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NRF2 AND P73 POLYMORPHISMS IN EGYPTIAN WOMEN WITH BREAST CANCER

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ABSTRACT

The aim of the study was to assess the role of Nrf2 promoter and P73 G4C14 to A4T14 polymorphisms in breast cancer and the potential relation to the onset of the disease. Eighty six female patients with breast tumor were included in this study. Nrf2 (rs6721961) and p73 (G4A) genetic polymorphisms in promoter and exon2 region respectively were investigated using PCR-CTPP assay. The genotype frequencies of the three genotypes of Nrf2 promoter SNP (CC, CA, AA) showed no significant difference between benign and malignant groups. Genotype frequencies for P73 G4A SNP (GG, GA) showed no significant difference between benign and malignant groups, no patient have the AA genotype. Regarding the onset of disease, the three Nrf2 genotypes in pre - and post-menopausal patients, showed that the distribution differ significantly in the 2 patients groups and that the AA genotype is significantly higher in the pre-menopausal patients compared to post-menopausal patients. Nrf2 (rs6721961) AA genotype might be related to early breast cancer onset. P73 G4A polymorphism shows no relation to both disease risk and disease onset. Therefore Nrf2 (rs6721961) promoter genotyping might be related to the risk of pre-menopausal breast cancer.

Key words: Breast cancer, Polymorphisms, Nrf2, P73.

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INTRODUCTION

Breast cancer is the second cancer in mortality affecting mostly females. It is the most frequent malignancy with high morbidity and mortality among women worldwide **(Gomes et al., 2012)**. It accounts for 22.9% of all female cancers worldwide **(Ferlay et al., 2010)**. Mortality in breast cancer patients is mostly caused by metastasis which is related to poor prognosis of breast cancer patients **(Fang et al., 2013)**. In Egypt, breast cancer is the commonest type of cancer in females as it represent (38.8%) of all female cancers (**Ibrahim et al., 2014**). Pathogenesis and progression of breast cancer are multifactorial processes affected by genetic, biological, and environmental factors, as well as lifestyle **(Porter, 2009)**.

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (hER-2) are the most important prognostic and predictive markers in breast cancer. Triple-negative breast cancer (TN), does not express ER, PR or hER-2. TN breast cancer cases are about 15–26% of all breast cancer cases. Women with TN breast cancer usually show poor prognosis. TN breast cancer is more likely to be aggressive and lead to visceral metastasis (**Pal et al., 2011**).

Nuclear factor erythroid 2-related factor 2 (Nrf2) functions mainly by activating the cellular antioxidant response through induction a wide range of genes transcription that combat the harmful effects of xenobiotics and oxidative stress. Nrf2 is constantly degraded by KEAP1, a negative regulator of Nrf2, via the ubiquitin–proteasome pathway under normal conditions. However, upon exposure to stimuli that inactivate KEAP1, stabilized Nrf2 accumulates in the nucleus and induces various cytoprotective genes **(Onodera et al., 2014)**. Activation of Nrf2 defense response has been shown to protect against neurodegenerative diseases, aging, diabetes, photo-oxidative stress, cardiovascular disease, pulmonary fibrosis and cancer **(Zhang 2006; Kensler et al., 2007; Lau et al., 2008)**. However, accumulation of Nrf2 in cancer cells has been shown to create an environment helpful for cell growth and protects against oxidative stress, chemotherapeutic agents, and radiotherapy **(Lau et al., 2008; Wang et al., 2008; Jaramillo and Zhang 2013)**. An association between nuclear Nrf2 accumulation and adverse outcome of the patients has been reported in the lung **(Solis et al., 2010; Inoue**

et al., 2012), gallbladder **(Wang et al., 2010)**, ovarian **(Konstantinopoulos et al., 2011),** and breast **(Onodera et al., 2014)** carcinomas. These findings suggest that Nrf2 is possibly involved in the growth and/or progression of these carcinomas. Many single nucleotide polymorphisms (SNP) have been identified in the Nrf2 gene. The promoter SNPs rs35652124 (A→G) and rs6721961 (C→A) were found to reduce the transcription activity of Nrf-2, decreasing Nrf-2-dependent gene transcription **(Shimoyama et al., 2014)**.

