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# DNA repair gene polymorphisms and susceptibility to familial breast cancer in a group of patients from Campinas, Brazil

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**ABSTRACT.** Several studies have reported that the genes involved in DNA repair and in the maintenance of genome integrity play a crucial role in protecting against mutations that lead to cancer. Epidemiologic evidence has shown that the inheritance of genetic variants at one or more loci results in a reduced DNA repair capacity and in an increased risk of cancer. Polymorphisms have been identified in several DNA repair genes, such as *XRCC1*, *XPD*, *XRCC3*, and *RAD51*, but the influence of specific genetic variants on repair phenotype and cancer risk has not yet been clarified. This was a case-control study design with three case groups: 53 women with breast cancer and family history; 33 women with sporadic breast cancer; 175 women with no breast cancer but with family history. The control group included 120 women with no

 

breast cancer and no family history. The PCR-RFLP method was used to analyze the *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *XRCC3-Thr241Met*, and *RAD51-G135C* polymorphisms. No statistically significant differences were found between the case groups and the control group for any of the polymorphisms analyzed, and also between the breast cancer and family history group and the sporadic breast cancer group. Sample sizes of women with breast cancer, whether familial or sporadic, were insufficient to show any small true differences between the groups, but we have to consider that currently there is no clear consensus with respect to the association of these polymorphisms with breast cancer risk. Considering the data available, it can be conjectured that if there is any risk association between these single-nucleotide polymorphisms and breast cancer, this risk will probably be minimal. The greater the risk associated with cancer, the smaller the sample size required to demonstrate this association, and the data of different studies are usually, therefore, more concordant.

**Key words:** Breast cancer, *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *XRCC3-Thr241Met*, *RAD51-G135C*, Polymorphisms

## INTRODUCTION

Many environmental factors, such as radiation, diet and the use of endogenous or exogenous estrogens, have been associated with the risk of developing breast cancer. Recently, it has been suggested that polymorphic differences may lead to differences in susceptibility to cancer development. Several studies have reported that the genes involved in DNA repair and in the maintenance of genome integrity play a crucial role in providing protection against the mutations that lead to cancer (Bohr, 1995; Jiricny and Nystrom-Lahti, 2000). Epidemiologic evidence has shown that the inheritance of genetic variants at one or more loci results in reduced DNA repair capacity and an increase in the risk of cancer (Helzlsouer et al., 1996; Sturgis et al., 1999). Polymorphisms in several DNA repair genes have been identified, but the influence of specific genetic variants on phenotype repair and on the risk of developing cancer has not yet been clarified.

*BRCA1* and *BRCA2* are two well-known breast cancer-susceptibility genes and their mutations account for most of the known hereditary carcinomas. BRCA proteins form complexes with other proteins involved in DNA repair such as *RAD51*. A missense mutation in *RAD51* (Arg150Glu) has been described in Japanese patients with bilateral breast cancer (Kato et al., 2000). Further studies suggest that *RAD51* (135 C/G) is a clinically significant modifier that raises breast cancer risk within the set of hereditary breast cancers (Levy-Lahad et al., 2001).

*XRCC3*, *XRCC1* and *XPD* belong to another group of genes that are involved in DNA repair and some polymorphisms in these genes are associated with increased breast cancer risk

(Liu et al., 1998). The Thr241Met genotype substitution in *XRCC3* is a non-conservative change that does not reside in the ATP-binding domains, which are the only functional domains that have been identified in the protein. This polymorphism is therefore likely to play a role in modifying the risk of breast cancer.

The *XRCC1* gene (X-ray repair cross-complementing gene) plays a role in the base excision repair pathway and has a *BRCA1* C-terminal domain (BRCT) which is characteristic of proteins involved in cycle checkpoint functions and DNA damage. The base excision repair system is activated by ionizing radiation and by alkylating agents that cause DNA base damage and strand breaks. The Arg399Gln polymorphism resides in the C-terminal domain of *XRCC1* within a relatively non-conserved region between BRCT domains. These results suggest that this DNA repair gene (*XRCC1*), a codon 399 genotype, may influence breast cancer risk, perhaps by modifying the effects of different forms of environmental exposure.

