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ORIGINAL ARTICLE

XPC Polymorphism and Risk for Lung Cancer in North Indian Patients Treated with Platinum Based Chemotherapy and Its Association with Clinical Outcomes

Shweta Lawania[1] · **Navneet Singh**[2] · **Digamber Behera**[2] · **Siddharth Sharma**[1]

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Abstract Xeroderma pigmentosum complementation group C plays an important role in the human repair system. As reported in previous studies its polymorphism are associated with lung cancer susceptibility. The purpose of this study is to investigate the association of *XPC* gene with lung cancer susceptibility, overall response and clinical outcomes amongst North Indians. A hospital based study of 370 lung cancer cases and 370 healthy controls was conducted and genotypes were determined using PCR-RFLP assay. Results were assessed using logistic linear regression adjusted for age, sex and smoking status. Survival analysis was conducted using Kaplan-Meier survival analysis and Cox regression analysis. The treatment outcomes of 167 lung cancer patients treated with platinum based chemotherapy were evaluated.The mutant genotypic variant of *XPC* Lys^{939}Gln has been associated with elevated risk of lung cancer(OR:2.30;95%CI:1.41-3.73;p=0.0007) whereas *XPC* Ala^{499}Val showed a highly protective effect (OR:0.25;95%CI:0.10-0.63;p=0.003). The mutant genotype of *XPC* Lys^{939}Gln presented a higher risk of developing lung cancer in heavy smokers (OR: 3.71; 95%CI:1.46-9.45; ***p=0.005***). The survival analysis presented that heterozygous genotype showed least survival in comparison with mutant genotype in *XPC* Ala^{499}Val genetic variant whereas no significant association was observed in *XPC* Lys^{939}Gln. In conclusion, *XPC* Lys^{939}Gln is associated with significant risk towards the lung cancer whereas on contrary *XPC* Ala^{499}Val shows a protective effect.

Keywords Lung cancer · Xeroderma pigmentosum group C;PCR-RFLP;overall survival · Platinum based chemotherapy

Abbreviations

ADCC	(Adenocarcinoma)
HR	(Hazard ratio)
MST	(Mean survival time)
ns	(Non synonymous single nucleotide
SNPs	polymorphism)
OR	(Odds ratio)
SCLC	(Small cell lung cancer)
SQCC	(Squamous cell carcinoma)
XPC	(Xeroderma pigmentosum group C)

Introduction

Lung cancer remains the most common cause for the cancer related deaths worldwide [1]. In India the incidence of lung cancer is increasing and in 2012, 1.8 million people were diagnosed with lung cancer [2].The increase in the consumption of cigarette smoking among the population is found to be the major cause of the disease [3]. Although evidence does suggest that only a small fraction of smokers (usually <20%) develop the disease,however it has also been postulated that individual susceptibility towards lung cancer can also be attributed to genetic variation and possible gene-environment interaction [4]. This susceptibility may result from inherited polymorphism in genes which control the carcinogen metabolism as well as the DNA repair mechanism [5].

✉ Siddharth Sharma
siddharthsharma.phd@thapar.edu

[1] Department of Biotechnology, Thapar University, Punjab 147002, India

[2] Department of Pulmonary Medicine, Post Graduate Institute of Medical Education & Research (PGIMER), Sector 14, Chandigarh, India