P73, which is a member of P53 family of transcription factors, has become one of the most wide studied proteins. P73 has similar cellular activities to those of P53, including binding and transactivation of P53-responsive genes and induction of apoptosis and cell cycle arrest, wherefore; P73 has tumor-suppressive activities (**Dötsch et al., 2010**). Also P73 plays unique roles in neuronal development and differentiation, metabolic control, and spermatogenesis and maintenance of male fertility **(Dötsch et al., 2010; Cutruzzola et al., 2014; Inoue et al., 2014)**. P73 have several isoforms with different actions. Several SNPs of P73 were found to be related to cancer and could help in predicting cancer risk and chemotherapeutic outcome **(Chen et al., 2009)**. P73 SNPs include G4C14-to-A4T14 which is a functional dinucleotide polymorphism at positions 4 (G→A) and 14 of the 50-untranslated region (50-UTR) of exon 2 of the P73 gene (C→T) (G4C14-to-A4T14, simply designed as G4A hereafter) **(Galli et al., 2009; Lee et al., 2010).**

This study aimed to assess the role of Nrf-2 promoter and P73 G4C14-to-A4T14 polymorphisms in breast cancer and their potential relation to the onset of the disease.

MATERIALS AND METHODS

This study included 86 female patients with breast tumors. They were admitted at the Department of Surgery in National Cancer Institute (NCI), Cairo University. They were divided into two sub-groups, first group includes 42 patients with malignant breast tumors, their age ranged from 28 to 78 (49.77±12.84), and 44 age matched patients with benign breast tumors. Regarding the disease onset, 22 of patients with breast cancer develop the disease at post-menopausal age, while 20 of them developed it at pre-menopausal age. Written

informed consent was obtained from all participants involved in our study.

Five ml blood sample was collected for DNA extraction. ER, PR and hER-2 were detected by immunohistostaining on 10% formalin-fixed paraffin embedded blocks for each patient following standard protocol of NCI. DNA extraction was done by commercially available kit (KAPA Express Extract kit, cat. KK 7101, USA). Genotyping was performed using (PCR-CTPP) PCR with confronting 2 -pair primers assay (**Hamajima et al., 2000)** using KAPA2G fast PCR kit (KAPA2G Fast PCR kit, cat. # KK 5008, USA) following the manufacturer instructions with some modification (increasing primer volume from 1.25 µl to 1.5µl /each primer/25µl reaction).

1- Nrf2 promoter polymorphism: The genotyping of Nrf2 (rs6721961) was performed using confronting pairs of primers **(Shimoyama et al., 2014)** as shown below:

Forward primer 1: CCCTGATTTGGAGGTGCAGAACC
Forward primer 2: GGGGAGATGTGGACAGCG
Reverse primer 1: GCGAACACGAGCTGCCGGA
Reverse primer 2: CTCCGTTTGCCTTTGACGAC

Region containing the polymorphism of Nrf2 was amplified by PCR with those primers with the initial denature at 95°C for 10 min followed by 30 cycles at 95°C for 1 min, at 58°C for 1 min, at 72°C for 1 min and a final extension step at 72°C for 5 min. PCR products were visualized on a 2% agarose gel with ethidium bromide staining. Genotyping was performed as follows; 282, 113 bp for CC genotype, 282, 205, 113 bp for CA genotype, and 282, 205 bp for AA genotype.

2- P73 exon 2 G4A polymorphism: The genotyping of P73 G4A polymorphism was performed using confronting pairs of primers **(Lee et al., 2010)** as shown below:

Forward primer 1: CCACGGATGGGTCTGATCC
Forward primer 2: CCTTCCTTCCTGCAGAGCG
Reverse primer 1: GGCCTCCAAGGGCAGCTT
Reverse primer 2: TTAGCCCAGCGAAGGTGG

For amplification, an initial denaturation step at 95°C for 10 min was followed by 35 cycles of 95°C for 1 min, 62°C for 45 seconds, and 72°C for 1 min, and a final extension step at 72°C for 5 min. The amplified DNA was visualized on a 2% agarose gel with ethidium bromide staining. The P73 G4A polymorphism was

genotyped as a 193 base pair band for the G allele, a 270 base pair band for the A allele, and a 428 base pair common band.

Statistical analysis: Data were assessed with Graph Pad prism software. Z- test and Fisher exact test were used to calculate the significance between genotype distributions in different studied groups. *P* value less than 0.05 was considered statistically significant.

RESULTS

The genotype frequencies of Nrf2 promoter SNP were 34.2% and 37.9% for AA in benign and malignant groups respectively, 43.9% and 40.5% for CC in benign and malignant groups respectively, 21.9 % and 21.6% for CA in benign and malignant groups respectively (Table 1 & Figure 1).

