Polymorphisms of the DNA Repair Genes *XRCC1* and *XRCC3* and Risk of Lung and Colorectal Cancer: A Case-Control Study in a Southern Italian Population

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Abstract. *Background: Genetic polymorphisms in DNA repair genes may influence individual variation in DNA repair capacity, which may be associated with a higher risk of developing cancer. Studies on the association between DNA repair gene polymorphisms and lung and colorectal cancer risk appear to be very limited. This study was designed to examine the polymorphisms associated with two DNA repair genes, namely XRCC1 Arg194Trp, XRCC1 Arg399Gln and XRCC3 Thr241Met, and to investigate their role as susceptibility markers for lung and colorectal cancer. Materials and Methods: A case-control study was conducted including 94 and 109 cases of lung and colorectal cancer, respectively, and 121 hospital-based age- and sex-matched healthy controls to examine the role of XRCC1 and XRCC3 genetic polymorphisms in the context of lung and colorectal cancer risk for a Southern Italian population. Genomic DNA isolated from 5 ml whole blood was used to genotype XRCC1 Arg194Trp, XRCC1 Arg399Gln and XRCC3 Thr241Met by means of polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. Results: No differences were observed among the studied groups with regard to the genotype distribution of XRCC1 codon 194 and 399, thus the risk for lung and colorectal cancer did not appear to be significantly influenced by polymorphisms of this gene. Significant differences were observed among the studied groups with regard to the genotype distribution of XRCC3 codon 241. In particular, the XRCC3 241Met allele was associated with an increased risk of lung and colorectal cancer. Conclusion: Our results showed no evidence of a relationship between the XRCC1 Arg194Trp and Arg399Gln polymorphisms and the risk of lung and colorectal cancer. On the other hand, they suggested an increased risk in individuals with the XRCC3 Thr241Met polymorphism thus warranting further study to definitively evaluate the role of DNA repair mechanisms in colorectal and lung cancer susceptibility.*

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Humans are routinely exposed to mutagenic and carcinogenic aromatic amines *via* smoking, well-cooked food and other sources (1). These chemicals can form DNA adducts *in vivo* (1) and thus lead to DNA damage. Different DNA repair systems maintain the integrity of the human genome, hence deficiency in the repair capacity due to mutations or polymorphisms in genes involved in DNA repair can lead to genomic instability that, in turn, is related to chromosomal instability syndromes and increased risk of developing various types of cancer (2, 3, 4).

Several polymorphisms in DNA repair genes (*e.g.*, *XPD, XPF, ERCC1, XRCC1, XRCC3, XPA, XPB, XPC* and *hOGG1*) representing different repair pathways have been reported (5, 6). Amongst the known genetic polymorphisms of the DNA repair genes, the x-ray cross-complementig group 1 and 3 (*XRCC1* and *XRCC3*) have been studied most commonly (7, 8). These DNA repair genes code for proteins involved in the repair of single-strand breaks (SSB) and in base excision repair (BER) of damaged bases caused by endogenous and exogenous oxidants (9, 10). The *XRCC1* protein is a scaffolding protein directly associated with polymerase and functions in a complex to facilitate the BER and single break-repair processes (7, 11, 12). Three polymorphisms occurring at conserved sequences in the *XRCC1* gene were reported by Shen *et al*. (13). These

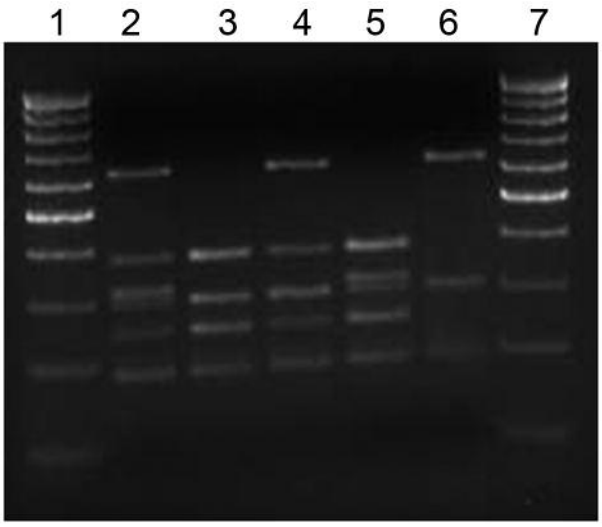

Figure 1. *Agarose gel electrophoresis patterns of a PCR-RFLP for the XRCC1 gene. Lanes 1 and 7: molecular weight marker. Lane 2: heterozygous for codon 194 and codon 399. Lane 3: homozygous for codon 194 and codon 399. Lane 4: homozygous for codon 194 and heterozygous for codon 399. Lane 5: heterozygous for codon 194 and homozygous for codon 399. Lane 6: homozygous for codon 194 and mutant homozygous for codon 399.*

