size, Her2 positivity, molecular type, and ER+/Her2-, while rs148626207 correlated positively with histological grade, but negatively with distant metastasis and triple-negative status. Breast cancer-susceptible and –protective 4-locus haplotypes were also identified. This is the first report that addresses the contribution of *NF-κB* variants to the pathogenesis of breast cancer in Middle Eastern-North African population, and the first to document positive association of rs3774937 with breast cancer.

Keywords Allele · Breast cancer · Haplotype · Metastasis · *NF-κB*

Abbreviations

CI	confidence intervals
HWE	Hardy–Weinberg equilibrium
MAF	minor allele frequency
NF-κB	Nuclear factor κB
OR	odds ratios

Introduction

Breast cancer is the leading cancer for women worldwide, and is the most frequent cancer among Arab women [1]. Breast cancer accounts about 30% of female cancers in Tunisia [2], with 1000 to 1500 new cases diagnosed per year [1, 2]. Due to its heterogeneous presentation, breast cancer is classified into distinct subtypes, which differ with respect to unique biology, survival outcome, and associated risk factors [3, 4]. The pathogenesis and overall prognosis of breast cancer is multifactorial, and results from interaction between modifiable (breastfeeding, oral contraceptive use), and non-modifiable (age, early menarche, late menopause, ethnicity, and genetic aberrations) factors [5, 6]. Insofar as inflammatory tumor environment modulates tumor promotion, cell proliferation and

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survival, and metastasis [7–9], specific inflammatory and immune response factors were described to serve a prognostic role in estimating overall and disease-free survival in breast cancer patients, irrespective of the treatment modality [7–10].

Nuclear factor κB (NF-κB) is a transcription factor, initially identified in the nuclei of mature B cells [11–13], and belongs to a family of transcription factors, which include NF-κB1 (p50/p101), NF-κB2 (p52/p100), RelA (P65), RelB, and c-Rel [14]. Members of *NF-κB* family interact with each other in exerting their effects in modulating downstream transcriptional activities as homo and/or heterodimers [13], of which the p50/p65 complex is the most significant. *NF-κB* activation is crucial for physiological and pathological processes, such as immunity, inflammation, stress responses, apoptosis, and tumorigenesis [13, 15]. *NF-κB* activation is triggered by an array of stimuli, and is central in the activation of intracellular signaling mechanisms [11, 13]. *NF-κB* is inhibited by binding its inhibitor, IκB, [16], and imbalance of NF-κB-IκB pathway is key to inflammation and dysregulated immunity, and cancer development and progression [11, 15], including breast cancer [17, 18]. In this regard, selective inhibition of NF-κB-activating pathway genes was demonstrated to sensitize breast cancer cell lines to doxorubicin [19]. While mutations of the *NF-κB* signaling pathway are not seen in solid tumors [15], a recent study documented the association of genetic variants of NF-κB1, the upstream kinase IKK2, and the IκBα and IκBε inhibitors with breast cancer [20].

Other (smaller) studies reported on the association of single nucleotide polymorphisms (SNP) in *NF-κB* gene with altered risk of breast cancer, often with inconclusive findings [8, 18]. Using a case-control study design, here we investigate the association between *NF-κB1* gene variants and the presence of breast cancer in Tunisian women. We also examined the contribution of possible modifying factors to the association of *NF-κB1* variants with breast cancer.

Subjects and Methods

Study Subjects

This was a retrospective case-control study, performed at the outpatient oncology service of Fattouma Bourguiba University Hospital (Monastir, Tunisia). Between February 2014 to March 2016, 207 women with breast cancer (mean age 49.7 ± 12.1 years), and 214 cancer-free university and hospital employees, or volunteer women (mean age 40.0 ± 9.8 years), who served as controls (Table 1). Breast cancer assessment was as per the guidelines of American Cancer Society (www.cancer.org), which included mammography and breast biopsy testing for confirmation of breast cancer; all cases had these procedures done. Blood samples were taken from study subjects in EDTA-containing tube for total genomic DNA extraction. The participants were interviewed using a structured questionnaire. The study was approved by the Ethics Committee of UCH Fattouma Bourguiba in Tunisia, and all participants and were required to sign an informed consent form before inclusion in the study.