Genotype frequencies for P73 G4A SNP were 52.94% and 44.73% for GA in benign and malignant groups respectively, 47.06% and 55.26% for GG in benign and malignant group respectively. AA genotype was not found in any case (Table 1 & Figure 2).

Table 1: Nrf2 and P73 genotype distribution in benign and malignant breast cancer patients.

Gene	**SNP**	**Genotype**	**Benign patients** (%)	**Malignant patients** (%)	***P-value***
Nrf2	rs6721961	AA CA CC	34 22 44	38 21 41	> 0.05
P73	G4A	GA GG	53 47	45 55	> 0.05

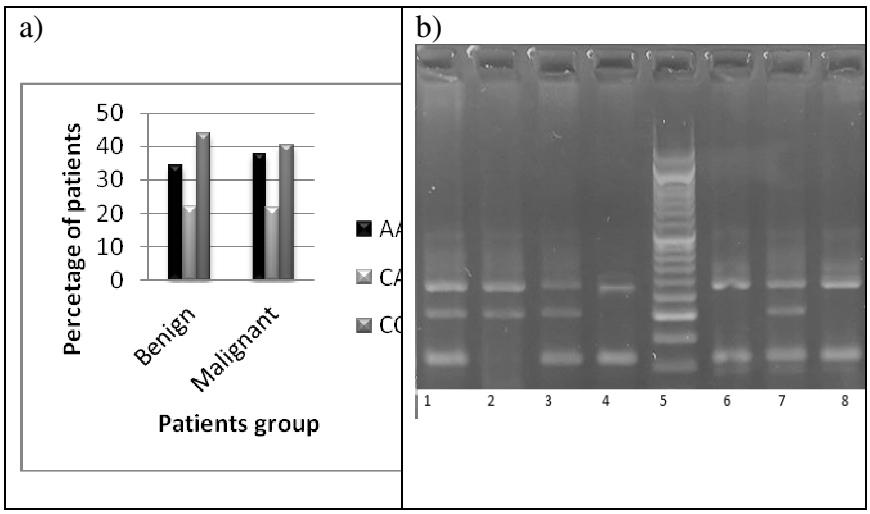

***Figure 1*: (a)** Nrf2 promoter genotype distribution among patients with benign and malignant breast tumors. **(b)** Gel showing genotype for promoter SNP of Nrf2 gene. Lanes (left to right) 1, 3, 7 CA genotype (282, 205, 113 bp), lane 2 AA genotype (205,282 bp) and lanes 4, 6, 8 CC genotype (282, 113 bp), lane 5(DNA ladder).

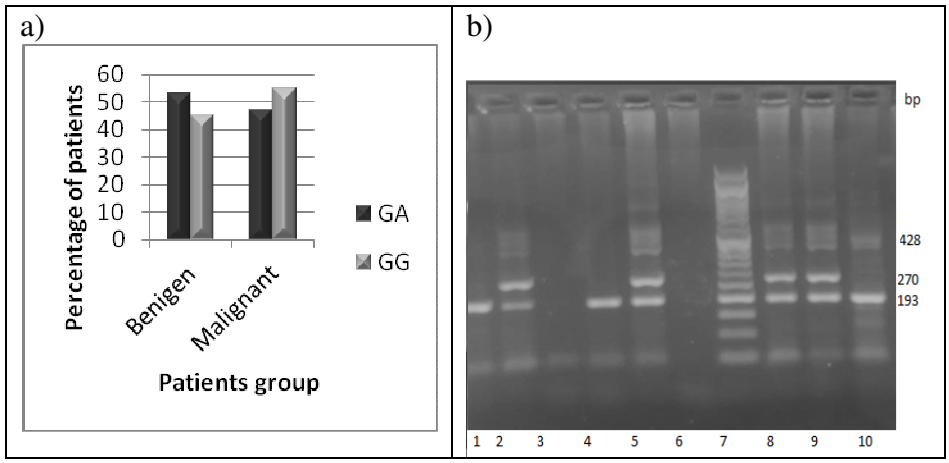

Figure 2: **(a)** P73 G4A genotype distribution among patients with benign and malignant breast tumors. **(b)** Gel showing genotype for G4C14-to-A4T14 SNP of P73 gene. Lanes (left to right) 2, 5, 8, 9 GA genotype (428, 270, 193 bp), lanes1, 4, 10 GG genotype (428, 193 bp), lane 7(DNA ladder).