coding polymorphisms, resulting in amino acid substitutions, were detected at codons 194 (Arg-Trp), 280 (Arg-His) and 399 (Arg-Gln). Many authors have analysed these polymorphisms in human populations and found a significant association between the Arg194Trp and Arg399Gln variants and increased risk of early-onset colorectal (14) and gastric (8, 15) cancer, in addition to head and neck (16, 17) and skin (18) cancer associated with the Arg194Trp variant, and breast (19, 20, 21), lung (22-29) and oesophageal (30) cancer, amongst others, associated with Arg399Gln polymorphism.

The *XRCC3* gene codes for a protein involved in homologous recombinational repair (HRR) for double strand breaks of DNA (DBSs) and cross-link repair in mammalian cells (31). During HRR, the XRCC3 protein interacts with Rad51 protein and likely contributes to maintain chromosome stability. A common polymorphism in exon 7 of the *XRCC3* gene results in an amino acid substitution at codon 241 (Thr241Met) that may affect the enzyme function and/or its interaction with other proteins involved in DNA damage and repair (31). Molecular epidemiological studies have proved the association between this *XRCC3* polymorphism and an increased risk of breast (32), lung (28, 33), skin (34, 35) and colorectal (36) cancer.

In the present study we used a case control design to investigate the association between three amino acid substitution variants of the DNA repair genes *XRCC1* (Arg194Trp and Arg399Gln) and *XRCC3* (Thr241Met) and lung and colorectal cancer risk in a Southern Italian population.

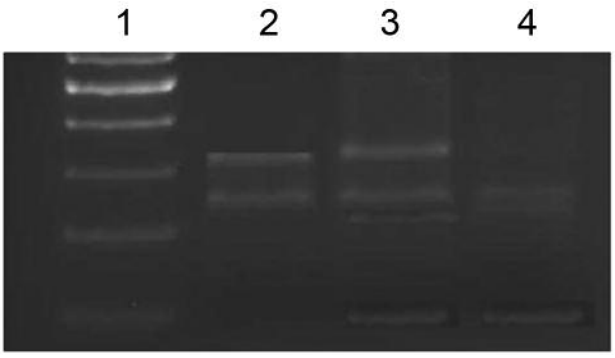

Figure 2. *Agarose gel electrophoresis patterns of a PCR-RFLP for the XRCC3 gene. Lane 1: molecular weight marker. Lane 2: homozygous for codon 241. Lane 3: heterozygous for codon 241. Lane 4: mutant homozygous for codon 241.*

Materials and Methods

All reagents were high grade and were purchased from Sigma Chemical Co. (St Louis, MO, USA). Blood samples were collected in Basilicata, a Southern Italian region, at the Centro di Riferimento Oncologico Regionale della Basilicata from 121 healthy individuals (57 males and 64 females, mean age of 65 years) used as controls, and 94 and 109 cases of lung and colorectal cancer patients, respectively, admitted to the same Institution. Written informed consent was obtained from all participants.

Approximately 5 ml of whole blood was collected from all study participants in sterile EDTA-coated vacutainers. DNA was extracted according to a salting-out protocol, and stored at –20˚C until used for genotyping.

Genotypic analyses of the *XRCC1* gene were carried out by multiplex PCR-RFLP, using primers (Sigma) for codons 399 [forward (F) 5'-TTGTGCTTTCTCTGTGTCCA-3' and reverse (R) 5'-TCCTC-CAGCCTTTTCTGATA-3'] and 194 (F 5'-GCCCCGTCCCAGGTA-3' and R 5'-AGCCCCAAGACCCTTTCACT-3'), which generate fragments of 615 and 491 bp, respectively (14). Briefly, PCR was performed in 50 μl reaction buffer containing 12.5 pmol of each primer, 0.2 mM of dNTPs, 3 mM of $MgCl_2$, 100 ng of DNA and 1 U of Taq DNA polymerase. The PCR products were digested overnight with 10 U of MspI at 37˚C. The wild-type Arg allele for codon 194 is identified by the presence of a 293 bp band and the mutant Trp allele by the presence of a 313 bp band (indicative of the absence of the MspI cutting site). For codon 399, the presence of two bands of 375 and 240 bp, respectively, identifies the mutant Gln allele (indicative of the absence of the MspI cutting site). A 178 bp band, resulting from an additional invariant MspI cutting site in the 491 bp amplified fragment, is always present and serves as an internal control for complete enzyme digestion (Figure 1).

