RESEARCH ARTICLE

The Codon 399 Arg/Gln XRCC1 Polymorphism is Associated with Lung Cancer in Indians

Kirmani Natukula[1,2], Kaiser Jamil[1]*, Usha Rani Pingali[2], Venkata Satya Suresh Attili[3], Umamaheshwar Rao Naidu Madireddy[4]

Abstract

Background: The XRCC1 (X-ray repair cross complimenting group-I) gene in BER (base excision repair) pathway is essential for DNA repair process. Polymorphisms in this gene are associated with variations in the repair efficiency which might predispose individuals to development of various cancers. Two variants of XRCC1gene (at codon 399), Gln/Gln and Arg/Gln, have been shown to be related to lowered DNA repair capacity and increased genomic instability in multiple studies. Hence our investigation focused on genotyping these variants to correlate with other multiple risk factors in lung cancer (NSCLC) patients since we hypothesized that these variants of the XRCC1 gene might influence disease susceptibility. Materials and Methods: We examined the frequency of the polymorphism in one hundred cases and an almost equal number of controls after recording their demographics with a structured questionnaire. Genomic DNA from blood samples was extracted for PCR studies, followed by RFLP to determine the variants. The significance of the data was statistically analyzed. Results: The three genotypes in cases and controls were Arg/Arg (40% and 54.45%); Gln/Gln (19% and 9.90%), and Arg/Gln (41.0% and 35.64%) respectively. Among these 3 genotypes, we found Gln/Gln and Arg/Gln to show association with lung cancer. Correlating these genotypes with several parameters, we also found that these two variants were associated with risk in males ($p<0.05$) and with smoking habits ($p<0.05$). In females Arg/Gln genotype showed association with stage of the disease ($p=0.04$). This is the first report in South Indian scenario where Arg399Gln genotypes were found to be associated with stage of the disease in females. Conclusions: It is concluded that XRCC1 genotypes Gln/Gln and Arg/Gln may influence cancer susceptibility in patients with smoking habits and these functional SNPs in XRCC1 gene may act as attractive candidate biomarkers in lung cancer for diagnosis and prognosis.

Keywords: Non small cell lung cancer (NSCLC) - x-ray repair cross complimenting group I (XRCC1)

Asian Pac J Cancer Prev, **14 (9)**, 5275-5279

Introduction

Lung cancer is a major public health problem representing most common cancer, and more than a million people in the world die from the disease each year. Risk factors for lung cancers can be related to environmental factors, genetic pre dispositions, compromised immune systems or viral infections. Many cancers are genetic diseases, resulting from gradual accumulation of mutational changes in the DNA that activate proto-oncogenes and inactivate tumour-suppressor genes leading to genetic instability which is further aggravated by DNA damage and errors made by the DNA maintenance and repair machinery so called "DNA repair genes" by Hoeijmakers (2001). Genetic polymorphisms in DNA repair genes are very common events. Sometimes these abnormalities may not be corrected due to mutations in DNA repair genes, further these mutations allow subsequent mutations to accumulate in the next generations. Many authors proved that consequent mutations in DNA repair enzyme gene polymorphism may not only alter the function, but can reduce the DNA repair capacity which may lead to cancer susceptibility (Knight et al., 1993; Wei et al., 1996; Spitz et al., 1997).

X-ray repair cross complimenting group I (XRCC1), a major DNA repair gene in the base excision repair (BER) pathway, acts as a scaffold of different activities involved in repair by interacting with components at the site of damage. Human XRCC1 is located on chromosome 19q13.2-13.3 (Thompson et al., 1989; Mohrenweiser and Jones 1998) and two known polymorphisms at codon 280 (exon9, base 27466 G to A, Arg to His) and codon 399 (exon10, base 28152 G to A, Arg to Gln) leads to amino acid substitution has been discussed by Shen et al. (1998)

*[1]Genetics Department, Bhagwan Mahavir Medical Research Centre, Masab tank, [2]Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, [3]Department of Medical Oncology, BIBI General Hospitals and Cancer Centre, [4]Central Research Institute of Unani Medicine, Hyderabad, India *For correspondence: kaiser.jamil@gmail.com*

and Schneider et al. (2008).

