Polymorphisms of the *CYP1A1*, *CYP2E1* and *XRCC1* Genes and Cancer Risk in a Southern Italian Population: A Case–Control Study

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Abstract. *Background: Polymorphisms in genes encoding enzymes involved in xenobiotic metabolism and/or in cellular defenses against carcinogen-induced DNA damage play an important role in determining individual cancer susceptibility. However, their distribution and association with cancer susceptibility can vary in different populations. Materials and Methods: A case–control study including 290 cancer patients (cases) and 242 controls was performed to evaluate the relationship between polymorphisms of cytochrome P450 (CYP)1A1 and CYP2E1 and X-ray repair complementing defective repair in Chinese hamster cells (XRCC)1 genes and the risk of developing cancer in a Southern Italian (Basilicata) population. Genomic DNA was isolated from 5 ml whole blood and genotyping was performed using a PCR-RFLP technique. Results: No significant differences were observed in the distribution of the CYP1A1, CYP2E1 and XRCC1 gene polymorphisms between the cases and controls in the population under study. Conclusion: The distribution of CYP1A1, CYP2E1 and XRCC1 gene polymorphisms in the Basilicata population is not different from that of other Italian regions or from that reported in the literature for Caucasian populations, and polymorphisms in these genes do not play an important role in determining cancer risk in the population under study.*

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Different individuals respond differently to exposure to environmental carcinogens due to a different genetic background (1). This different genetic susceptibility is associated with polymorphisms in genes that can affect every step of carcinogenesis, from exposure to carcinogens to tumor development (2-4). Most carcinogens require metabolic activation in the human body in order to exert their carcinogenic effects. Generally, phase I enzymes can activate the carcinogens directly and produce more active metabolites. Phase II enzymes detoxify and process the activited metabolites for final breakdown or excretion (1). Thus, major cancer susceptibility genes include genes coding for type I and II metabolism enzymes, molecules involved in DNA repair mechanisms and those affecting cell proliferation rate (2-4).

Cytochrome P450 (CYP) isoenzymes are the most important phase I enzymes and play an important role in the oxidation of chemical compounds, such as polycyclic aromatic hydrocarbons (PAH), often resulting in the formation of highly reactive compounds that are the ultimate carcinogens (5). *CYP1A1* encodes a key enzyme in phase I bioactivation of xenobiotics. This gene belongs to the CYP1 sub-family and encodes for the enzyme aryl hydrocarbon hydroxylase, which catalyzes the first step in the metabolism of PAH, such as those found in cigarette smoke, transforming them into active carcinogens. An isoleucine to valine (Ile-Val) substitution in the binding region of the enzyme results in a two-fold increase in microsomal enzyme activity (6). About 10% of the Caucasian population expresses this variant form of the CYP1A1 enzyme, which is associated with an increased risk of bronchial, laryngeal and oral cavity tumors among smokers (5, 6).

The *CYP2E1* gene belongs to the CYP2 family and encodes the enzyme *N,N*-dimethyl-nitrosamino-*N*-dimethylase, which catalyzes the oxidation of many low molecular weight pro-carcinogens such as benzene, styrene and nitrosamine (7). This

enzyme is also believed to participate in the oxidation of other compounds, such as ethanol, to produce reactive free radicals that may initiate lipid peroxidation and also contribute to carcinogenesis (7). The variant c2 allele, recognized by *Rsa* I digestion in the 5'-flanking region of the gene, appears to be associated with decreased enzyme activity. The presence of this allele has been related to cancer susceptibility and its frequency is variable, but relatively low in different populations, being around 5% in Caucasians (7).