Polymorphism of the *XRCC3* gene was determined by PCR-RFLP using codon 241 primers (F 5'-TTGGGGCCTCTTTGAGA-3' and R 5'-AACGGCTGAGGGTCTTCT-3'), as previously described by David-Beabes *et al.* (23). The 50 μl PCR mixture contained 100 ng of DNA, 0.8 μM of each primer, 0.2 mM of dNTPs, 3 mM of $MgCl_2$ and 1 U of Taq DNA polymerase. The 552 bp amplified product was digested overnight with 5 U of NlaIII at 37˚C. The wild-type allele Thr was identified by the presence of 239 and 313 bp bands, while the mutant allele Met was represented by 105, 208 and 239 bp bands (Figure 2).

Table I. *Characteristic details for the cases and controls.*

Variable	Cases, n (%) (N=203)	Controls, n (%) (N=121)
Gender		
Male	141 (69)	57 (47)
Female	62 (31)	64 (53)
Mean age (years)	65	65
Colon	109 (54)	/
Lung	94 (46)	/

The Chi-square test was utilized to compare the groups with regard to genotype frequencies and putative risk factors such as age, gender and type of carcinoma. A probability level (p) of less than 0.05 was used as cut-off for significance.

Results

More men (61%) than women (39%) participated in this study (Table I). The mean age for both groups was 65 years. Amongst cancer patients, 94 suffered from lung cancer (46%) and 109 from colon cancer (54%).

The genotypic distributions of the three polymorphisms for both cancer cases and controls are shown in Table II.

The frequencies for the *XRCC1* 194Trp, *XRCC1* 399Gln and *XRCC3* 241Met alleles and their distribution in the control group were in agreement with those found in other Caucasian populations. The genotype frequencies of the *XRCC1* 194 and *XRCC1* 399 polymorphisms were similar in cases and controls and showed no significant association with lung or colorectal cancer. In the case of the *XRCC3* codon 241 polymorphism, the genotype frequency of homozygote (Met/Met) was different between cases and controls; in fact, it was significantly higher in colorectal and lung cancer (p=0.05 and p=0.01, respectively; Table II).

The frequency of *XRCC1* 194, *XRCC1* 399 and *XRCC3* 241 polymorphisms were also evaluated in cases and controls according to sex and age (Tables III and IV), with a cut-off for age set at sixty-five years. The genotype frequencies of the *XRCC1* 194 and 399 polymorphisms were similar in case and control males, even though allele frequencies of polymorphisms 194Trp and 399Gln were slightly higher in colorectal and lung cancer patients albeit not statistically significant (Table III). Instead, the genotype frequencies of the *XRCC3* 241 polymorphisms were different in the three male groups. The wild-type genotype (Thr/Thr) was higher in male controls than cases, whereas genotype frequencies of heterozygotes (Thr/Met) and homozygotes (Met/Met) were statistically higher in colorectal and lung cancer patients (p=0.01).

Table II. *Distribution of polymorphisms in cases and controls*

Genotype	Controls, n (%) (N=121)	Cancer cases	
		Colon, n (%) (N=109)	Lung, n (%) (N=94)
XRCC1 Arg194Trp			
Arg/Arg (CC)	104 (86)	94 (86)	78 (83)
Arg/Trp (CT)	17 (14)	11 (10)	9 (10)
Trp/Trp (TT)	0	4 (4)	7 (7)
Arg/Trp+Trp/Trp	17 (14)	15 (14)	17 (16)
XRCC1 Arg399Gln			
Arg/Arg (GG)	53 (44)	46 (42)	42 (45)
Arg/Gln (GA)	61 (50)	54 (50)	41 (41)
Gln/Gln (AA)	7 (6)	9 (8)	11 (11)
Arg/Gln+Gln/Gln	68 (56)	63 (58)	52 (55)
XRCC3 Thr241Met			
Thr/Thr (CC)	67 (55)	40 (37)	31 (33)
Thr/Met (CT)	46 (38)	43 (39)	33 (35)
Met/Met (TT)	8 (7)	26 (24)	30 (30)
Thr/Met+Met/Met	54 (45)	69 (63)	63 (63)

In the three female groups, the *XRCC1* 194 and 399 genotypes and the allele frequency distributions, among cases and controls were different. In particular, genotype frequencies of *XRCC1* 194Trp, *XRCC1* 399Gln and *XRCC3* 241Met variants were slightly higher in controls than cases, probably because of a numerical difference between groups.