DNA repair mechanism plays a crucial role in protecting genome from the damage caused by tobacco smoke and radiation [6]. Tobacco smoke consists of many carcinogens that leads to DNA bulky adduct, crosslinks, oxidative damage and DNA strand breaks. The major repair pathway which eliminates these lesions caused by smoking is the nucleotide excision repair (NER) pathway [7].NER is controlled by the sequential assembly of repair proteins at the site of lesion.It is a complex pathway which requires thirty different proteins to carry out a multistep cut and patch mechanism [8].DNA repair Capacity (DRC) of the NER pathway is responsible for maintaining the normal cellular functions and varies in general population [9]. An important key enzyme involved in the NER pathway is Xeroderma pigmentosum complementation group C gene (*XPC*). *XPC* gene encodes a 940 amino-acid proteininvolved in DNA damage recognition [10]. Two common polymorphic sites of the *XPC* gene have been investigated in different forms of cancer: A-to-C transition in exon 15 resulting in a lysine-to-glutamine transition at position 939 ($Lys^{939}Gln$; rs2228001), located in the interaction domain with transcription factor IIH (TFIIH) and the second one involves a C-to-T transition in exon 8 which results in the substitution of alanine for valine at codon 499 ($Ala^{499}Val$) in the interaction domain with hHRAD23 protein. Both these polymorphic sites are suggested to be in linkage disequilibrium with each other [11].

Previous studies have suggested an association of *XPC* polymorphisms with the occurrences of various forms of cancer such as gastric,head and neck,breast,renal,esophageal, colorectal, adenoma,oral,pancreatic and lung cancer [12, 13]but the results were inconclusive. These findings suggested that the effects of both polymorphisms remain ambiguous, and further investigations are needed to resolve these discrepancies.

Therefore, in the present study we have investigated the association of the two polymorphic sites in the *XPC* gene towards susceptibility for lung cancer (LC) and histological sub-types, furthermore we have also evaluated the role of both these SNPs towards the clinical outcome (overall survival) and response to platinum based chemotherapytreatment.

Material and Methods

Study Subjects

The current study recruited 370 lung cancer patients and 370 healthy controls. This study was approved by the Institutional Ethics Committee board of the Post Graduate Institute of medical education and research (PGIMER), Chandigarh.From each subject 5 ml of blood sample was collected for polymorphism studies. All subjects were genetically unrelated ethnic North Indians. Only lung cancer patients who were histopathologically confirmed were selected. The controls selected were hospital based and were not diagnosed with any cancer but visited the hospital for routine health check-up. All the patients and controls were obtained from the department of pulmonary medicine, Post Graduate Institute of medical education and research (PGIMER), Chandigarh. All the histopathologically recruited patients were diagnosed as having non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). There were no age, gender, smoking, histological or TNM stage restrictions, but patients with a prior history of cancer were excluded from this study. All the subjects were interviewed after obtaining informed consent from them. A detailed questionnaire regarding demographic and life time history of smoking were obtained from all of the subjects. Information regarding tobacco habits included smoking of cigarette or beedi (a native cigarette-like stick of coarse tobacco hand-rolled in a dry tembuhurni leaf). As an indication of cumulative smoking exposure, pack-years were calculated by the following formula: [(cigarettes or beedis per day/20) X years smoked]. While medical information of cases, including histology, TNM classification, clinical staging, primary tumor size, involvement of lymph node and metastasis were obtained from medical records of the hospital. The follow-up data of the patients were obtained telephonically using the information of the patient as mentioned in the clinical records.

Genotyping of XPC $A^{939}C$ and $C^{499}T$ Polymorphisms

Genomic DNA was extracted from the leukocyte pellet obtained from blood sample according to the protocol of Sodhi et al. [14].The *XPC* exon 9 $C^{499}T$ and *XPC* exon 15 $A^{939}C$ polymorphism was detected using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. For the $A^{939}C$ polymorphism PCR amplification was carried out using the following set of primers XPC^{939} (F)-5-ACC AGC TCT CAA GCA GAA GC-3 and XPC^{939} (R)-CTG CCT CAG TTT GCC TTC TC-3(33). In the case of *XPC* exon 9 $C^{499}T$ polymorphism the primers used were:XPC^{499} (F) 5-TAA GGA CCC AAG CTT GCC CG-3; and XPC^{499} (R) 5-CCC ACT TTT CCT CCT GCT CAC AG-3(33).The amplification for both sites was carried out in 25ul volume with approximately 50 ng of DNA, 0.5 μM of each primer, 200 μM of dNTP, 1X PCR buffer, 1.5 mM of $MgCl_2$, 100 μg BSA and IU of Taq Polymerase(DNAzyme II DNA Polymerase, Thermo Scientific). The PCR profile consisted of melting step of 94 °C for 5 min and followed by 30 cycles of 94 °C for 45 s, 56 °C for 30s and 72 °C for 45 s for the *XPC* $A^{939}C$ $A^{939}C$polymorphism.In case of *XPC* $C^{499}T$, the annealing temperature of 63 °C was used whereas all others conditions were same as that of *XPC* $A^{939}C$.After confirmation of successful PCR amplification by 1.5% agarose gel electrophoresis, PCR products of *XPC* $A^{939}C$(281 bp) and *XPC* $A^{499}T$(152 bp) were digested overnight by 5 U of *PvuII*and*SacI*(New England Biolabs, MA, USA) at 37 °C