The *XPD* gene is involved in the nucleotide-excision repair pathway. This protein repairs a wide range of structurally unrelated lesions, such as bulky adducts and thymidine dimers (Braithwaite et al., 1999). It has been reported that normal individuals with the *XPD* 751Gln variant form a higher number of DNA adducts than never-smoking individuals with the *XPD* 751Lys polymorphism (Matullo et al., 2001b). Therefore, these polymorphisms could also be involved in modifying susceptibility to carcinogenesis of the breast.

Breast cancer is the principal cause of death from cancer in women in Brazil as well as in most of the more developed countries. Furthermore, to our knowledge, the prevalence of these polymorphic DNA repair genes has not yet been established in the Brazilian population. Moreover, the possible association of these genotypic variants with breast cancer susceptibility has not yet been fully evaluated.

The aim of this study was to determine the frequency of *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *XRCC3-Thr241Met*, and *RAD51-G135C* in a sample of women in Campinas, Brazil, and to evaluate their association with breast cancer susceptibility, using a case-control study.

## MATERIAL AND METHODS

### Patient selection

Women were enrolled into four groups as follows: 53 women with breast cancer and family history of breast cancer; 33 women with sporadic breast carcinoma; 175 women with no breast cancer but with family history, and 120 women with no breast cancer and no family history. The last group served as the control group for this study. The women with breast cancer who were included in this study were receiving care at the Centro de Atenção Integral à Saúde da Mulher (CAISM), UNICAMP, Brazil. The criteria for inviting the women with a family history of breast cancer to participate in the study were: early onset (less than 35 years of age); bilateral carcinoma; more than three cases of breast cancer and more than one case of ovarian cancer in the family; more than two first-degree relatives involved, and male breast cancer. The women who did not have breast cancer were selected from volunteers among hospital personnel in the region of Campinas, and were classified according to family history of breast cancer. Those with more than three cases of breast cancer and more than one case of ovarian cancer in the family, or who had one or more first-degree relatives with breast cancer, or who had a

case of male breast cancer in the family, were considered to have a positive family history. The control group was made up of women who had no known cases of breast cancer in any relative, first-degree or otherwise.

## PCR-RFLP analysis

DNA was isolated from peripheral leukocytes obtained from the women. Polymerase chain reaction (PCR) followed by enzymatic digestion (RFLP) was used for genotyping the *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *XRCC3-Thr241Met*, and *RAD51-G135C* polymorphisms. All the PCR reactions were carried out in a total reaction volume of 50 µL containing nearly 100 ng genomic DNA, 1 U Taq polymerase in 1X PCR buffer, 1.5 mM $MgCl_2$, 0.2 mM dNTPs, and 0.20 µM of each primer. Thermal cycling conditions were as follows: initial denaturation step at 95°C for 3 min, 35 cycles of PCR consisting of 95°C for 30 s, 60°, 55°, 60°, and 53°C for 30 s for *XPD*, *XRCC1*, *XRCC3*, and *RAD51* genes, respectively, and 72°C for 30 s, followed by a final extension step at 72°C for 10 min.

The *XPD-Lys751Gln* polymorphism was determined using the following primers: sense, 5'-CTGCTCAGCCTGGAGCAGCTAGAATCAGAGGAGACGCTG-3'; anti-sense, 5'-AAGACCTTCTAGCACCACCG-3', resulting in a 161-bp PCR product. This was digested with *Pst*I restriction enzyme. The digestion resulted in 41- and 120-bp fragments corresponding to the *Gln751* allelic variant or a 161-bp fragment containing the *Lys751* allele.

The *XRCC1-Arg399Gln* polymorphism was determined using the following primers: sense, 5'-CAAGTACAGCCAGGTCCTAG-3'; antisense, 5'-CCTTCCCTCATCTGGAGTAC-3'. The 248-bp PCR product was digested with *Nci*I restriction enzyme. The *Arg399* allele was represented by fragments of 89 and 159 bp, and the *Gln399* allele (variant allele) was not digested.