Table 1 Characteristics of breast cancer cases and control women

		Cases	Controls	*P* [a]
Age at study entry		49.7 ± 12.1	40.0 ± 9.8	<0.001
Body mass index (kg/m^2)		28.7 ± 5.1	26.8 ± 4.9	<0.001
	<30 kg/m^2	136 (65.7) [b]	150 (70.8)	0.294
	30+ kg/m^2	71 (34.3)	62 (29.2)	
Menarche (yr)		12.5 ± 1.4	12.1 ± 1	0.003
Menopause status	Pre-	111 (53.6)	151 (70.6)	<0.001
	Post-	96 (46.4)	63 (29.4)	
Breast feeding		155 (74.9)	189 (88.3)	<0.001
Oral contraceptive use		53 (25.6)	32 (15.0)	0.007
Histology	Ductal	199 (96.1)		
	Lobular	8 (3.9)		
Cancer type	Sporadic	151 (72.9)		
	Familial	56 (27.1)		
ER/PR status	ER- PR-	60 (29.0)		
	ER+ PR-	39 (18.8)		
	ER+ PR+	108 (52.2)		
Hormone replacement therapy		90 (44.3)		
Surgery		135 (66.2)		
Radiotherapy		106 (52.2)		

[a] Student t-test (continuous variables), ANOVA (categorical variables)

[b] Number of subjects (percent total)

NF-κB1 Genotyping

We reviewed the existing literature, and selected two intragenic missense SNPs (rs147574894/I552V and rs148626207/M860 T) and two intron variants (rs3.774937 and rs1598859), based on their association with breast cancer. Genomic DNA was extracted from the peripheral venous blood of study participants using QIAamp DNA Blood Mini Kit (Qiagen, Inc., Manchester, UK). *NF-κB* genotyping was performed by VIC- and FAM-labelled allelic discrimination method using TaqMan assays, which were ordered as assay-on-demand from Applied Biosystems (Foster City, NJ). The reaction was performed on StepOne Plus real-time PCR system, according to manufacturer's instructions (Applied Biosystems). Replicate blinded duplicate samples were included to assess genotyping reproducibility and the duplication concordance was 100%.

Statistical Analysis

Statistical analysis was done using SPSS version 23 (IBM; Armonk, NY). Continuous and categorical variables were presented as means (± SD), were expressed as percent total. Differences in means were assessed by Student's *t*-test, and Pearson χ^2 test were used for assessing inter–group significance. Hardy–Weinberg equilibrium (HWE) was tested by Haploview (www.broad.mit.edu/mpg/haploview). Power calculation for detecting association between *NF-κB* variants and breast cancer was done using Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/cgi-bin/cc2k.cgi). The parameters used were 207 breast cancer patients and 214 control women, genotypic relative risk for heterozygote (1/2) and minor allele homozygous (2/2), and the MAF for breast cancer cases and controls for the tested SNPs, and assuming a 11.27 per 100,000 prevalence of breast cancer in Tunisia. Assuming these parameters, we calculated the overall power (72.2%) as the average power of the four tested SNPs.

Haploview was used to check linkage disequilibrium (LD) between SNPs, beside their haplotype patterns. *NF-κB* haplotypes was reconstructed by the expectation maximization algorithm. Of the theoretical 16 4-locus haplotypes, only 4 were found to be common (frequency > 2%), and thus were included in further analysis. Taking the control group as reference (OR = 1.00), logistic regression analysis was used for determination of the odds ratios (OR) and 95% confidence intervals (95%CI) associated with breast cancer risk. We controlled for the confounders age, BMI, menarche, menopause status, history of breast feeding, and previous use of oral contraceptives in multivariate logistic regression analysis. Statistical significance was set at $P < 0.05$.

Results

Study Subjects

The demographic and clinical characteristics of study participants are shown in Table 1. Mean age at inclusion of study ($P < 0.001$), BMI ($P < 0.001$), menarche ($P = 0.003$), menopause status ($P < 0.001$), history of breast feeding ($P < 0.001$), and previous use of oral contraceptives ($P = 0.007$) were significantly different between breast cancer cases and control women. Accordingly, these were selected as the main covariates that were controlled for in subsequent analysis. The majority of breast cancers had ductal histology (96.1%), was sporadic in nature (72.9%), and was ER- and PR-positive (52.1%). Breast cancer treatment consisted of combined hormone replacement therapy (CHRT; 44.3%), surgery (66.2%), and radiotherapy (52.2%).