overnight. In case of *XPC* $A^{939}C$ the resulting fragments were separated on 2.5% agarose gel electrophoresis. The variant C allele had a *PvuII* restriction site that resulted in bands of 150 and 131 bp and the wild-type A allele lacked the restriction site and therefore produced a single 281 bp band. For the *XPC* $A^{499}T$ gene the digestion products were separated on a 6% polyacrylamide gel and stained with silver staining. The wild-type (152 bp) C allele produces fragments of 131 and 21 bp and the mutant (T) allele produces a single 152 bp fragment. For both the *XPC* polymorphisms, 15% of the samples were also repeated using the same assay. These results were all 100% concordant.

Statistical Analysis

Differences in distribution of certain demographic variables such as age, sex, smoking status, pack-years smoked were calculatedusing the Chi-square tests ($\chi 2$ test) for the categorical data and Student's *t*-test for continuous variables. The frequencies of the *XPC*genotypes and alleles between the cases and controls were evaluated by using thePearson's $\chi 2$ test. Multivariate logistic regression was used to evaluate the associations between *XPC* variants and risk for lung cancer by computing the odds ratio (OR) and their 95%CI after adjustment for age, sex and smoking status. To compare the observed and expected genotypic frequencies among the control and case subjects Hardy-Weinberg equilibrium was tested by a goodness-of-fit $\chi 2$ test.In addition to overall association analysis, stratified analysis was performed to estimate risk for subgroups formed on the basis of smoking status, tumor histology and clinic-pathological features.Haplotype analysis for the both SNPs was performed and the D' value and r^2 was calculated with the SHEsis software (25)(http://202.120.31.177/myAnalysis.php).The associations between overall survival and genotype were estimated using the Kaplan-Meier method and Logranktest. Survival time was calculated from the date ofcancer diagnosis to the date of death. Univariate and multivariable Cox proportional hazards regression models were performed to estimate crude hazard ratio (HR) or adjusted HR and their 95% confidence intervals (CIs). The Cox regression model was also used to determine factors predictive of cancer prognosis, with a significant level of $P < 0.05$ for entering and $P > 0.10$ for removal of the variables.Tumor response was evaluated every 4 cycles of chemotherapy according to Response Evaluation Criteria in Solid Tumor Group (RECIST). Patients show complete response (CR) or partial response (PR) were defined as "responders", and patients with stable disease (SD) or progressive disease were defined as "non-responders".All *p* values were two sided, and a *p*-value of <0.05 was considered statistically significant. All the statistical analyses were performed with MedCalc Statistical Software version 15.11.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

Results

Demographic Characteristics of Lung Cancer Cases and Healthy Controls

The current study was a hospital based case-control study which evaluated the potential role of *XPC* polymorphism and its risk associated with lung cancer. A total of 740 subjects were recruited which included 370 cases and 370 healthy controls. The subjects various demographic characteristics such as age, gender, smoking status, pack years, histological subtypes, TNM staging and other clinical parameters are summarized in Table 1. Mean age of lung cancer cases was

Table 1 Demographic characteristics among cases and control patients in North Indian population