The *XRCC3-Thr241Met* polymorphism was determined using the following primers: sense, 5'-GCCTGGTGGTCATCGACTC-3'; anti-sense, 5'-ACAGGGCTCTGGAAGGC ACTGCTCAGCTCACGCACC-3', resulting in a 136-bp PCR product. This was digested with *Nco*I restriction enzyme. The *Thr241* allele was represented by 39- and 97-bp fragments, and the *Met241* allele (variant allele) was not digested.

The *RAD51-G135C* polymorphism was determined using the following primers: sense, 5'-TGGGAACTGCAACTCATCTGG-3'; anti-sense, 5'-GCGCTCCTCTCTCCAGCA-3', resulting in a 157-bp PCR product. This was digested with *Mva*I restriction enzyme. The digestion resulted in 86- and 71-bp fragments corresponding to the *G135* allele, or a 161-bp fragment representing the *C135* allele (variant allele).

The PCR products were visualized by electrophoresis on 2% agarose gel, and the digestion products were visualized by electrophoresis on 3% agarose gel. PCR followed by enzymatic digestion was performed for genotyping the *XRCC1-Arg399Gln*, *RAD51-G135C*, *XPD-Lys751Gln*, and *XRCC3-Thr241Met* polymorphisms.

## Statistical analysis

Chi-square analysis ($\chi^2$ tests) was used to test the association between the genotypes and alleles in relation to the cases and controls. $P < 0.05$ was used as the criterion of significance. The odds ratio (OR) and their 95% confidence intervals (CI) were calculated to esti-

mate the strength of the association between polymorphism genotype alleles and cases and controls.

## RESULTS

No statistically significant differences were observed in the alleles or in the genotype frequencies of the *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *XRCC3-Thr241Met*, and *RAD51-G135C* gene polymorphisms between the control group and the women with breast cancer and family history of breast cancer (Table 1), between the control group and the women with sporadic breast cancer (Table 2), nor between the control group and the women with no breast cancer but with a family history of breast cancer (Table 3).

The women with sporadic breast cancer showed an incidence of 45.5, 48.5 and 6.1%, respectively, for the *Thr/Thr*, *Thr/Met*, and *Met/Met* genotypes of the *XRCC3* gene, whereas the control group showed 57.6, 29.7, and 12.7% for the same genotypes. The *Thr/Met* genotype frequency came close to statistical significance with an OR of 2.07 and 95% CI of 0.85-5.06, considering the *Thr/Thr* genotype as reference (Table 3).

Because we were interested in the association between the genotype found in cases of sporadic cancer and the genotype identified in cases of women with a family history of breast cancer, these data were also analyzed. However, we found no statistically significant difference in the variant allele frequencies of these DNA repair genotypes (Table 4).

## DISCUSSION

The present study examined whether polymorphisms in four DNA repair genes involved in base excision, nucleotide excision, and homologous double-stranded DNA repair pathways are related to the development of familial breast cancer. We found no association between familial breast cancer and the *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *XRCC3-Thr241Met*, and *RAD51-G135C* polymorphisms in this study population.

Evidence suggests that the difference in DNA repair capacity among individuals is genetically determined. The phenotype of reduced repair capacity for one pathway is independent from the phenotype for any other pathway (Chu and Mayne, 1996), which is consistent with the hypothesis that DNA repair is genetically regulated. Measurement of repair capacity in twins (Pero et al., 1983) and the elevated frequency of individuals with reduced repair capacity among relatives of cancer patients provide further evidence that repair capacity is a genetic trait (Kovacs and Almendral, 1987; Pero et al.,1989).

This variation in DNA repair capacity has characteristics that would be expected from cancer susceptibility genes since it may be the reduced function of the proteins encoded by these alleles rather than the absence of this function that causes disease. These proteins exist at polymorphic frequency in the general population, and they exhibit incomplete penetrance (Mohrenweiser and Jones, 1998; Shen et al., 1998).