DNA repair pathways are responsible for maintaining the integrity of the genome in the face of environmental insults and general DNA replication errors, playing a role in protecting it against mutations that might lead to cancer (8). Thus, polymorphisms of DNA repair enzymes, such as X-ray repair complementing defective repair in Chinese hamster cells (XRCC)1, may contribute to an increased risk of environmental carcinogenesis. The *XRCC1* gene codes for a scaffolding protein that directly associates with other proteins such as DNA polymerase α, PARP (ADP-ribose polymerase) and DNA ligase III in a complex that mediates the processes of base excision repair (BER) or single-strand break repair (9). Two major polymorphisms have been identified in the *XRCC1* gene characterized by a C→T substitution leading to the amino acid change arginine (Arg) to triptophan (Trp) at codon 194 in exon 6 or by a G→A substitution causing an arginine (Arg) to glutamine (Gln) change at codon 399 in exon 10 of the gene. These changes in conserved protein sites may alter the BER capacity, increasing the chances of DNA damage (10). The Arg399Gln variant is more frequent and both have been related to several types of cancer including head and neck, colorectal, gastric, esophageal, breast and lung carcinomas (11).

In this case–control study, the distribution of the major polymorphisms in the *CYP1A1, CYP2E1* and *XRCC1* genes was evaluated in a Southern Italian population and their relation to individual cancer risk determined.

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 (CROB-IRCCS) between 2004 and 2007. All the enrolled participants were resident in Basilicata and included 242 healthy individuals (mean age of 64 years: range 50-78 years) admitted to the hospital for routine blood tests who had no personal and/or family history of cancer, used as controls, and 290 cancer patients (cases) (mean age of 65 years: range 34-78 years; mean age at diagnosis of 50 years) (Table I). The study was approved by the local ethical committee and all the participants signed an informed consent.

All subjects enrolled in the study provided a sample of blood (approximately 5 ml) in sterile EDTA-coated vacutainers. Genomic DNA was isolated from peripheral leukocytes by proteinase K digestion and salting-out extraction, as previously reported (12, 13) and stored at –20˚C until use.

Table I. *Characteristics of the population under study*

Variable	Cases, n (%) (N=290)	Controls, n (%) (N=242)
Gender		
Male	178 (69)	112 (47)
Female	112 (31)	130 (53)
Mean age (years)	65	64

Analysis of CYP1A1 and CYP2E1 gene polymorphisms. The A4889G polymorphism in exon 7 of the *CYP1A1* gene (Ile-Val substitution) and the c1/c2 polymorphism in the 5'- flanking region of the *CYP2E1* gene were analyzed by a PCR-RFLP method (13).

Briefly, PCR was performed in 50 μl of a reaction buffer containing 50 ng of genomic DNA, 1× PCR buffer, 0.2 mM MgCl, 2, 5 pmol of each primer, 0.2 nM of each dNTP and 2.0 U of Taq polymerase. The primers used for *CYP1A1* were: forward (F) 5'-GAACTGCCACTTCAGCTGTC-3' and reverse (R) 5'-GAAAGACCTCCCAGCGGTCA-3'. The primers used for *CYP2E1* were: F 5'-CCAGTCGAGTCTACATTGTCA-3' and R 5'-TTCATTCTGTCTTCTAACTGG-3'. The following conditions were used for amplification: 94˚C for 5 min, followed by 35 cycles consisting of denaturation at 94˚C for 60 s, annealing at 53˚C for 90 s and extension at 74˚C for 30 s. The PCR products (187 bp for *CYP1A1* and 410 bp for *CYP2E1*) were digested with *HincII* and RsaI restriction enzymes, respectively (37˚C overnight) and subjected to electrophoresis on a 3% agarose gel. According to the digestion products genotypes were classified as: wild-type homozygote (Ile/Ile) characterized by two bands of 48 and 139 bp and heterozygote (Ile/Val) characterized by four bands of 48, 120, 139 and 19 bp (Figure 1A). A rare mutant homozygote (Val/Val) status characterized by three bands of 48, 120 and 19 bp can also be identified by this method. Similarly, the *CYP2E1* genotypes were classified as: a predominant wild-type homozygote (c1/c1) status characterized by two bands of 360 and 50 bp and a heterozygote status (c1/c2) characterized by three bands of 410, 360 and 50 bp (Figure 1B). The rare mutant homozygote (c2/c2) status is characterized by only a 410 bp band.