Evaluating the data according to age, the frequency of *XRCC1* 194, *XRCC1* 399 and *XRCC3* 241 polymorphisms was different between cases and controls (Table IV). In particular, in the <65 year-old group the genotype frequency of the *XRCC1* 194Trp variant was slightly higher in controls than cases, probably because of a numerical difference between subgroups. In contrast, in the same group (<65 years), the genotype distributions of *XRCC1* 399Gln and *XRCC3* 241Met variants were higher in cases than controls, especially for the *XRCC3* 241Met allele. In fact, the frequency of the *XRCC3* 241Met variant in the <65 year-old group was higher in lung cancer (32%) than in colorectal cancer (19%; p=0.05) patients and in controls (9%; p=0.01) (Table IV).

In the >65 year-old group, the genotype frequencies of the *XRCC1* 194 and 399 polymorphisms were similar in cases and controls. The allele frequency of polymorphism 194Trp was higher in colorectal and lung cancer, but this difference was not statistically significant. The genotype frequencies of the *XRCC3* 241 polymorphism were different in the three subgroups. In particular, the *XRCC3* 241Met variant was higher in colorectal (27%) and lung cancer patients (37%) than in controls (4%) and this difference was statistically significant (p=0.01; Table IV).

Table III. *Distribution of polymorphisms in cases and controls according to sex.*

Genotype	Males, n (%)			Females, n (%)		
	Controls (N=57)	Colon cancer (N=60)	Lung cancer (N=81)	Controls (N=64)	Colon cancer (N=49)	Lung cancer (N=13)
XRCC1 Arg194Trp						
Arg/Arg (CC)	52 (91)	50 (83)	66 (81)	52 (81)	44 (90)	12 (92)
Arg/Trp (CT)	5 (9)	6 (10)	8 (10)	12 (19)	5 (10)	1 (8)
Trp/Trp (TT)	0	4 (7)	7 (9)	0	0	0
Arg/Trp+Trp/Trp	5 (9)	10 (17)	15 (19)	12 (19)	5 (10)	1 (8)
XRCC1 Arg399Gln						
Arg/Arg (GG)	23 (40)	24 (40)	34 (42)	30 (47)	22 (45)	8 (62)
Arg/Gln (GA)	31 (54)	28 (47)	36 (44)	30 (47)	26 (53)	5 (38)
Gln/Gln (AA)	3 (6)	8 (13)	11 (14)	4 (6)	1 (2)	0
Arg/Gln+Gln/Gln	34 (60)	36 (60)	47 (58)	34 (53)	27 (55)	5 (38)
XRCC3 Thr241Met						
Thr/Thr (CC)	46 (81)	26 (43)	25 (31)	21 (33)	17 (35)	6 (46)
Thr/Met (CT)	9 (16)	19 (32)	27 (33)	37 (58)	21 (43)	6 (46)
Met/Met (TT)	2 (3)	15 (25)	29 (36)	6 (9)	11 (22)	1 (8)
Thr/Met+Met/Met	11 (19)	34 (57)	56 (69)	43 (67)	32 (65)	7 (54)

Table IV. *Distribution of polymorphisms in cases and controls according to age.*

Genotype	<65 Years, n (%)			>65 Years, n (%)		
	Controls (N=67)	Colon cancer (N=42)	Lung cancer (N=37)	Controls (N=54)	Colon cancer (N=67)	Lung cancer (N=77)
XRCC1 Arg194Trp						
Arg/Arg (CC)	54 (80)	37 (88)	34 (92)	50 (93)	57 (85)	44 (77)
Arg/Trp (CT)	13 (20)	3 (7)	2 (5)	4 (7)	8 (12)	7 (12)
Trp/Trp (TT)	0	2 (5)	1 (3)	0	2 (3)	6 (11)
Arg/Trp+Trp/Trp	13 (20)	5 (12)	3 (8)	4 (7)	10 (15)	13 (23)
XRCC1 Arg399Gln						
Arg/Arg (GG)	32 (48)	18 (43)	15 (40)	21 (39)	28 (42)	27 (47)
Arg/Gln (GA)	32 (48)	18 (43)	18 (49)	29 (54)	36 (54)	23 (40)
Gln/Gln (AA)	3 (4)	6 (14)	4 (11)	4 (7)	3 (4)	7 (13)
Arg/Gln+Gln/Gln	35 (52)	24 (57)	22 (60)	33 (61)	39 (58)	30 (53)
XRCC3 Thr241Met						
Thr/Thr (CC)	37 (55)	20 (48)	11 (30)	30 (55)	22 (33)	20 (35)
Thr/Met (CT)	24 (36)	14 (33)	14 (38)	22 (41)	27 (40)	19 (33)
Met/Met (TT)	6 (9)	8 (19)	12 (32)	2 (4)	18 (27)	18 (32)
Thr/Met+Met/Met	30 (45)	22 (52)	26 (70)	24 (45)	45 (67)	37 (65)