The *XRCC1-Arg399Gln* gene polymorphism has been studied as a risk factor for various cancers. The variant *Gln* allele has been linked to an increased risk of lung cancer (Divine et al., 2001; Zhou et al., 2003), head and neck cancer (Sturgis et al., 1999) and possibly stomach cancer (Shen et al., 2000). On the other hand, this allele was reported to be associated with a reduced risk of bladder cancer (Stern et al., 2001), esophageal cancer (Lee et al., 2002) and

**Table 1.** Frequency of *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *RAD51-G135C*, and *XRCC3-Thr241Met* polymorphisms in a group of women without breast cancer but familial history and control individuals.

| Polymorphism | Cases (%) | Controls (%) | P[a] | OR (95% CI)[b] |
|---|---|---|---|---|
| *XRCC1-Arg399Gln* | | | | |
| Allele | | | | |
| Gln | 119 (34.0) | 70 (29.4) | 0.24 | 1.24 (0.85-1.79) |
| Arg | 231 (66.0) | 168 (70.6) | | |
| Genotype | | | | |
| Arg/Arg | 79 (45.1) | 59 (49.6) | 0.42 | 1.00 |
| Arg/Gln | 73 (41.7) | 50 (42.0) | | 1.09 (0.65-1.84) |
| Gln/Gln | 23 (13.1) | 10 (8.4) | | 1.72 (0.71-4.21) |
| *XPD-Lys751Gln* | | | | |
| Allele | | | | |
| Gln | 105 (29.7) | 70 (29.9) | 0.95 | 0.99 (0.68-1.44) |
| Lys | 249 (70.3) | 164 (70.1) | | |
| Genotype | | | | |
| Lys/Lys | 93 (52.5) | 58 (49.6) | 0.59 | 1.00 |
| Lys/Gln | 63 (35.6) | 48 (41.0) | | 0.82 (0.48-1.39) |
| Gln/Gln | 21 (11.9) | 11 (9.4) | | 1.19 (0.50-2.86) |
| *RAD51-G135C* | | | | |
| Allele | | | | |
| C | 26 (7.7) | 19 (8.0) | 0.90 | 0.96 (0.50-1.86) |
| G | 312 (92.3) | 219 (92.0) | | |
| Genotype | | | | |
| GG | 144 (85.2) | 103 (86.6) | 0.29 | 1.00 |
| GC | 24 (14.2) | 13 (10.9) | | 1.32 (0.61-2.89) |
| CC | 1 (0.6) | 3 (2.5) | | 0.24 (0.01-2.61) |
| *XRCC3-Thr241Met* | | | | |
| Allele | | | | |
| Met | 115 (33.0) | 65 (27.5) | 0.16 | 1.30 (0.89-1.90) |
| Thr | 233 (67.0) | 171 (72.5) | | |
| Genotype | | | | |
| Thr/Thr | 88 (50.6) | 68 (57.6) | 0.45 | 1.00 |
| Thr/Met | 57 (32.8) | 35 (29.7) | | 1.26 (0.72-2.21) |
| Met/Met | 29 (16.7) | 15 (12.7) | | 1.49 (0.70-2.19) |

[a]Chi-square. [b]Crude odds ratio (OR). 95% CI = confidence interval at 95%.

non-melanoma skin cancer (Nelson et al., 2002). Null association was also reported for lung cancer (Cavalieri et al., 2000; Nelson et al., 2002). In relation to breast cancer, Duell et al. (2002) reported a positive association between breast cancer and *XRCC1* codon *399 Arg/Gln* or *Gln/Gln* genotypes compared with *Arg/Arg* among African Americans but not in white American women. Shu et al. (2003) showed that the *XRCC1-Arg399Gln* gene polymorphism alone did not appear to play a substantial role in the risk of breast cancer among Chinese women. Smith et al. (2003) found no association between the *XRCC1-399 Gln/Gln* genotype and breast cancer. However, other studies showed an increased risk of breast cancer with this

**Table 2.** Frequency of *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *RAD51-G135C*, and *XRCC3-Thr241Met* polymorphisms in a group of women with breast cancer and family history of breast cancer versus control individuals.