Association between XRCC1 variants in DNA repair gene and cancer risk was reported (Hu et al., 2005; Yin et al., 2007). In 2007, Pachouri et al. (2007) in a case control study examined the association of polymorphism in a XRCC1 gene and lung cancer risk, and found the polymorphism at codon 399 was protective in lung cancer. Sabitha et al. (2009) reported that amino acid substitution (Arg399Gln) may alter the phenotype of the XRCC1 protein resulting in deficient DNA repair capacity leading to risk in Head and Neck cancer, but this relationship is complex. A recent study by Karkucak et al. (2012) reported no association of XRCC1 gene Arg399Gln polymorphism in lung cancer risk. But variations between individuals, lacking DNA repair capacity in humans may be prone to risk of various cancers as reported by Hu et al. (2011) in Glioma, gastric cancer by Engin et al. (2011) and Kumar et al. (2012) reported risk in Head and neck cancers.

Many studies proved that individuals with the 399Gln allele were not able to repair DNA damage and therefore had significant risk of Lung carcinogenesis. But the functional consequences still remain unknown. Hence in this case control study, we investigated the relationship between the clinical and demographic parameters and their associations with the genotypes of XRCC1 gene leading to the risk of lung cancer in south Indian patients.

Materials and Methods

The Project was approved by the Institutional Ethics Committee of Mahavir Hospital and Research Centre (Hyderabad) in accordance with the Helsinki Declaration.

Enrolment of study subjects: In this study a total of 100 patients, with Non small cell lung cancer (pathologically, histologically/cytologically confirmed) between June 2009 to November 2012 were enrolled. The disease was determined clinically through FNAC, malignant cytology in pleural effusion, and bronchoscopy by Pathologists. Equal number of (N=101) age and sex matched control subjects were enrolled and informed consent was taken from all the subjects. Recording of demographic details was in a structured questionnaire carried out by direct interview and referring the medical records. The parameters included the patient's age, gender, contact information, smoking status, the date of first visit and diagnosis were recorded. Apart from this treatment information, site and stage of the disease were also recorded.

Blood sample collection:

Two milliliters of venous blood was collected from patients in the K2-EDTA vacutainers after obtaining informed consent from the patients and volunteers. The Inclusion criteria were those cases with confirmed lung malignancy as diagnosed by the pathologist. Control subjects also gave informed consent prior to collecting the blood samples.

Genotyping-XRCC 1 codon 399

Genomic DNA was isolated from blood samples of lung cancer cases and controls on the same day of sample collection by salting out method (Miller et al., 1988). XRCC1 codon 399 genotyping was done by Polymerase chain reaction (PCR) followed by Restriction length polymorphism (RFLP) as described by Sabitha et al. (2009) with modification of annealing temperature. Presence of 615 bp product confirms the standardization of gene for PCR (Figure 1A).

PCR product was subjected to restriction digestion with Msp1 (Fermentas, cat no: ER0541). Since the G to A transition in exon 10 of XRCC1 abolishes the recognition site for Msp1 enzyme, the Gln/Gln genotype yielded an undigested band of 615 bp, Arg/Arg resulted in two fragments of 376bp and 239bp and Arg/Gln genotype with three fragments of 615bp, 376 bp and 239 bp (Figure 1B).

Statistical analysis

Statistical analyses were carried out using the EPI7 (Epi Info TM Version 7 for Windows). Odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding p-values for each genotype controlling age, Sex, Smoking habits, Histological types as covariates by computational analysis. The p values of <0.05 were considered statistically significant.