Variable	Cases, n (%) $N = 370$	Controls, n (%) $N = 370$	p^a – value
Age (years) Mean ± SD Range	58.11 ± 10.44	53.83 ± 10.18	<0.0001
Gender			0.91
Male	319(86.21%)	319(86.21%)	
Female	51(13.78%)	51(13.78%)	
Smoking Status			
Smokers	303(81.89%)	276(74.59%)	0.0205
Non – Smokers	67(18.10%)	94(25.40%)	
Pack Years			
Mean ± SD	24.97 ± 35.04	17.88 ± 19.45	<0.0001
Histological Types			
SQCC	135(36.48%)		
ADCC	120(32.43%)		
SCLC	111(30%)		
Others	4(1.08%)		
Unknown	0(0.0)		
TNM Staging			
I	3(0.81%)		
II	10(2.70%)		
III	175(45.94%)		
IV	163(44.05%)		
Unclassified	19(5.13%)		
Tumor Size			
Tx	11(2.97%)		
T1	16(4.32%)		
T2	42(11.35%)		
T3	85(22.97%)		
T4	191(51.62%)		
Unknown	25(6.75%)		
Lymph Node Involvement			
N0	49(16.3)		
N1	36(12)		
N2	111(37)		
N3	72(24)		
UNKNOWN	32(10.7)		
Metastasis			
M0	182(49.18%)		
M1	163(44.05%)		
Unknown	25(6.75%)		

All *p*values are two – sided.$p < 0.05$ was considered statistically significant

SD Standard Deviation, *n* total number of case patients or control subjects

[a] *p*-values were derived from Pearson Chi–square test except age; Student t-test was used for age

58.11 ± 10.44 (range 29–86), whereas mean age of controls was 53.83 ± 10.18(range 22–83). There were 319(86.21%) males and 51(13.78%) females in both the control and case groups. Hence, no significant difference had been observed between the distribution of males and females, suggesting adequate matching (p = 0.91).In the present study, 81.89% cases were smokers and 18.10% were non-smokers when compared with controls having 74.59% of smokers and 25.4% non-smokers. Smoking was further elaborated in terms of pack years. Pack years were significantly higher amongst cases in comparison with controls (24.97 ± 35.04 vs 17.88 ± 19.45,p < 0.0001). From the total of 370 cases, 135(36.48%) patients were classified with Squamous cell carcinoma(SQCC), 120(32.43%) with Adenocarcinoma(ADCC) and 111(30%) with SCLC. Out of 370 cases, TNM staging data were available for 351 (94.86%) patients (Stage I:3(0.81%), II: 10(2.7%), III: 175(45.94%), IV:163 (44.05%). Lung cancer subjects with T1 and T2 tumor size constituted 4.32% and 11.35% while T3and T4 were 22.97% and 51.62% of the total subjects. The frequencies for lymph node involvement classified as: N0 with 16.3% of the patients whereas N1, N2, N3 with 12%, 37%, and 24% respectively. The available data includes 49.18% cases which do not have any metastasis (M0) while 44.05% cases predict involvement of distant metastasis(M1).