| Polymorphism | Cases (%) | Controls (%) | P[a] | OR (95% CI)[b] |
|---|---|---|---|---|
| *XRCC1-Arg399Gln* | | | | |
| Allele | | | | |
| Gln | 31 (29.2) | 70 (29.4) | 0.98 | 0.99 (0.58-1.69) |
| Arg | 75 (70.8) | 168 (70.6) | | |
| Genotype | | | | |
| Arg/Arg | 26 (49.1) | 59 (49.6) | 0.98 | 1.00 |
| Arg/Gln | 23 (43.3) | 50 (42.0) | | 1.04 (0.50-2.17) |
| Gln/Gln | 4 (7.5) | 10 (8.4) | | 0.91 (0.22-3.57) |
| *XPD-Lys751Gln* | | | | |
| Allele | | | | |
| Gln | 30 (28.3) | 70 (29.9) | 0.76 | 0.92 (0.54-1.58) |
| Lys | 76 (71.7) | 164 (70.1) | | |
| Genotype | | | | |
| Lys/Lys | 30 (56.5) | 58 (49.6) | 0.37 | 1.00 |
| Lys/Gln | 16 (30.2) | 48 (41.0) | | 0.64 (0.30-1.40) |
| Gln/Gln | 7 (13.2) | 11 (9.4) | | 1.23 (0.38-3.90) |
| *RAD51-G135C* | | | | |
| Allele | | | | |
| C | 6 (6.3) | 19 (8.0) | 0.59 | 0.77 (0.26-2.12) |
| G | 90 (93.7) | 219 (92.0) | | |
| Genotype | | | | |
| GG | 42 (87.5) | 103 (86.6) | 0.52 | 1.00 |
| GC | 6 (12.5) | 13 (10.9) | | 1.13 (0.36-3.48) |
| CC | 0 (0.0) | 3 (2.5) | | NA |
| *XRCC3-Thr241Met* | | | | |
| Allele | | | | |
| Met | 32 (30.8) | 65 (27.5) | 0.54 | 1.17 (0.68-2.00) |
| Thr | 72 (69.2) | 171 (72.5) | | |
| Genotype | | | | |
| Thr/Thr | 27 (51.9) | 68 (57.6) | 0.78 | 1.00 |
| Thr/Met | 18 (34.6) | 35 (29.7) | | 1.30 (0.59-2.84) |
| Met/Met | 7 (13.5) | 15 (12.7) | | 1.18 (0.38-3.3) |

[a]Chi-square. [b]Crude odds ratio (OR). NA, not applicable. 95% CI = confidence interval at 95%.

polymorphism (Sigurdson et al., 2004; Figueiredo et al., 2004; Han et al., 2004a,b).

The *XRCC3* gene is involved in the homologous recombinational pathway of the DNA double-strand break repair and interacts directly with *RAD51* (Liu et al., 1998; Johnson and Jasin, 2001). No association was found between this polymorphism and lung cancer (Sugimura et al., 1999; Xing et al., 2001), squamous cell carcinoma of the head and neck (Wikman et al., 2000; Benhamou et al., 2004), gastric cancer (Shen et al., 2004) or basal cell carcinoma (Jacobsen et al., 2003). A positive association that achieved statistical significance was shown between the *XRCC3* gene and melanoma and bladder cancer (Winsey et al., 2000; Matullo et al., 2001a);

**Table 3.** Frequency of *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *RAD51-G135C*, and *XRCC3-Thr241Met* polymorphisms in a group of women with sporadic breast carcinoma and control individuals.