Results

Demographic parameters of cases (n=100) and controls (n=101) are presented in Table 1. Number of males were 73 (75%) and females 27 (27%) in cases, and in controls 86 (85.15%) were males and 15 (14.85%) females. Mean age for cases was 56.14 years (both sexes included) and 48.07 years in control group (both sexes included). Age factor appeared to be significant (p=0.0001) with respect to the disease status, cases were more in older age group. Among the cases 51% were smokers and 49% were non smokers and in controls 36 (35.643%) were smokers and 65 (64.356%) were non smokers. Smoking habit was found to significant with lung cancer risk in both cases and controls where p showed <0.05. In histology-subtypes, out of 100 cases 55% were diagnosed as adenocarcinoma,

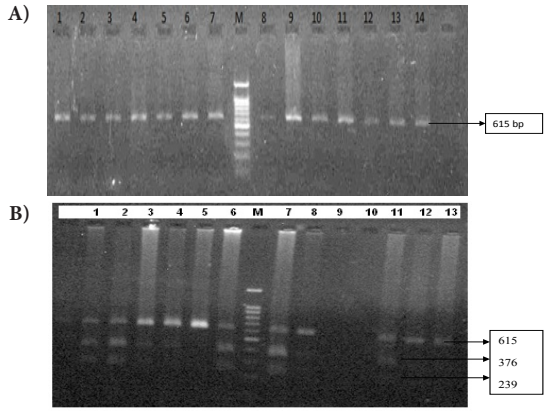

Figure 1. Agarose Gel. A) Showing 615 bp of amplified PCR product of XRCC1 gene Lane 1-7 and 8-14 showing 615 bp product of XRCC1 gene Lane M=100 bp DNA ladder; and **B)** Showing RFLP Products of XRCC1 Gene Lane 1-4,6,7,11and13 Arg/Gln genotypes (615bpand 376, 239 bp) Lane 5and8 GlnGln genotypes (615bp) Lane M-100 bp DNA marker

29% were squamous cell carcinoma and 16% were undifferentiated in nature. When we compared the histological sub-types who were smokers and non-smokers, we did not find significant difference (p≥0.5) similarly we did not find much difference in the other two subtypes of NSCLC (p≥0.5) Regarding the stage of the disease 35% were stage III and 65% were stage IV disease. Comparing the disease Stages among smokers and non-smokers, we found significant differences (p<0.05) incidentally, both in cases and controls males were more in numbers compared with females (Table 1).

Genotype distribution results are presented in Table 2. To enhance statistical power of the genotypes to detect their association with the risk of the disease, we compared the three genotypes in cases and controls. We found that the frequency of Wild type was (Arg/Arg) 40% and 54.45%, Homozyous mutation (Gln/Gln) were 19% and 9.90% and Heterozygous genotype Arg/Gln were 41% and 35.64% in cases and controls respectively. Statistically the Odds ratio for Gln/Gln genotype was (OD: 2.613, X^2: 4.85, p=0.02) and for Arg/Gln (OD: 1.566, X^2: 5.042, p=0.02) which was significant when compared with controls. Any among these two variants Gln/Gln or Arg/Gln were found to be significantly associated with lung cancer when compared with control group.

Comparing the Genotypes of all the males in cases versus controls (n=82 Vs n=73), we found significant differences as shown here: Gln/Gln (OD: 0.333, X^2: 4.630) and Arg/Gln (OD: 0.690, X^2: 4.770) where p=0.03 (Table 2). Therefore it is believed that genotyping this codon-399 of XRCC1 gene is very important to determine the susceptibility factor to lung cancer risk.

But in the female group (cases versus controls) none of the genotypes showed significant differences between cases and controls where the p value was greater than 0.05 (Table 2).

The distribution of three genotypes in smokers and non smokers in the cases (n=82) were found to be (Arg/Arg) 24.5% and 57.14%, (Gln/Gln) 27.45% and 10.20% and (Arg/Gln) 49.01% and 32.65%. Here we found that any variant eighter Gln/Gln or Arg/Gln with smoking habit was associated with higher risk of lung cancer. But smoking habit with Gln/Gln genotype was found to be more highly significant (OD: 6.533, X^2: 9.887) p=0.001 compared with Arg/Gln (OD: 3.646, X^2: 4.192) p=0.04 which is also significant but to a lesser extent comparatively (Table 2).

Since we had very less number of female cases in this cohort study to determine the genotype significance, the values which are being presented as significant (Table 2) have to be repeated with more number of female cases. However overall in the cases we found the significance of this codon-399 polymorphism of XRCC1 gene.

When we correlated the stage of the disease with genotypes we found that females with Arg/Gln genotypes showed significance where p=0.04. While other genotypes did not show significance with the stage of the disease where p>0.05. (Table 3).