Genotypic and Allelic Distribution of XPC Lys^{939}Gln and XPC Ala^{499}Val

The allelic and genotypic frequencies of two *XPC*polymorphic variants, Lys^{939}Gln and Ala^{499}Val are shown in Table 2. Genotypic frequencies of *XPC* Lys^{939}Gln among controls (n = 370; χ2 = 0.002,df = 1,p = 0.95) and cases(n = 370, χ^2 = 0.222;df = 1,p = 0.63) were in Hardy-Weinberg equilibrium, suggesting no sample biasness for control and cases. However, the genotypic frequencies for the other variant, *XPC* Ala^{499}Val for both control(n = 370, χ^2 = 23.2,df = 1,p = 0.00)and cases (n = 370 χ^2 = 32.71,df = 1,p = 0.00) were not in Hardy-Weinberg Equilibrium, suggesting population stratification,migration and random mating within the sample set.The frequency of the wild genotype of *XPC* A^{939}C gene (AA) in lung cancer subjects was found to be less represented as compared to the controls (35.94 vs 44.86%),. However as shown in Table 2 the frequency of the mutant genotype for *XPC* A^{939}C was over represented in cases as comparedto controls, thus overall there was a significant difference among the genotypic distribution between cases and controls (χ^2 = 9.07,df = 2,p = 0.01).Minor allelic frequency(MAF) calculated for *XPC* A^{939}C in controls was 0.33 whereas in cases it was0.40,suggesting a significant difference among the sample population. In case of *XPC* variant, C^{499}T the frequency of the mutant genotype (TT) was found to be more represented in the control group as compared to the cases (6.21 vs 1.89%), overall there was a significant difference in the distribution of genotypes between the controls and cases (χ^2 = 12.22,df = 2,p = 0.002). Furthermore, the MAF calculated for control and cases was 0.34, 0.28 respectively, suggesting that both the variant allele was found to be more pronounced in the controlsthancases.

Table 2 also showed the lung cancer risk related to the *XPC* polymorphisms. Adjusted ORs and 95% CIs were calculated using the logistic regression analysis using the more common genotype as the reference group. Homozygous wild genotype AA(A^{939}C) and CC(C^{499}T) were considered as reference genotypes with which the variant genotypes were compared. In case of the *XPC* Lys^{939}Gly polymorphism, it was observed that individuals carrying both the mutant alleles (CC) had a 2-fold elevated risk for lung cancer which was found to be significant (OR = 2.30; 95%CI:1.41–3.73; p = **0.0007**). Whereas in subjects with heterozygote genotypes (AC), the risk was less pronounced as compared to the mutant genotype but was reported to be significant (OR = 1.44; 95%CI: 1.04–1.99; p = 0.02). When both the genotypes were combined as a single genotype (AC + CC) and compared with the reference genotype a significant association towards lung cancer risk was also observed (OR = 1.60; 95%CI: 1.18–2.17; p = 0.002).

Lung cancer cases were further segregated into histological subgroups in order to evaluate the risk of susceptibility amongst these subgroups. As indicated in Table 2 the subjects carrying the mutant genotype (CC) for *XPC* Lys^{939}Gly polymorphism were at higher risk for all sub-groups of lung cancer as compared to subjects with heterozygous genotypes, however amongst the different histological sub-types; it was observed that subjects with mutant genotype had a 4 and 3-fold increased risk for ADCC (OR = 4.72; 95%CI: 2.16–10.32; p < **0.0001**) and SQCC (OR = 3.06, 95%CI:1.58–5.92; p = **0.009**)which was found to be highly significant.

For*XPC* Ala^{499}Val genotype it was observed that individuals with mutant (TT) genotype had the least risk for lung cancer (OR = 0.25; 95%CI: 0.10–0.63; p = **0.003**) indicating a protective effect towards the development of the disease. However when stratified according to histological sub-types; ADCC subjects with mutant genotype showed the lowest risk for lung cancer (OR = 0.12, 95%CI: 0.15–0.96; p = 0.04). However no such significant association was observed in any other sub-types of lung cancer.

For the current study, we analyzed haplotypes using SHEsis program platform (Table 3). The two SNPs were in linkage disequilibrium in this study population (D = 0.039, r^2 = 0.00). The haplotypes were composed of two coding SNPs. There was a statistically significant difference in the overall haplotype distribution between cases and controls (Global χ^2test = 18.811, p = **0.0003**). We considered the

Table 2 Distribution of genotypes of XPC polymorphism depicting their association with Lung cancer risk and its histological subtypes