| Polymorphism | Cases (%) | Controls (%) | P[a] | OR (95% CI)[b] |
|---|---|---|---|---|
| *XRCC1-Arg399Gln* | | | | |
| Allele | | | | |
| Gln | 16 (24.2) | 70 (29.4) | 0.41 | 0.77 (0.39-1.50) |
| Arg | 50 (75.8) | 168 (70.6) | | |
| Genotype | | | | |
| Arg/Arg | 20 (60.6) | 59 (49.6) | 0.47 | 1.00 |
| Arg/Gln | 10 (30.3) | 50 (42.0) | | 0.59 (0.23-1.48) |
| Gln/Gln | 3 (9.1) | 10 (8.4) | | 0.89 (0.17-4.03) |
| *XPD-Lys751Gln* | | | | |
| Allele | | | | |
| Gln | 24 (36.4) | 70 (29.9) | 0.32 | 1.34 (0.22-2.47) |
| Lys | 42 (63.6) | 164 (70.1) | | |
| Genotype | | | | |
| Lys/Lys | 13 (39.4) | 58 (49.6) | 0.58 | 1.00 |
| Lys/Gln | 16 (48.5) | 48 (41.0) | | 1.49 (0.60-3.68) |
| Gln/Gln | 4 (12.1) | 11 (9.4) | | 1.62 (0.37-6.83) |
| *RAD51-G135C* | | | | |
| Allele | | | | |
| C | 5 (8.3) | 19 (8.0) | 0.55 | 1.05 (0.33-3.15) |
| G | 55 (91.7) | 219 (92.0) | | |
| Genotype | | | | |
| GG | 26 (86.7) | 103 (86.6) | 0.96 | 1.00 |
| GC | 3 (10.0) | 13 (10.9) | | 0.91 (0.19-3.82) |
| CC | 1 (3.3) | 3 (2.5) | | 0.76 (0.07-19.71) |
| *XRCC3-Thr241Met* | | | | |
| Allele | | | | |
| Met | 20 (30.3) | 65 (27.5) | 0.66 | 1.14 (0.60-2.16) |
| Thr | 46 (69.7) | 171 (72.5) | | |
| Genotype | | | | |
| Thr/Thr | 15 (45.5) | 68 (57.6) | 0.11 | 1.00 |
| Thr/Met | 16 (48.5) | 35 (29.7) | | 2.07 (0.85-5.06) |
| Met/Met | 2 (6.1) | 15 (12.7) | | 0.60 (0.09-3.25) |

[a]Chi-square. [b]Crude odds ratio (OR). 95% CI = confidence interval at 95%.

however, these results were not confirmed in subsequent, larger studies (Duan et al., 2002; Stern et al., 2002). In relation to *XRCC3-T241m*, Han et al. (2004a) observed no significant elevation in the risk for breast cancer. There was some evidence of a combined effect of body mass index and this polymorphism on risk estimates, which led the investigators to suggest that this polymorphism may influence breast cancer risk by modifying the effect of risk factors such as family history (Figueiredo et al., 2004). Smith et al. (2003) provided evidence that a variant of the *XRCC3* gene, particularly when found in combination with other variants, contributes to breast cancer susceptibility.

Our study on genotype *Thr/Met* of *XRCC3* gene polymorphisms showed results close

**Table 4.** Statistical analysis of *XRCC1-Arg399Gln*, *XPD-Lys751Gln*, *RAD51-G135C*, and *XRCC3-Thr241Met* polymorphisms in women with sporadic breast carcinoma and women with breast cancer and family history of breast cancer.

| Polymorphism | Sporadic breast carcinoma | Familial breast carcinoma | P[a] | OR (95% CI)[b] |
|---|---|---|---|---|
| *XRCC1-Arg399Gln* | | | | |
| Allele | | | | |
| Gln | 16 (24.2) | 31 (29.2) | 0.47 | 0.77 (0.36-1.65) |
| Arg | 50 (75.8) | 75 (70.8) | | |
| Genotype | | | | |
| Arg/Arg | 20 (60.6) | 26 (49.1) | 0.48 | 1.00 |
| Arg/Gln | 10 (30.3) | 23 (43.3) | | 0.54 (0.19-1.51) |
| Gln/Gln | 3 (9.1) | 4 (7.5) | | 1.01 (0.16-6.27) |
| *XPD-Lys751Gln* | | | | |
| Allele | | | | |
| Gln | 24 (36.4) | 30 (28.3) | 0.74 | 1.11 (0.56-2.20) |
| Lys | 42 (63.6) | 76 (71.7) | | |
| Genotype | | | | |
| Lys/Lys | 13 (39.4) | 30 (56.5) | 0.22 | 1.00 |
| Lys/Gln | 16 (48.5) | 16 (30.2) | | 2.24 (0.79-6.43) |
| Gln/Gln | 4 (12.1) | 7 (13.2) | | 1.19 (0.25-5.55) |
| *RAD51-G135C* | | | | |
| Allele | | | | |
| C | 5 (8.3) | 6 (6.3) | 0.42 | 1.36 (0.34-5.37) |
| G | 55 (91.7) | 90 (93.7) | | |
| Genotype | | | | |
| GG | 26 (86.7) | 42 (87.5) | 0.43 | 1.00 |
| GC | 3 (10.0) | 6 (12.5) | | 0.71 (0.13-3.45) |
| CC | 1 (3.3) | 0 (0.0) | | NA |
| *XRCC3-Thr241Met* | | | | |
| Allele | | | | |
| Met | 20 (30.3) | 32 (30.8) | 0.72 | 0.88 (0.42-1.84) |
| Thr | 46 (69.7) | 72 (69.2) | | |
| Genotype | | | | |
| Thr/Thr | 15 (45.5) | 27 (51.9) | 0.34 | 1.00 |
| Thr/Met | 16 (48.5) | 18 (34.6) | | 1.57 (0.57-4.35) |
| Met/Met | 2 (6.1) | 7 (13.5) | | 0.47 (0.06-2.90) |