Table 1. Demographic Distribution of Cases and Controls

Characteristics		Cases (n=101)	Controls (n=101)	Odds Ration	Test Statistics 95%CI	p value
Gender	Males	73 (73%)	86 (86%)	0.4716	0.233-0.953	0.04*
	Females	27 (27%)	15 (14.85%)			
	Mean age (both Sex) (years)	56.14	48.07	T=4.69	-11.4-4.6	0.0001*
Smoking status	Smokers	51 (51%)	36 (35.64%)	1.879	1.067-3.3074	0.03*
	Non smokers	49 (49%)	65 (65%)			
		Smokers	Non Smokers	Odds Ratio	95% CI	p value
Histology (both sexes)	Adenocarcinoma	24	31	0.6194	0.20-1.369	0.235
	Squamous Cell	14	15	0.96	0.404-2.278	0.926
	Undifferentiated	11	5	2.66	0.850-8.336	0.08
Stage	IIIB (n=35)	10	25	0.234	0.096-0.570	0.0009*
	IV (n=65)	41	24			

*Significance: p<0.05

Table 3. XRCC1 codon 399 Genotyping Distribution in Stage IIIB and Stage IV Disease in Males and Females

Genotype	Males (n=73)					Femles (n=23)				
	IIIB (n=25)	IV (n=48)	Odds Ratio	X^2	p value	IIIB (n=10)	IV (n=17)	Odds Ratio	X^2	p value
Arg/Arg	13 (52%)	18 (37.5%)	1.0**	1.0**	1.0**			1.0**	1.0**	1.0**
Gln/Gln	4 (16%)	10 (20.83%)	0.55	0.68	0.4	1 (10%)	4 (23.52%)	2	0.397	0.528
Arg/Gln	8 (32%)	20 (41.7%)	0.55	0.48%	0.488	8 (80%)	5 (29.41%)	12.8	4.04	0.04*

*Significance: p<0.05; **Used as reference group

Table 2. Genotyping Distribution of XRCC1 Codon 399

Genotype	Cases and Controls					Males: Cases Versus Controls					Females: Cases Versus Controls					Smoker and Nonsmokers in Male and Female Cases				
	Cases (n=100)	Controls (n=101)	Odds Ratio	X^2	p value	Cases (n=82)	Controls (n=73)	Odds Ratio	X^2	p value	Cases (n=19)	Controls (n=27)	Odds Ratio	X^2	p value	Cases (n=51)	Controls (n=49)	Odds Ratio	X^2	p value
Arg/Arg	40 (40%)	55 (54.45%)	1.0**	1.0**	1.0**	45 (54.88%)	30 (41.09%)	1.0**	1.0**	1.0**	10 (52.63%)	10 (37.03%)	1.0*	1.0*	1.0*	12 (24.5%)	28 (57.14%)	1.0**	1.0**	1.0**
Gln/Gln	19 (19%)	10 (9.90%)	2.613	4.85	0.02*	7 (8.53%)	14 (19.17%)	0.333	4.63	0.03*	3 (15.79%)	5 (18.51%)	0.6	0.306	0.579	14 (27.45%)	5 (10.20%)	6.5333	9.887	0.001*
Arg/Gln	41 (41%)	36 (35.64%)	1.566	5.042	0.02*	30 (36.60%)	29 (39.73%)	0.69	4.77	0.028*	6 (31.58%)	12 (44.44%)	0.5	0.173	0.6773	25 (49.01%)	16 (32.65%)	3.646	4.192	0.04*