		Overall lung cancer			SQCC			ADCC			SCLC		
XPC lys^{939}gly	Controls n (%) $N = 370$	Cases N (%) $N = 370$	AOR (95% CI) [b]	p^a	Cases n(%) $N = 135$	AOR (95% CI) [b]	p^a	Cases n(%) $N = 120$	AOR (95% CI) [b]	p^a	Cases n(%) $N = 111$	AOR (95% CI) [b]	p^a
AA	166(44.86)	133(35.94)	1.00 (Reference)		42(31.11)	1.00 (Reference)		39(32.5)	1.0(Reference)		51(45.9)	1.00 (Reference)	
AC	164(44.32)	174(47.02)	1.44 (1.04–1.99)	0.02	68(50.37)	1.81(1.14–2.88)	0.011	59(49.1)	2.15(2.28–3.63)	0.0039	46(41.4)	1.12(0.69–1.82)	0.62
CC	40(10.8)	63(17.02)	2.30 (1.41–3.73)	0.0007	25(18.51)	3.06(1.58–5.92)	0.0009	22(18.3)	4.72 (2.16 10.3)	<0.0001	14(12.6)	2.30(1.41–3.73)	0.0007
AC + CC	204(55.13)	237(64.05)	1.60 (1.18–2.17)	0.002	93(68.88)	2.03(1.31–3.15)	0.0014	81(67.5)	0.86(0.47–1.56)	0.063	60 (54.0)	1.19(0.76–1.87)	0.438
A Allele	496(67.03)	440(59.46)											
C Allele	244(32.97)	300(40.54)											
MAF	0.33	0.40											
XPC Ala^{499}Val													
CC	138(37.29)	169(45.67)	1.00 (Reference)		62(45.92)	1.00 (Reference)		58(48.3)	1.00 (Reference)		47(42.34)	1.00 (Reference)	
CT	209(56)	194(52.43)	0.76(0.56–1.04)	0.088	70(51.85)	0.69 (0.45–1.05)	0.82	61(50.8)	0.749(0.48–1.1)	0.192	61(54.9)	0.76(0.48–1.2)	0.25
TT	23(6.21)	7 (1.89)	0.25(0.105–0.63)	0.003	3 (2.2)	0.28 (0.07–0.98)	0.39	1 (0.83)	0.12(0.15–0.96)	0.04	3 (2.7)	0.44(0.12–1.50)	0.21
TC + TT	232(62.02)	201(54.32)	0.72(0.53–0.97)	0.034	73 (54.07)	0.64 (0.42–0.98)	0.84	62 (51.6)	0.70 (0.45–1.08)	0.113	64 (57)	0.91(0.57–1.43)	0.68
C Allele	485 (65.54)	532 (71.89)											
T Allele	255 (34.45)	208(28.10)											
MAF	0.34	0.28											

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

[b] AdjustedOdds ratios, 95% confidence intervals and their corresponding *p*-values were calculated by logistic regression analysis after adjusting for age, gender and smoking status

ADCC Adenocarcinoma, *SQCC* Squamous cell carcinoma, *SCLC* Small cell lung carcinoma

Table 3 XPC Haplotypes and their association with lung cancer risk

XPC $Lys^{939}Gln$ & XPC $Ala^{499}Val$	Case frequency, n (%)	Control frequency, n (%)	OR (95% CI)[a]	*p*-value[b]
A-C	0.418 (309)	0.449 (331)	0.883 (0.719–1.08)	0.236
A-T	0.176(130)	0.226 (167)	0.735(0.56–0.94)	0.018
C-C	0.301 (222)	0.207 (153)	1.65(1.301–2.09)	3.31e-005
C-T	0.105 (77)	0.119 (87)	0.866(0.626–1.19)	0.383

[a] Two-sided χ^2 test for either haplotypic distribution or frequencies between the cases and controls

[b] Global χ^2 test = 18.811, *p*-value=0.0003

individuals with 939A-499C haplotype as the reference group for OR estimations. The C-C haplotypewas associated with increased risk of lung cancer (OR = 1.65; 95%CI; 1.30–2.09; $p = 3.31e\text{-}005$). Among individuals having the A-T haplotype there was a reduced risk of lung cancer (OR = 0.73; 95%CI; .56–.94; $p = 0.018$). All other haplotypes (CT) did not show any significant effect.