[a]Chi-square. [b]Crude odds ratio (OR). NA, not applicable. 95% CI = confidence interval at 95%.

to statistical significance with an OR of 2.07 and 95% CI of 0.85-5.06, considering the *Thr/Thr* genotype as a reference. Interestingly, this result was observed in women with sporadic breast cancer but not in those with breast cancer and family history. The study group of women with sporadic breast cancer included 33 patients and this sample may be statistically underpowered to show true differences or to reject any difference among the groups compared.

*XPD-L751G* is the most commonly studied polymorphism of this gene, and no statistically significant findings have ever been reported with respect to any increased risk of bladder

cancer (Matullo et al., 2001a), skin basal cell cancer (Vogel et al., 2001), non-small cell lung cancer (Butkiewicz et al., 2001), or melanoma (Winsey et al., 2000). This polymorphism appears to be connected with smoking status and may increase cancer risk among non-smokers (Zhou et al., 2002). In relation to breast cancer, subjects with the *Gln/Gln* genotype at codon 751 were found to have higher adduct levels in tumor tissue than in tissue from benign breast disease controls (Tang et al., 2002). Forsti et al. (2004) searched for low-penetrant genes by measuring the frequencies of single-nucleotide polymorphisms for the following genes: *NBS1*, *XPC*, *XPD*, *XRCC1*, *XRCC3*, *MTHFR*, and *cyclin D1*. They concluded that none of the polymorphisms tested were associated with breast cancer, with the probable exception of *XPD*. In fact, there is little data on the association between breast cancer risk and *XPD* polymorphism.

The product of the *RAD51* gene works in conjunction with *BRCA1* and *BRCA2* in the repair of double-stranded DNA breaks. Jakubowska et al. (2003) suggested that *RAD51* may be a genetic modifier of breast cancer risk in *BRCA1* carriers in the Polish population. Kadouri et al. (2004) showed that in non-carrier breast cancer cases, bearing *RAD51-G135C* was not associated with breast cancer risk, but they suggested that the risk may be significantly elevated in carriers of *BRCA2* mutations who also carry a *RAD51-135C* allele. In *BRCA1* carriers and non-carriers, no effect of this single-nucleotide polymorphism was found. Blasiak et al. (2003) suggested that the *G/C* polymorphism of the *RAD51* gene may not be directly involved in the development and/or progression of breast cancer; therefore, it may not be useful as an independent marker of this disease.

The functional significance of the single-nucleotide polymorphism of the DNA-repair gene in DNA repair and human breast cancer risk is currently the subject of intense study, and there are many challenges that must be met. The results available should be interpreted with caution and other more conclusive studies should be carried out. The discrepancies between the results currently available could be due to different subject sample sizes and different study designs. Diverse environmental exposure could also contribute to divergent results.

The results of this study do not provide insights into the function of these polymorphisms at the cellular level, but they do indicate that these DNA-repair gene polymorphisms are not significantly associated with familial breast cancer in the study population. The sample sizes of the groups of women with breast cancer, women with familial breast cancer and women with sporadic breast cancer were not sufficiently large to detect any true differences between the groups, but we have to consider that currently there is no clear consensus with respect to the association of these polymorphisms with breast cancer risk. Considering the data available, it can be conjectured that if there is any risk association between these single-nucleotide polymorphisms and breast cancer, this risk will probably be minimal. The greater the risk associated with cancer, the smaller the sample size that would be required to demonstrate this association, and the data of different studies are usually, therefore, more concordant.

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