*Significance: p<0.05; **Used as reference group

Discussion

DNA repair pathways play a vital role in maintaining genetic integrity and it is becoming clear that defects in repair pathways are connected to many different types of diseases including cancers. DNA repair systems maintain genomic integrity, in the face of environmental insults with various kinds of carcinogens, exposures like nicotine, occupational environmental exposures including pesticides (Kirmani et al., 2010). DNA repair maintains the integrity of the human genome by reducing the mutation frequency of cancer-related genes. XRCC1 plays a major role in the multi-step base excision repair pathways where non bulky base adducts produced by methylation, oxidation, reduction or fragmentation of base by ionization radiation or oxidation damages are removed (Yu et al., 1999). Various types of carcinoma were investigated for XRCC1 Arg399Gln polymorphism, namely esophageal cancer, prostate cancer, colorectal cancer, lung cancer (Park et al., 2002) and hepatocellular carcinoma. All of these studies found that the 399 Gln allele was associated with a higher risk of cancer than the othe genotypes like-399Arg allele in XRCC1 gene. In a previous study by Divine et al. (2001) also reported Gln allele is more frequent in lung cancer. In our study also we found a positive association with Gln/Gln and Arg/Gln genotype with lung cancer where $p<0.05$. We observed potential risk factor with genetic polymorphism and lung cancer risk. Previous studies conducted in south Indian population by Kiran et al. (2010) also supports our data where genotyping of Gln/Gln and Arg/Gln have shown a high risk in cancer cases. The frequency of homozygous wild genotype (Gln) of codon 399 as observed in the present study was comparable with earlier reports from Indian population (Sreeja et al., 2008; Gangwar et al., 2009). Recent study conducted by Guo (2013), reported that heterozygous genotype (Arg/Gln) had much higher risk than other genotypes in Northeastern Chinese lung cancer population. Other Asian countries who investigated on the same polymorphism in their population showed that the results differed. Chen (2002) and Zhang et al. (2005) found no association with Chinese population with XRCC1 codon 399. The results are complex and contradictory with each others. But majority of the reports considered this to be a lung cancer risk factor in various populations.

Lung cancer was a rare entity in the early 1900s but has since become far more prevalent in western countries than India and recently, it surpassed heart disease as the leading cause of smoking-related mortality including in India. Cigarette smoke is a major cause of a variety of malignancies including cancer of the head and neck, esophageal and lung. Cigarette smoke contains a myriad of genotoxic agents and carcinogens such as nitrosamine 4-(methylnitosamino)-1-(3-pyridyl)-1-butanone (NNK) which is cancer causing agent. During the 1950s, the evidence was clearly sufficient to establish the carcinogenicity of tobacco smoking leading to lung carcinogenesis by various authors (Doll, 1998). In our previous epidemiological studies we also reported that cigarette smoke plays an important role as an environmental etiological factor in the development of lung cancer (Kirmani et al., 2010). In the present study, we found that smoking contributed to higher risk in cancer cases compared with controls (Table 1) and when compared between smokers and non smokers, smokers were definitely at higher risk in cases (Table 5). Nemours reports are available in smoker populations where XRCC1 gene polymorphism leads to lung cancer risk (Divine et al., 2001; Misra 2003; Schneider et al., 2005; Ryk et al., 2006; De Ruyck et al., 2007; Sreeja et al., 2008). An interesting finding from our study was that males were at higher risk than females with XRCC1 polymorphism when compared with controls. Because exposure to smoking and other environmental and occupational carcinogens exposures like pesticides (Kirmani et al., 2010) were far more common in "male jobs". Regarding the stage of the disease or cancer progressing to a higher stage; the female group with Arg/Gln genotype showed significance for disease progression or advancement of the disease OD:12.8, X^2: 4.04, $p=0.04$*. Further, correlation for gender group versus stage of the disease–(stage III and Stage IV) with genotypes; we found no significance with this association between these parameters. This data were consistent with earlier reports on risk of cancer of the breast (Duell et al., 2001), bladder and lung (Ratnasinghe et al., 2001), thyroid carcer (Fard-Esfahani et al., 2011), bladder cancer (Mao et al., 2013), and colorectal cancer (Nissar et al., 2013). It is therefore obvious that XRCC1 codon 399 may be associated with altered function of the coding products and thus contribute to the individual's genetic susceptibility to lung cancer.

In conclusion, after stratification for variables, such as, age, gender, smoking and histology type of cases the XRCC1 genotypes eighter Gln/Gln or Arg/Gln were found to be associated with a significantly increased risk of lung cancer. Smoking contributed to even higher risk for lung cancer compared with controls. In cases, smoking habit contributed to be associated with variant genotypes either Gln/Gln or Arg/Gln. Male group showed higher risk than females with or without polymorphism in XRCC1 gene. Present results and those of other recent epidemiological studies of XRCC1 Arg399Gln suggest that Base excision repair (BER) represents an important pathway for future molecular epidemiological studies and for determining biomarkers for lung cancer.