Interactive Effect of Smoking on the Genetic Variants and Its Association with Lung Cancer Susceptibility

Table 4 shows the correlation between *XPC* polymorphic variants $A^{939}C$ and $C^{499}T$ and smoking and its association with lung cancer risk.The sample population is divided into two subgroups: smokers and non-smokers. The smokers were further divided into heavy and light smokers. The patients who had smoked less than or equal to 25pack years are grouped under light smokers whereas more than 25 pack years are grouped as heavy smokers. Smokers carrying the mutant (CC) genotype of the *XPC*$A^{939}C$ gene were found to have 2-fold elevated risk for lung cancer as compared (OR = 2.55; 95% CI: 1.46–4.45; $p = \mathbf{0.001}$) to smokers having the wild type genotype (AA),a similar trend was also seen in subjects who were hetero-zygotes (OR = 1.53; 95%CI:1.06–2.20; $p = 0.02$),however the effect was less pronounced. Furthermore, it was observed that heavy smokers with the mutant (CC) genotype for $Lys^{939}Gly$ were at significantly higher risk (OR = 3.71, 95%CI = 1.46–9.45; $\boldsymbol{p = 0.005}$) than light smokers (OR = 2.18, 95%CI = 1.10–4.28; $p = 0.02$). In case of the $C^{499}T$ genotype, no such association was observed between smoking and associated risk towards lung cancer with the any genotypic combinations of the $C^{499}T$ gene.

Table 4 Distribution of genotypes of XPC polymorphism according to their smoking status and its association with lung cancer risk

	Smokers				Non smokers			
XPC $Lys^{939}Gln$	Controls n (%) *N* = 276	Cases n (%) *N* = 303	AOR (95% CI)[b]	p^a	Controls n (%) *N* = 94	Cases n (%) *N* = 67	AOR (95% CI) [b]	p^a
AA	131(47.4)	111(36.6)	1.00 (Reference)		35	22(32.8)	1.00 (Reference)	
AC	119(43.1)	142(46.8)	1.53(1.06–2.2)	0.021	45	32(47.7)	1.25(0.59–2.61)	0.55
CC	26(9.42)	50(16.5)	2.55(1.46–4.45)	0.001	14	13(19.4)	2.05(0.76–5.56)	0.15
AC + CC	145(52.5)	50(16.5)	1.71(1.21–2.42)	0.002	59	45(67.16)	1.40(0.70–2.79)	0.32
XPC $Ala^{499}Val$								
AA	156(56.52)	167(55.11)	1.00 (Reference)		38(40.4)	36(53.7)		
AC	20(7.26)	174(57.42)	0.809(0.571–1.14)	0.23	53(56.3)	31(46.2)	0.614(0.316–1.19)	0.150
CC	100(36.23)	7(2.3)	0.334(0.133–0.835)	0.02	3(3.19)		0.0(0.0–0.0)	0.993
AC + CC	120(43.47)	181(59.73)	0.758(0.537–1.14)	0.116	56(59.5)	31(46.2)	0.587 (0.302–1.13)	0.115
	HEAVY SMOKER				LIGHT SMOKER			
XPC $Lys^{939}Gln$	Controlsn (%) *N* = 104	Casesn (%) *N* = 141	AOR (95% CI) [b]	p^a	Controlsn (%) *N* = 174	Casesn (%) *N* = 162	AOR (95% CI) [b]	p^a
AA	47(45.14)	45 (31.91)	1.00 (Reference)		85 (48.85)	66 (40.74)	1.00 (Reference)	
AC	49 (47.11)	69 (48.93)	1.54 (0.87–2.72)	0.13	71 (40.80)	73 (45.06)	1.24 (0.77–1.97)	0.36
CC	8 (7.69)	27(19.14)	3.71 (1.46–9.45)	0.005	18 (10.34)	23 (14.19)	2.18 (1.10–4.28)	0.02
AC + CC	57 (54.80)	96 (68.08)	1.84 (1.07–3.16)	0.02	89 (51.14)	96 (59.25)	1.43 (0.943–2.17)	0.09
XPC $Ala^{499}Val$								
CC	39(37.5)	65(46.09)	1.00 (Reference)		62(35.63)	68(41.97)	1.00 (Reference)	
CT	55(52.8)	73(51.77)	0.952(0.49–1.82)	0.88	102(58.62)	90(55.55)	0.86(0.54–1.36)	0.52
TT	10(9.61)	3(2.12)	0.299(0.05–1.50)	1.43	10(5.74)	4(2.46)	0.51 (0.14–1.77)	0.29
CT + TT	65(62.5)	76(53.90)	0.882 (0.96–1.66)	0.69	112(64.36)	94(58.02)	0.82 (0.52–1.30)	0.41