Regarding the disease onset, the three Nrf2 genotypes in pre - and post-menopausal patients, showed that the distribution differ significantly in the 2 patients groups ($p < 0.05$). Nrf2 rs6721961 SNP shows different genotype distribution between pre- and post-menopausal breast cancer patients. CA genotype is significantly higher in post-menopausal patients compared to pre-menopausal patients ($p < 0.05$). It is also noted that the frequency of AA genotype is significantly lower in post-menopausal breast cancer cases compared to the C allele carrier genotypes (CC & CA) ($P< 0.05$). On the other hand, the genotype AA is not significantly related to premenopausal cases when compared with genotypes CA & CC (Figure 3). The genotype AA is significantly higher in premenopausal than in postmenopausal cases ($P< 0.05$) (Table 2).

P73 G4A SNP showed no significant difference in genotype frequencies or distribution in pre- and post-menopausal breast cancer patients (Table 2).

Table 2: Nrf2 and P73 genotype distribution in post and pre-menopausal with malignant breast cancer patients.

Gene	**SNP**	**Genotype**	**Post-menopausal patients** (%)	**Pre-menopausal patients** (%)	***P-value***
Nrf2	rs6721961	CC CA AA	41 41 18	40 5 55	< 0.05
P73	G4A	GG GA	50 50	58 42	> 0.05

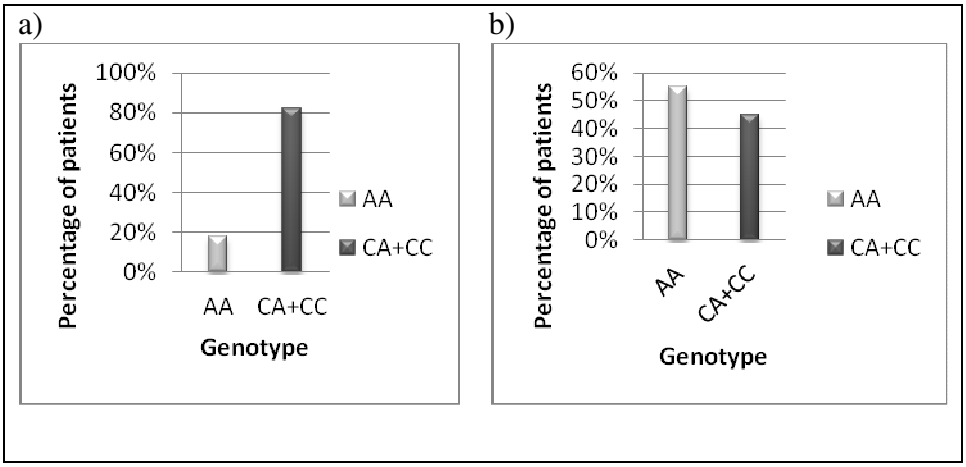

Figure 3: Genotype distribution of Nrf2 rs6721961 SNP in: **(a)** Post-menopausal patients with malignant breast tumor. **(b)** Pre-menopausal patients with malignant breast tumor.

Among patients with malignant breast tumor there were 76.2% positive to both ER and PR and 23.8% negative for both receptors. Only 19% of these patients were positive to hER-2. None of the three receptors show a significant relation with the genotype distribution. Regarding triple negative breast cancer patients, they were all of homozygous Nrf2 genotype (50% were CC, 50% were AA). The heterozygous genotype (CA) is absent in this group. TN group showed marked (although statistically non-significant due to small group number) predominance of the heterozygous genotype of P73 G4A (80% were GA).

DISCUSSION

Breast cancer is one of the most malignant threats against women worldwide. Patient phenotype is closely associated with tumor behaviour, progression and treatment response **(von Minkwitz et al., 2011).**

Among women in Egypt, breast cancer is a challenging health problem coming on top of all malignancies with poor outcome compared to international figures **(Ferlay et al., 2010).** Many studies showed that age at diagnosis of breast cancer in Arab countries is a

decade younger than that in Western countries (**El Saghir et al., 2006; El Saghir et al., 2007**).

Defective Nrf2 signaling pathway may increase cancer susceptibility. Targeting Nrf2 is shown to effectively enhance chemotherapeutic agent in suppression of tumor growth in several animal models (**Manandhar et al., 2012)**. Genetic polymorphisms of Nrf2 on several SNPs (including rs6721961) were associated with breast cancer risk (**Hartikainen et al., 2012**).