Acknowledgements

We are grateful to the Oncologists and the Pathologists for their cooperation and help in selecting our study group and for permitting us to collect their medical histories. We are thankful to all the patients for their cooperation and participation in this study. We thank BIBI General Hospitals and Cancer Centre for samples. We thank Bhagwan Mahavir Medical Research Centre and MGNIRSA, Hyderabad for facilities provided for this study. We thank the Dean, and staff of the Department of Clinical Pharmacology and therapeutics of Nizams' Institute of Medical Sciences (NIMS) for their encouragement and support for this study.

References

Chen S, Tang D, Xue K, et al (2002). DNA repair gene XRCC1 and XPD polymorphisms and risk of lung cancer in a chinese population. *Carcinogenesis*, **23**, 1321-5.

De Ruyck K, Szaumkessel M, De Rudder I, et al (2007). Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk. *Mutat Res*, **631**, 101-10.

Divine KK, Gilliland FD, Crowell RE, et al (2001). The XRCC1 399 Glutamine allele is a risk factor for adenocarcinoma of the lung. *Mutat Res*, **461**, 273-8.

Doll R (1998). Uncovering the effects of smoking: historical perspective. *Stat Methods Med Res*, **7**, 87-117.

Duell EJ, Millikan RC, Pittman GS, et al (2001). Polymorphism in the DNA repair gene XRCC1 and breast cancer. *Cancer Epidemiol Biomarkers Prev*, **10**, 217-22.

Engin AB, Karahalil B, Karakaya AE, et al (2011). Association between XRCC1 Arg399gln and p53 arg72pro polymorphisms and the risk of gastric and colorectal cancer in Turkish population. *Arh Hig Rada Toksikol*, **62**, 207-14.

Fard-Esfahani P, Fard-Esfahani A, Fayaz S, et al (2011). Association of Arg194Trp, Arg280His and Arg399Gln polymorphisms in x-ray repair cross-complementing group 1 gene and risk of differentiated thyroid carcinoma in Iran. *Iranian Biomedical J*, **15**, 73-8.

Gangwar R, Manchanda PK, Mittal RD (2009). Implications of XRCC1, XPD and APE1 gene polymorphism in North Indian population: a comparative approach in different ethnic groups worldwide. *Genetica*, **136**, 163-9.

Guo S, Li X, Gao M, et al (2013). The Relationship between XRCC1 and XRCC3 gene polymorphisms and lung cancer risk in Northeastern Chinese. *Plos One*, **8**, 1-5.

Hoeijmakers JH (2001). Genome maintenance mechanisms for preventing cancer. *Nature*, **411**, 366-74.

Hu XB, Feng Z, Fan YC, et al (2005). XRCC1 polymorphism and cancer risk: a meta analysis of 38 case-control studies. *Cancer Epidemiol Biomarkers prev*, **143**, 1810-8.

Hu XB, Feng Z, Fan YC, et al (2011). Polymorphisms in DNA repair gene XRCC1 and increased genetic susceptibility to glioma. *Asian Pac J Cancer Prev*, **12**, 2981-4.

Karkucak M, Yakut T, Evrensel T, et al (2012). XRCC1 gene polymorphisms and risk of lung cancer in Turkish patients. *Int J Hum Genet*, **12**, 113-7.

Kiran M, Saxena R, Kaur J (2010). Distribution of XRCC1 genotypes in north Indian population. *Indian J Med Res*, **131**, 71-5.

Kirmani N, Jamil K, Naidu MUR (2010). Occupational and environmental carcinogens in epidemiology of lung cancer in South Indian population. *Biol Med*, **2**, 1-11.

Knight RD, Parshad R, Price FM, et al (1993). X-ray-induced chromatid damage in relation to DNA repair and cancer incidence in family members. *Int J Cancer*, **54**, 589-93.

Kumar A, Pant MC, Singh HS, et al (2012). Associated risk of XRCC1 and XPD cross talk and life style factors in progression of head and neck cancer in north Indian population. *Mut Res*, **729**, 24-34.