Analysis of XRCC1 gene polymorphisms. The genotypic analysis of the *XRCC1* gene was carried out as previously reported (10). Briefly, a multiplex PCR-RFLP was performed, using primers amplifying a DNA fragment including codons 399 (F 5'-TTGTGCTTTCTCTGTGTCCA-3' and R 5'-TCCTCCAGCCTTTTCTGATA-3') or 194 (F 5'-GCCCCGTCCCAGGTA-3' and R 5'-AGCCCCAAGACCCTTTCACT-3'), which generate a fragment of 615 and 491 bp, respectively. PCR was performed in 50 μl reaction buffer as previously described. The PCR products were digested overnight with 10 U of *MspI* at 37˚C. The wild-type Arg allele for codon 194 was 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, identified the wild-type Arg allele, while the uncut 615 bp band identified 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, was always present and served as an internal control for complete enzyme digestion (Figure 2).

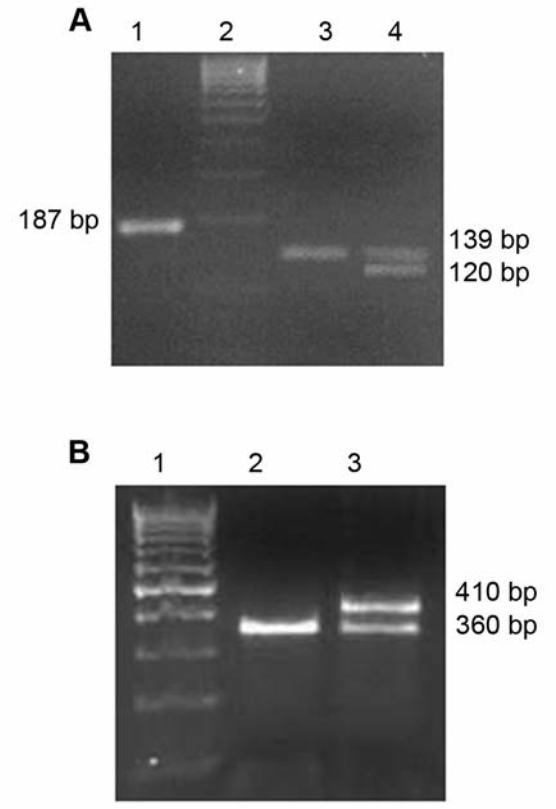

Figure 1. *Analysis of CYP1A1 and CYP2E1 gene polymorphisms by PCR-RFLP. A: CYP1A1 genotype (PCR products digested with HincII restriction enzyme). Lane 1: Undigested PCR product; lane 2: DNA molecular weight marker; lane 3: homozygote wild-type Ile/Ile genotype; lane 4: heterozygote Ile/Val genotype. B: CYP2E1 genotype (PCR products digested with RsaI restriction enzyme). Lane 1: DNA molecular weight marker; lane 2: homozygote wild-type c1/c1 genotype; lane 3: heterozygote c1/c2 genotype.*

Statistical analysis. The association between variables was calculated using contingency table methods and tested for significance using the Fisher Chi-square test. The results were considered statistically significant when the p-value was <0.05.

Results

The 290 cases represented an unselected population of patients and included different types of cancer representative of the cancer distribution within the Basilicata region with colorectal and breast carcinomas being the most represented (Table II). The *CYP1A1* and *CYP2E1* genotypes and their frequency of distribution in the cases and controls are shown in Table III.