Association Studies

Table 2 summarizes the association between *NF-κB* variants and breast cancer among case-control subjects. Genotype distribution of rs1598859, rs147574894 and rs148626207, but not rs3774937 ($P = 0.044$), were in HWE among study subjects. Minor allele frequencies (MAF) of rs3774937 ($P = 0.012$) was higher, while MAF of rs147574894 was lower ($P = 0.021$) among breast cancer patients than control women, thereby imparting disease susceptibility [OR (95% CI) = 1.49 (1.09–2.03)] and protective [OR (95% CI) = 0.11 (0.01–0.89)] nature to these variants, respectively.

Table 3 summarizes the results of the association analyses between breast cancer and *NF-κB* genotypes under the additive, dominant and recessive genetic models. A significant association of rs3774937 ($P = 0.023$, OR [95% CI] = 1.57 [1.06–2.32]) and rs147574894 ($P = 0.041$, OR [95% CI] = 0.15 [0.02–1.32]) with breast cancer was seen under the dominant model only. None of the tested *NF-κB* SNPs were associated with altered breast cancer under the additive or recessive genetic models.

Influence of *NF-κB* SNPs on Breast Cancer Parameters

We investigated the possible association of *NF-κB* SNPs with relevant clinicopathological characteristics in patients with breast cancer. As detailed in Table 4, Histological type and grade, and molecular type, Her2 positivity and ER+/Her2- status were positively, while distant metastasis was negatively correlated with carriage of rs3774937. On the other hand, carriage of rs147574894 minor allele negatively correlated with histological type and grade, along with tumor size, Her2 positivity, molecular type, and ER+/Her2- status. Furthermore, carriage of rs148626207 minor allele was positively correlated with histological grade, but negatively correlated with distant metastasis and triple negative status.

Table 2 Risk of breast cancer associated with *NF-κB* SNPs

SNP	Region	Position	Alleles	HWE	MAF cases	MAF controls	*P*	χ2	OR (95% CI)
rs3774937	Intron	102,513,096	T:C	0.044	0.29	0.22	0.012	6.21	1.49 (1.09–2.03)
rs1598859	Intron	102,585,287	T:C	0.14	0.30	0.29	0.538	0.37	1.10 (0.82–1.48)
rs147574894	Coding: V552I	102,600,911	A:G	0.21	0.005	0.02	0.021	6.21	0.11 (0.01–0.89)
rs148626207	Coding: T860 M	102,612,593	T:C	1.00	0.002	0.01	0.118	2.83	5.22 (0.61–44.87)

Table 3 Effects of *NF-κB* SNP genotypes on the risk of breast cancer according to different genetic models

		Genotype Distribution		Additive Model		Dominant Model		Recessive Model	
		Cases	Controls	*P* [a]	OR (5% CI)	*P* [a]	OR (5% CI)	*P* [a]	OR (5% CI)
rs3774937	T/T	26 (12.6)	18 (8.4)	0.067	1.00 (Reference)	T/T vs. T/C + C/C		T/T + T/C vs. C/C	
	T/C	70 (33.8)	58 (27.1)		1.50 (0.98–2.30)	**0.023**	**1.57 (1.06–2.32)**	0.16	1.56 (0.83–2.95)
	C/C	111 (53.6)	138 (64.5)		1.80 (0.94–3.44)				
rs1598859	T/T	105 (50.7)	118 (55.1)	0.56	1.00 (Reference)	T/T vs. T/C + C/C		T/T + T/C vs. C/C	
	T/C	78 (37.7)	70 (32.7)		1.25 (0.83–1.90)	0.36	1.19 (0.81–1.75)	0.86	0.95 (0.53–1.71)
	C/C	26 (12.2)	24 (11.6)		1.04 (0.56–1.92)				
rs147574894	A/A	206 (99.5)	205 (96.7)	0.11	1.00 (Reference)	A/A vs. A/G + G/G		A/A + A/G vs. G/G	
	A/G	1 (0.5)	5 (2.4)		0.17 (0.02–1.56)	**0.041**	**0.15 (0.02–1.32)**	0.29	0.00 (0.00 – NA)
	G/G	0 (0.0)	2 (0.9)		0.00 (0.00 – NA)				
rs148626207	T/T	202 (97.6)	213 (99.5)	0.079	1.00 (Reference)				
	T/C	5 (2.4)	1 (0.5)		5.27 (0.61–45.52)				

Boldface indicates statistically significant differences

[a] Adjusted *P* value; BMI, menarche, menopausal status, breast feeding, and previous use of oral contraceptives being the variables that were controlled for