Discussion

There is increasing evidence that genetic variation leads to different DNA repair capacities in the human population. Hence, common polymorphisms can play a role in an individual's genetic susceptibility to cancer (2). Very few studies have investigated the role of polymorphisms of the DNA repair genes *XRCC1* and *XRCC3* in the risk of colorectal and lung cancer. We conducted a case-control study to investigate the relationship between the polymorphisms *XRCC1* Arg194Trp and Arg399Gln and *XRCC3* Thr241Met and the risk of colorectal and lung cancer in a Southern Italian population. These polymorphisms result in amino acid substitution of two important DNA repair genes involved in BER and HRR.

In this study, we did not find an association between *XRCC1* and lung cancer, even if we did find a slight increas in the percentage of *XRCC1* 194Trp and 399Gln alleles in the cases. The lack of an association with the cancer groups may be due to the small sample size. Our results indicate

that the *XRCC1* Arg194Trp and Arg399Gln polymorphisms may predispose to the development of colorectal and lung cancer. These results are not in agreement with those reported by Abdel-Rahman *et al*. (14). The *XRCC1* Arg194Trp and Arg399Gln polymorphisms might have subtle and multiple influences on cancer formation, which depend on other genetic factors or environmental exposures. Carcinogenesis is a complex process and interrelated pathways of biological response to DNA damage exist in which multiple genetic mechanisms are involved. To our knowledge, no studies have been reported on the association between *XRCC1* Arg194Trp and Arg399Gln polymorphisms and lung cancer. A possible relationship between *XRCC1* Arg399Gln polymorphism and cancer in general has been investigated in several studies, although results remain inconsistent. A few studies observed that 399Gln allele carries had significantly increased DNA adduct levels, sister chromosome exchange frequency, or other indicators of reduced DNA repair capacity (1).

A significant association was found between the *XRCC3* Thr241Met polymorphism and colorectal and lung cancer in our study. This *XRCC3* codon 241 polymorphism was shown to have a significant association with colorectal (36) and lung (33) cancer risk; hence, our findings are in agreement with those reported by Mort *et al*. (36). The XRCC3 protein is one of five identified paralogs of the strand-exchange protein RAD51 in humans and functions through complex interactions with other relevant proteins to repair double-strand breaks and maintain genome integrity in multiple phases of homologous recombination. *XRCC3*-deficient hamster cells showed a high frequency of multiple centrosomes and abnormal spindle formation. Polymorphisms of this gene may result in a reduced DNA repair capacity, but direct functional research evidence is absent and epidemiological research results are inconclusive at present.

To the best of our knowledge, this study is the first to report on *XRCC1* codon 194, *XRCC1* codon 399 and *XRCC3* codon 241 polymorphisms in relation to the risk of colorectal and lung cancer for a Southern Italian population. As previously reported for GST polymorphisms, distribution of these polymorphisms was not different from what reported for other Caucasian populations (37). Our results suggest that genetic polymorphism of the *XRCC3* gene may be associated with an individual's susceptibility to colorectal and lung cancer. The divergence in results from different studies on *XRCC1* codon 194 and *XRCC1* codon 399 polymorphisms may be related to variation in carcinogenic exposure and ethnic origin of the studied population. Acknowledging the relatively limited sample size of the groups, further studies incorporating a larger sample size and/or another ethnic population are needed to confirm the genetic role of DNA repair mechanisms in regard to colorectal and lung cancer susceptibility.

Conclusion

Among the three genetic polymorphisms included in our study, only the *XRCC3* codon 241 polymorphism displayed a relationship with colorectal and lung neoplasia. According to our results, there is no evidence of an increased risk for colorectal and lung cancer in individuals with *XRCC1* Arg194Trp and Arg399Gln polymorphisms.

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