The *CYP1A1* heterozygous genotype was found in 14 (5%) of the cancer patients and in 18 (7%) of the controls, while the *CYP2E1* heterozygous genotype was found in 12 (4%) of the cancer patients and in 20 (8%) of the controls

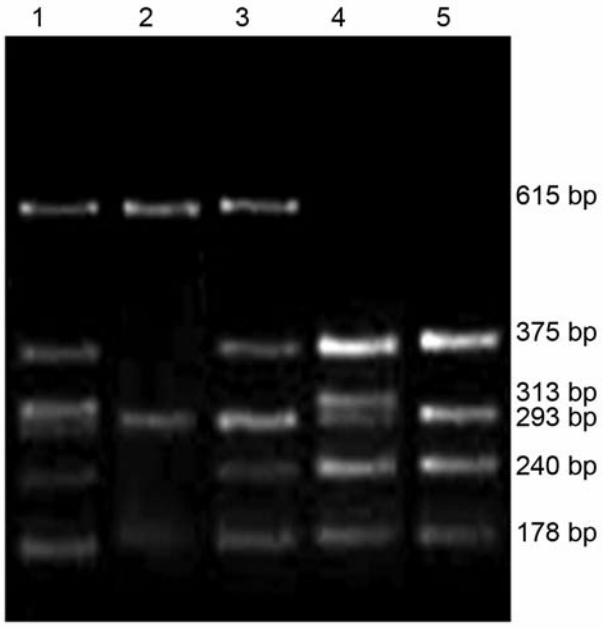

Figure 2. *Analysis of XRCC1 gene polymorphisms by PCR-RFLP. PCR products digested with MspI restriction enzyme. Lanes 1: Heterozygote for codon 194 and codon 399; lane 2: homozygote wild-type for codons 194 and mutant homozygote for codon 399; lane 3: homozygote wild-type for codon 194 and heterozygote for codon 399; lane 4: heterozygote for codon 194 and homozygote for codon 399; lane 5: homozygote wild-type for codon 194 and for codon 399.*

Table II. *Distribution of different types of cancer amongst the cases (n=290).*

Type of cancer	n	(%)
Colorectal cancer	104	(36)
Breast/ovarian cancer	42	(15)
Gastric cancer	14	(5)
Biliary tract/pancreas	12	(4)
Lung cancer	38	(13)
Urinary tract	32	(11)
Skin cancer	4	(1)
Lymphoma	8	(3)
Other	36	(12)

Table III. *Distribution of CYP1A1 and CYP2E1 gene polymorphisms in cases and controls.*

	CYP1A1				*CYP2E1*			
	Cases n (%)		Controls n (%)			Cases n (%)		Controls n (%)	
Total	290		242			290		242	
Ile/Ile	276	(95)	224	(93)	c1/c1	278	(96)	222	(92)
Ile/Val	14	(5)	18	(7)	c1/c2	12	(4)	20	(8)
Val/Val	0	(0)	0	(0)	c2/c2	0	(0)	0	(0)

Table IV. *Distribution of CYP1A1 and CYP2E1 polymorphisms in cancer patients and in controls stratified by sex and age.*

	Cases				Controls			
	Males n (%)	Females n (%)	≤60 years n (%)	>60 years n (%)	Males n (%)	Females n (%)	≤60 years n (%)	>60 years n (%)
Total	178	112	102	188	112	130	62	180
CYP1A1								
Ile/Ile:	170 (95)	106 (95)	98 (96)	178 (95)	106 (95)	118 (91)	58 (94)	166 (92)
Ile/Val:	8 (5)	6 (5)	4 (4)	10 (5)	6 (5)	12 (9)	4 (6)	14 (8)
Val/Val:	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CYP2E1								
c1/c1:	174 (98)	104 (93)	98 (96)	180 (96)	110 (89)	122 (94)	56 (90)	168 (93)
c1/c2:	4 (2)	8 (7)	4 (4)	8 (4)	121 (11)	8 (6)	6 (10)	12 (7)
c2/c2:	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table V. *Distribution of CYP1A1 and CPY2E1 polymorphisms with respect to tumor type.*