Mao Y, Xu X, Lin Y et al (2013). Quantitative assessment of the associations between XRCC1 polymorphisms and bladder cancer risk. *World J Surg Oncol,* **11**, 58.

Miller SL, Dykes DD, Polesky HF (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nuc Acid Res*, **16**, 12-5.

Misra RR, Ratnasinghe D, Tangrea JA, et al (2003). Polymorphisms in the DNA repair genes XPD, XRCC1, XRCC3, and APE/ref-1, and the risk of lung cancer among male smokers in Finland. *Cancer Lett*, **191**, 171-8.

Mohrenweiser HW, Jones IM (1998). Variation in DNA repair is a factor in cancer susceptibility: a paradigm for the promises and perils of individual and population risk estimation? *Mutat Res*, **400**, 15-24.

Nissar S, Lone TA, Banday MZ, et al (2013). Arg399Gln polymorphism of XRCC1 gene and risk of colorectal cancer in Kashmir: a case control study. *Oncology Letters*, **5**, 959-63.

Pachouri SS, Sobti RC, Kaur P, et al (2007). Constrasting impact of DNA repair gene XRCC1 polymorphism Arg399Gln and Arg 194 Trp on the risk of lung cancer in the north-Indian population. *DNA Cell Biol*, **26**, 186-91.

Park JY, Lee SY, Jeon HS, et al (2002). Polymorphism of the DNA repair gene XRCC1 and risk of primary lung cancer. *Cancer Epidemiol Biomarkers Prev*, **11**, 23-7.

Ratnasinghe D, Yao SX, Tangrea JA, et al (2001). Polymorphism of the DNA repair gene XRCC1 and lung cancer risk. *Cancer Epidemiol Biomarkers Prev*, **10**, 119-23.

Ryk C, Kumar R, Thirumaran RK, et al (2006). Polymorphisms in the DNA repair genes XRCC1, APEX1, XRCC3 and NBS1, and the risk for lung cancer in never-and ever-smokers. *Lung Cancer*, **54**, 285-92.

Sabitha K, Vishnuvardhan MR, Kaiser J (2009). Mutation in XRCC1 gene alters the genetic risks of Head and Neck cancer patients. *Int J Cancer Research*, **5**, 58-68.

Schneider J, Classen V, Bernges U, et al (2005). XRCC1 polymorphism and lung cancer risk in relation to tobacco smoking. *Int J Mol Med*, **16**, 709-16.

Schneider J, Classen V, Helmig S (2008). XRCC1 polymorphism and lung cancer risk. *Expert Rev Mol Diagn*, **8**, 761-80.

Shen MR, Jones IM, Mohrenweiser H (1998). Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. *Cancer Res*, **58**, 604-8.

Spitz MR, Mc Pherson RS, Jiang HH, et al (1997). Correlates of mutagen sensitivity in patients with upper aerodigestive tract cancer. *Cancer Epidemiol Biomark Prev*, **6**, 687-9.

Sreeja L, Syamala VS, Syamala V, et al (2008). Prognostic importance of DNA repair gene polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln in lung cancer patients from India. *J Cancer Res Clin Oncol*, **134**, 645-52.

Thompson LH, Bachinski LL, Stallings RL, et al (1989). Complementation of repair gene mutations on the hemizygous chromosome 9 in CHO: a third repair gene on human chromosome 19. *Genomics*, **5**, 670-9.

Wei Q, Cheng L, Hong WK, et al (1996). Reduced DNA repair capacity in lung cancer patients. *Cancer Res*, **56**, 4103-7.

Yin J, Vogel U, Ma Y, et al (2007). The DNA repair gene XRCC1 and genetic susceptibility of lung cancer in northeastern Chainese population. *Lung Cancer*, **56**, 153-60.

Yu Z, Chen J, Ford BN, et al (1999). Human DNA repair systems: an overview. *Environ Mol Mutagen*, **33**, 3-20.

Zhang X, Miao X, Liang G, et al (2005). Polymorphisms in DNA base excision repair genes ADPRT and XRCC1 and risk of lung cancer. *Cancer Res*, **6**, 722-6.