Haploview Analysis

Next, we evaluated the interaction between the tested *NF-κB* SNPs and their mode of inheritance by analyzing 4-locus haplotype distribution in breast cancer cases and control women. *NF-κB* haplotypes containing rs3774937, rs1598859, rs147574894 and rs148626207 were constructed based on the prevalence of individual SNPs and LD between them. We defined "common haplotype" as those with frequencies >2% of the total haplotypes. Accordingly, only 4 of the theoretical 16 haplotypes were found to be common, capturing 98.2% of the haplotype pool. Reduced frequency of haplotype TTAT ($P = 1.2 \times 10^{-3}$), and increased frequency of haplotypes TCAT ($P = 0.03$), and CTAT ($P = 1.0 \times 10^{-4}$) was seen in breast cancer cases compared to control women. Of these, only TTAT ($P = 1.5 \times 10^{-3}$) and CTAT ($P = 2.0 \times 10^{-4}$) after adjusting for age, BMI, menarche, menopause status, history of breast feeding, and previous use of oral contraceptives, thereby conferring disease protection and susceptibility nature to these haplotypes, respectively (Table 5).

Discussion

Insofar as variations within the *NF-κB* gene (*NFKB1*), and inhibitory protein (*NFKBIA*) modulate the NF-κB function, thus facilitating tumor development, and as variation in *NFKB1* (and *NFKBIA*) control the levels of both factors, this study examined the association of four variants in *NF-κB* with breast cancer. Of the four selected *NF-κB* SNPs, rs3774937 is more common in women with breast cancer, while rs147574894 (I552V) was present at lower frequencies when compared to healthy women. Furthermore, rs34945627 minor allele was associated with worse breast cancer prognosis, namely histology, molecular type and Her2 positivity, while carriage of rs147574894 was linked with favorable disease prognosis. This is the first report

Table 4 Correlation between *NF-κB* variants and clinical parameters

	rs3774937		rs1598859		rs147574894		rs148626207	
Parameter	r	*P*	r	*P*	r	*P*	r	*P*
Histological type	**0.119**	**0.015**	0.047	0.340	**−0.102**	**0.036**	0.077	0.113
Histological grade	**0.099**	**0.043**	0.046	0.346	**−0.099**	**0.042**	**0.111**	**0.022**
Tumor size	0.080	0.100	0.055	0.261	**−0.103**	**0.035**	0.048	0.323
Distant metastasis	**−0.101**	**0.039**	−0.042	0.389	0.092	0.060	**−0.133**	**0.006**
ER-PR status	0.093	0.058	0.069	0.156	−0.088	0.070	0.064	0.187
Her2 positive	**0.101**	**0.037**	0.022	0.656	**−0.102**	**0.036**	0.090	0.066
Molecular type	**0.124**	**0.011**	0.015	0.761	**−0.104**	**0.034**	0.069	0.158
ER+ / Her2-negative	**0.119**	**0.015**	0.012	0.808	**−0.104**	**0.032**	0.069	0.155
Triple negativity	−0.086	0.079	−0.050	0.303	0.095	0.051	**−0.098**	**0.043**

Boldface indicates statistically significant differences

Table 5 4-Locus Haplotype distribution in breast cancer patients and control women

Haplotype	Frequency	Patients	Controls	*P*	OR (95% CI)	*aP*	aOR (95% CI)
T T A T	0.649	0.594	0.700		1.00 (REFERENCE)		1.00 (REFERENCE)
C C A T	0.201	0.192	0.208	0.74	1.06 (0.76–1.47)	0.85	1.04 (0.72–1.49)
T **C** A T	0.082	0.104	0.064	0.03	1.72 (1.06–2.81)	0.12	1.53 (0.90–2.62)
C T A T	0.050	0.096	0.008	1.0×10^{-4}	10.40 (3.18–33.98)	2.0×10^{-4}	11.05 (3.14–38.87)

aP = Adjusted *P* value; BMI, menarche, menopausal status, breast feeding, and previous use of oral contraceptives being the variables that were controlled for

that addresses the association of these four *NF-κB* variants with breast cancer in a Middle Eastern-North African population, and the first to document the positive association of the intronic variant, rs3774937, with breast cancer.

NF-κB is a member of transcription factor family, consisting of five heterodimeric transcription factors [13], which regulate the transcription of genes involved in inflammation, cell proliferation, anti-apoptosis/pro-survival, angiogenesis, and metalloproteinase production [12, 16], and is central to the proliferation of the mammary epithelium [21, 22]. Based on its well documented role in modulating oncogenic events, such as proliferation and metastasis [17, 23], and apoptosis [13, 15], a role for *NF-κB* in the initiation and progression of breast cancer was suggested [17, 24]. While previous studies confirmed an association of breast cancer with genetic variations in genes in *NF-κB* pathway [8, 24, 25], the contribution of *NF-κB* gene variants to the risk of breast cancer yielded often inconsistent findings [8, 9, 18]. While not the scope of the current study, this is likely attributed to the fact that the association of *NF-κB* pathway with the progression of breast cancer, and overall patient survival, result from epistatic interactions of multiple loci, more so than single locus effects.