		Genotype								
		CYP1A1			*CYP2E1*					
Tumor type	Total	Ile/Ile n (%)	Ile/Val n (%)	Val/Val n (%)	c1/c1 n (%)	c1/c2 n (%)	c2/c2 n (%)
Colorectal cancer	104	102 (98)	2 (2)	0 (0)	98 (94)	6 (6)	0 (0)
Breast/ovarian cancer	42	40 (95)	2 (5)	0 (0)	42 (100)	0 (0)	0 (0)
Gastric cancer	14	12 (86)	2 (14)	0 (0)	14 (100)	0 (0)	0 (0)
Biliary tract/pancreas	12	10 (83)	2 (17)	0 (0)	10 (83)	2 (17)	0 (0)
Lung cancer	38	38 (100)	0 (0)	0 (0)	38 (100)	0 (0)	0 (0)
Urinary tract	32	30 (94)	2 (6)	0 (0)	30 (94)	2 (6)	0 (0)
Skin cancer	4	4 (100)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)
Lymphoma	8	8 (100)	0 (0)	0 (0)	6 (75)	2 (25)	0 (0)
Other	36	32 (89)	4 (11)	0 (0)	36 (100)	0 (0)	0 (0)

(Table III). Thus, the frequency of heterozygosity was more frequent in the controls than in the cases for both genes, but the differences were not significant (p=0.1). No mutant homozygotes were identified for either of the genes in the cases or in the controls.

When the frequency of the *CYP1A1* and *CYP2E1* alleles was analysed in relation to sex, the frequency of the *CYP1A1* Ile/Val genotype appeared to be the same in the cancer patients (5%) for both males and females, while in the controls its frequency was double in the females (9%) compared to the males (5%) (Table IV). As for the *CYP2E1* c1/c2 genotype, it was detected in 4 males (2%) and in 8 females (7%) amongst the cases, while it was more represented in the males (11%) than in the females (6%) in the controls. None of the differences observed was significant. The frequency of the *CYP1A1* and *CYP2E1* alleles was also evaluated according to age using sixty year cut-off to distinguish young from old subjects. The frequency of the *CYP1A1* Ile/Val genotype in the control group was 6% and 8% for the young and old subjects, respectively. The corresponding values for the case population were 4% and 5% (Table IV) and these differences were not significant. Similarly, the frequency of the *CYP2E1* c1/c2 genotype in the control group was 10% and 7% for the young and old subjects, respectively, while it was 4% for both young and old subjects for the cases. Analysing the results according to tumor type, the frequency of the *CYP1A1* Ile/Val genotype was 0% in lymphomas and 2% in colorectal, 5% in breast/ovarian, 14% in gastric, 17% in biliary tract/pancreas and 6% in urinary tract carcinomas (Table V). The frequency of the *CYP2E1* c1/c2 genotype was 25% in lymphomas and 6% in colorectal, 17% in biliary tract/pancreas and 6% in urinary tract carcinomas (Table V). None of the differences observed was significant.

Table VI. *Distribution of XRCC1 gene polymorphisms in cases and controls.*

	XRCC1-194			*XRCC1*-399	
	Cases n (%)	Controls n (%)		Cases n (%)	Controls n (%)
Total	290	242		290	242
Arg/Arg	253 (87)	208 (86)	Arg/Arg	129 (44)	106 (44)
Arg/Trp	37 (13)	34 (14)	Arg/Gln	133 (46)	122 (50)
Trp/Trp	0 (0)	0 (0)	Gln/Gln	28 (10)	14 (6)

The distribution of the *XRCC1* 194 and *XRCC1* 399 alleles among the cases and controls is presented in Table VI. The frequencies of the polymorphisms at both sites were similar in the cases and controls, the differences being not significant (p=0.1). However, it is noteworthy that while for codon 399 all three possible genotypes (Arg/Arg, Arg/Gln, Gln/Gln) were detected, for the 194 codon, no mutant homozygotes (Gln/Gln) were detected in the populations analyzed.