In the current study, Nrf2 rs6721961 genotype CC was found in more than 40% of studied patients with benign or malignant breast tumours. Different ethnicities might have different genotype distribution, for example, **Shimoyama et al. (2014)** reported that CC is the least common Nrf2 rs6721961 genotype in Japanese people in general. Nrf2 promoter rs6721961 (C→A) polymorphism was found to reduce the transcription activity of Nrf2, possibly resulting in decreased Nrf2-dependent gene transcription. This promoter polymorphism was shown to have functional significance affecting basal Nrf2 expression and function (**Marzec et al., 2007**). Nrf2 gene transcription activity was significantly high in rs6721961 C wild-type compared to rs6721961 A variant. Decreased Nrf2 transcription is shown to be related to some types of cancer, and Nrf2 inducers show cancer preventive effect **(Mitsuishi et al., 2012).** Thus, the presence of the homozygous A allele genotype might explain the occurrence of breast cancer earlier (premenopausal) in the Nrf2 rs6721961 AA patients in the current study. The CA genotype was significantly higher in postmenopausal patients with malignant breast tumors suggesting that the heterozygous genotype might be related to delayed disease onset. However, this point requires further investigation.

In the current study, TN patients were all homozygous to Nrf-2 (50% were CC, 50% were AA). The heterozygous genotype is absent in this group.

Two SNPs at position 4 (G to A) and 14 (C to T) in P73 gene have been identified, the two polymorphisms are in complete linkage disequilibrium with one another. There are several studies indicating that subjects with the A allele variants may have an increased risk of certain types of cancer. Functional analysis implies that this common p73 polymorphism may contribute to cancer development and progression (**Li et al., 2007**). In the current study, no patient had the

AA genotype, which is the least common genotype in P73 G4A polymorphisms **(Li et al., 2007).**

The current study results showed no statistically significant difference in P73 G4A between malignant and benign breast tumor patients groups. This suggests that the A allele might be not related to breast cancer risk. **Liu et al., (2014)** found that A allele isn't related to gastric cancer risk. Further study is required to assess a potential effect of ethnicity on P73 G4A relation to breast cancer risk in Egyptians. **Wang et al. (2012)** reported such effect in Caucasians.

TN group shows marked (although statistically non-significant due to small group number) predominance of the A allele carriers genotype of P73 G4A (80% were GA). While **Hu et al. (2011)** reported that GA genotype is related to most types of cancers in general**, Zhou and Wu (2012)** reported that the GG genotype is related to increased risk of TN breast cancer. This point requires further investigations.

In conclusion, Nrf2 (rs6721961) promoter genotyping might be related to the risk of the development of breast cancer in pre-menopausal age in Egyptian patients. P73 G4A SNP showed no relation to malignancy occurrence or onset in the same patients.

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الملخص العربى

التعدد الجيني للجين Nrf2 والجين P73 فى السيدات المصريات المصابات بسرطان الثدى

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الهدف من الدراسة هو تقييم دور التعدد الجينى للجين Nrf2 وللجين p73 في سرطان الثدي والعلاقة المحتملة لظهور المرض. اشتملت الدراسه على ستة وثمانين سيدة ممن يعانون من ورم الثدي. وتم تحديد الانماط الجينيه للجين Nrf2 (rs6721961) و الجين p73(G4A) باستخدام نوع معين من تفاعل البوليمراز المتسلسل. وكان الفارق في توزيع الانماط الجينية للجين Nrf2 الثلاثة (CC, CA, AA) غير ذي دلالة إحصائية بين مجموعتي الأورام الخبيثة والأورام الحميدة وكان توزيع الانماط الجينية للجين P73 G4A (GG, GA) غير ذي دلالة إحصائية بين مجموعتي الأورام الخبيثة والأورام الحميدة ولم يظهر النمط الجيني AA في اي مريضة . وفيما يتعلق ببداية ظهور المرض، اظهرت الانماط الجينية الثلاث للجين Nrf2 في مرحلة ما قبل وبعد انقطاع الطمث، اختلافا ذا دلالة احصائية في مجموعتي المرضى وأن النمط الجيني AA هو الاعلى في المرضى قبل انقطاع الطمث مقارنة مع المرضى في مرحلة ما بعد انقطاع الطمث . والنمط الجيني AA للجين Nrf2 (rs6721961) قد يكون ذا صلة بظهور سرطان الثدي المبكر. التعدد الجيني للجين P73(G4A) ليس له علاقة بخطورة المرض وبداية ظهور أعراض المرض. ولذلك قد يكون النمط الجينى للجين Nrf (rs6721961) مرتبطا بخطورة الإصابة بسرطان الثدي قبل انقطاع الطمث.