MAF of rs3774937 (0.25) and rs1598859 (0.29) established for (control) healthy Tunisians were intermediate between the frequencies of Europeans and Africans, but were lower than the frequencies of Asians (www.ncbi.nlm.nih.gov/projects/SNP/snp). On the other hand, the low MAF established for rs147574894 (I552V) and rs148626207 (M860 T) is consistent with the low frequencies of both variants among Caucasian and non-Caucasian populations. Collectively, this reflects the genetic makeup of present Tunisians, which is admixture of ancestral Africans and later Europeans.

Our results showed that the missense variant rs147574894 (I5521V) was negatively associated with breast cancer, notably with regard to histological type and grade, tumor size, and receptor positivity. As rs147574894 alters the association of *NF-κB* with FXR, HNF4, and Hdx transcription factors, and FXR activation plays a crucial role in reducing the proliferation of breast cancer cell [26, 27], particularly in postmenopausal women [6], this may explain the apparent favorable effect of I552V on overall breast cancer outcome. Given the low frequency of the I552V among cases and controls, these results should be evaluated with caution. Larger study group on well-defined breast cancer phenotypes are needed to confirm, or alternatively rule out the contribution of this variant to breast cancer risk.

On the other hand, the intronic rs1598859 variant, while not associated with altered risk of breast cancer individually, it appears to exert an interactive/modifying effect on the rs3774937 variant. This was evident by the loss of rs3774937 effect when rs1598859 minor allele was present in the 4-locus haplotype. Given the relatively small sample size and study design, these results can be considered preliminary, and thus require validation using larger prospective studies, which will confirm or alternatively rule out any possible interaction between these two intronic variants in dictating overall risk of breast cancer.

While the biology behind the effect of NF-κB, and SNP-SNP interaction between these variants within a haplotype is speculative at this stage, it is likely that *NF-κB* SNPs may influence gene expression, in particular those involved with cell survival and inflammation-associated carcinogenesis [15]. In addition, the carriage of the *NF-κB* SNP may influence breast cancer risk by altering *NF-κB* binding to its target, including Erα and elements of the signaling cascade.

Our results show that allelic variants in *NFKB1* gene influence the outcome of breast cancer. Since Her2/ER status, triple negative status, or other (hormonal) determines breast cancer metastatic potential (4,28), patient subgroups analysis demonstrated mixed association of rs3774937 and rs147574894 (I552V) with breast cancer phenotype and outcome. Given the limited number of cases in the patient subgroups, especially for I552V carriers, these results should be interpreted with caution. Given its case-control design, our study could not address an important, yet difficult challenge, namely the association of the different variants of *NFKB1* with tumor progression from primary to metastases. Despite this shortcoming, our results underscore the diagnostic and likely prognostic utility of *NF-κB* genotype analysis in breast cancer.

Our study has several strengths. The study population is ethnically homogeneous (only Tunisian Arab women), and the controls are representative carry the same risk of environmental exposure of breast cancer, thereby minimizing the problems of differences in genetic background inherent in gene association studies, and that potential covariates were controlled for. Further, MAF of the four tested SNPs is consistent with those established

for related populations, and the association studies were done at the allele and haplotype levels, thus strengthening the conclusions derived from this study. However, there were some limitations that necessitated caution in the interpretation of results, notably the relatively small sample size, which was not sufficient to capture the true level of association between *NF-κB* variants with breast cancer risk and associated features. Also, only 4 SNPs were analyzed, thus raising the possibility of missing important associations between other *NF-κB* variants with overall breast cancer risk. Furthermore, while study subjects were restricting to Tunisian Arab women using self-declared ethnic origin, the possibility of admixture as confounder remains unanswered. Despite these shortcomings, results of this study suggest association between the risk of breast cancer and SNPs in *NF-κB* gene. Further studies are warranted that examine this association.

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SM Sample processing and drafting the article.
SZ Patient screening and referral.
HB Patient screening and referral.
WB analysis and interpretation of data.
TM drafting the article.
WYA Project leader and guarantor for the article.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest to declare.

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