The frequency of the *XRCC1* 194 and *XRCC1* 399 polymorphisms in both groups was also evaluated according to sex and age. In the cases, the *XRCC1* Arg194Trp polymorphism was observed in 31 (17%) male patients and in 6 (5%) females, while in the control group it was detected in 26 females (20%) and in 8 males (7%) (Table VII). The Arg399Gln polymorphism was detected in a heterozygous form in 79 males (45%) and in 54 females (48%) in the cases and in 61 males (54%) and 61 females (47%) in the control group. The mutant homozygote was observed in 22 males (12%) and in 6 females (5%) within the cases and in 4 males (4%) and 10 females (8%) of the control group. None of the differences observed was significant. Regarding the age, using the sixty year cut-off value, the frequency of the *XRCC1* Arg194Trp polymorphism in the control group was 19% and 12% for young and old subjects, respectively; the corresponding values for the case population were 7% and 16% (Table VII). These differences were not significant, nor were those for the distribution of the polymorphisms at codon 399. In order to investigate the relationship of the *XRCC1* polymorphisms at codons 194 and 399 with specific types of cancer, the occurrence of the *XRCC1* genotypes was evaluated in cancer patients stratified according to disease (Table VIII). The frequency of the *XRCC1* Arg194Trp polymorphism was highest in the patients with colorectal (14%), urinary tract (25%) and other types of cancer (22%). The frequency of the heterozygous *XRCC1* Arg399Gln polymorphism was quite high in most of the cancer types including 43% in colorectal, 47% in lung, 52% in breast/ovarian, 72% in gastric and 75% in urinary tract carcinomas; moreover, a mutant homozygote status was higher in gastric (14%), biliary tract/pancreas (33%) and skin (50%) carcinomas than in all the other types of tumors. However, these differences were not significant.

Discussion

To the best of our knowledge, this study was the first to analyse polymorphisms in the *CYP1A1, CYP2E1* and *XRCC1* genes in a Southern Italian population and to correlate the results with the individual cancer risk. For the *CYP1A1* and *CYP2E1* genes, the frequency of the homozygote wild-type and the heterozygote genotypes was not different between the cancer patients and the healthy individuals. Mutant homozygotes were not found, in agreement with the available data for Caucasians (2-4, 6, 7). These findings suggest that the *CYP1A1* and *CYP2E1* polymorphisms do not significantly influence the individual risk of developing cancer, at least when considering the population of the Basilicata region in South Italy. Although not expected, these findings were not surprising since inconsistent results have been reported in the literature regarding the relationship between these two genes and cancer risk (1, 5-7, 14, 15).

Regarding the *XRCC1* Arg194Trp and Arg399Gln polymorphisms, although some slight differences were observed between the cases and controls, no significant differences were detected, even when the data were stratified according to tumor type, age or sex. The lack of an association between the *XRCC1* polymorphisms and individual cancer risk was in agreement with our previous study which failed to find an association between the same polymorphisms and the risk of colorectal and lung cancer in the same population (13).

The distributions of the studied polymorphisms appeared not to be different from those reported for other Caucasian populations. The available data suggest that the incidence of cancer is lower in the Basilicata region compared to other Italian regions as well as other Caucasian populations (16). The present study therefore suggest that factors, other than *CYP1A1*, *CYP2E1* and *XRCC1* polymorphisms, are responsible for this low incidence of cancer. Taken together with the results of our previous studies (12, 13), genetic factors seem unlikely to be involved in this phenomenon which is more probably due to environmental and/or lifestyle factors.

The lack of association between the analysed polymorphisms and cancer risk might also have been due to the small sample size. However, it is worth noting that contrasting results have been reported in the literature and these inconsistencies may well also be related to variations in carcinogenic exposure and ethnic origin of the populations enrolled in the different studies (14, 15, 17). This observation further supports the need to extend this type of analysis to different populations, especially when dealing with populations, such as the one from the Basilicata region, which

Table VII. *Distribution of XRCC1 polymorphisms in cancer patients and in healthy controls stratified by sex and age.*

	CODON 194						CODON 399					
	Case	n	(%)	Controls	n	(%)	Cases	n	(%)	Controls	n	(%)
Males	Total:	178			112			178			112	
	Arg/Arg:	147	(83)	Arg/Arg:	104	(93)	Arg/Arg:	77	(43)	Arg/Arg:	47	(42)
	Arg/Trp:	31	(17)	Arg/Trp:	8	(7)	Arg/Gln:	79	(45)	Arg/Gln:	61	(54)
	Trp/Trp:	0	(0)	Trp/Trp:		(0)	Gln/Gln:	22	(12)	Gln/Gln:	4	(4)
Females	Total:	112			130			112			130	
	Arg/Arg:	106	(95)	Arg/Arg:	104	(80)	Arg/Arg:	52	(46)	Arg/Arg:	59	(45)
	Arg/Trp:	6	(5)	Arg/Trp:	26	(20)	Arg/Gln:	54	(48)	Arg/Gln:	61	(47)
	Trp/Trp:		0(0)	Trp/Trp:	0	(0)	Gln/Gln:	6	(5)	Gln/Gln:	10	(8)
≤60 years	Total:	102			62			102			62	
	Arg/Arg:	95	(93)	Arg/Arg:	50	(81)	Arg/Arg:	37	(36)	Arg/Arg:	24	(39)
	Arg/Trp:	7	(7)	Arg/Trp:	12	(19)	Arg/Gln:	46	(45)	Arg/Gln:	34	(55)
	Trp/Trp:	0	(0)	Trp/Trp:	0	(0)	Gln/Gln:	19	(19)	Gln/Gln:	4	(6)
>60 years	Total:	188			180			188			180	
	Arg/Arg:	158	(84)	Arg/Arg:	158	(88)	Arg/Arg:	92	(49)	Arg/Arg:	82	(46)
	Arg/Trp:	30	(16)	Arg/Trp:	22	(12)	Arg/Gln:	87	(46)	Arg/Gln:	88	(49)
	Trp/Trp:	0	(0)	Trp/Trp:	0	(0)	Gln/Gln:	9	(5)	Gln/Gln:	10	(5)

Table VIII. *Distribution of XRCC1 polymorphisms with respect to tumor type.*

		Genotype											
		CODON 194						CODON 399					
		Arg/Arg		Arg/Trp		Trp/Trp		Arg/Arg		Arg/Gln		Gln/Gln	
Tumor type	Total	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Colorectal cancer	104	90	(86)	14	(14)	0	(0)	49	(47)	45	(43)	10	(10)
Breast/ovarian cancer	42	40	(95)	2	(5)	0	(0)	18	(43)	22	(52)	2	(5)
Gastric cancer	14	14	(100)	0	(0)	0	(0)	2	(14)	10	(72)		2 (14)
Biliary tract/pancreas	12	12	(100)	0	(0)	0	(0)	6	(50)	2	(17)	4	(33)
Lung cancer	38	34	(89)	4	(11)	0	(0)	16	(42)	18	(47)	4	(11)
Urinary tract	32	24	(75)	8	(25)	0	(0)	6	(19)	24	(75)	2	(6)
Skin cancer	4	4	(100)	0	(0)	0	(0)	2	(50)	0	(0)	2	(50)
Lymphoma	8	8	(100)	0	(0)	0	(0)	4	(50)	4	(50)	0	(0)
Other	36	28	(78)	8	(22)	0	(0)	24	(67)	10	(28)	2	(5)

for geographical and cultural reasons has been isolated from the other surrounding regions for decades. In conclusion, acknowledging the relatively small size of the analysed groups, the polymorphisms in the *CYP1A1, CYP2E1* and *XRCC1* genes displayed a lack of association with the risk of developing a neoplastic disease in the population under study, and their distribution did not differ compared to other Caucasian populations, warranting further studies to explain the reduced incidence of cancer reported in this Southern Italian region.

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