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

[b] Adjusted Odds ratios, 95% confidence intervals and their corresponding *p*-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status.

Combined Effect of both Polymorphic Variant XPC Lys^{939}Gln and XPC Ala^{499}Val on Lung Cancer Risk

Different genotypic combinations of two *XPC* variants were analyzed to find out their association with lung cancer risk in order to evaluate gene-gene interaction between the two *XPC* polymorphic variants (Table 5). A 2-fold risk of lung cancer was observed in subjects carrying either variant alleles (AC + CT) for both the polymorphic variants,however this effect was not significant (OR = 1.90; 95%CI: 0.91–3.94; $p = 0.446$).No association was observed in othercombined *XPC*genotypesin the current study.

Relationship of Clinic-Pathological Features and Variant Genotypes in Lung Cancer Patients

To determine association between the two polymorphic variants of *XPC*, (A^{939}C, C^{499}T) and clinic-pathological parameters we divided patients on the basis of stage of cancer(III vs IV), primary tumor extension (T3 + T4 vs T1 + T2) and metastatic status(positive vs negative) (Table 6). No significant association was observed between staging/tumor metastasis and *XPC* variants. However, higher frequency of *XPC*A^{939}C heterozygous genotype (AC) was observed in patients with T3/T4 tumor as compared to patients with T1/T2 tumor, therefore a 3.5 fold risk for lung cancer was observed for subject with T3/T4 tumor extension and heterozygous genotypeofthe*XPC* A^{939}C as compared to patients with T1/T2 tumor size (OR = 3.54, 95%CI: 1.71–7.51, $p = 0.0006$). No association was observed for *XPC^{499}T* genetic variant and clinic pathological features.

Associations of XPCSNPs with Overall Survival of Patients with Lung Cancer and Specific Histological sub-Types

Univariate analyses using Kaplan-Meier curves and log-rank tests was performed so to evaluate the association of the *XPC* polymorphism with overall survival of patients as shown in Table 7.The distribution of observed genotypes in the patients agreed with those estimated from the Hardy–Weinberg equilibrium ($\chi 2 = 0.07$; $P = 0.78$; for *XPC Lys^{939}Gln*). Since the frequency of the mutant genotype in case of *XPC C^{499}T* was less, we combined the heterozygous and mutant genotype as a single group and compared the OS with the wild genotype. As shown in Table 7 the variant genotypes for *XPC Ala^{499}Val* were associated with shorter survival as compared to the wild type genotype (median survival time, 6.23 months versus 7.20 months,log-rank $p = 0.44$ Fig. 1a). In the multivariate Cox proportional hazards regression analysis, no significant association was observed between the *XPCAla^{499}Val* mutant genotype and overall lung cancer survival (HR = 0.89, 95% CI = 0.66–1.19). However when stratified according to histology ADCC patients with the variant genotype had a longer survival as compared to ADCC patients with wild type genotype (MST, 10.33 months versus 6.70 months log-rank $p = 0.03$, Fig. 1c). No such association was observed neither for SQCC (Fig. 1b) nor for SCLC (Fig. 1d) patients. Furthermore, in the multivariate Cox model as shown in Table 7, ADCC subjects with CT/TT genotype of *XPC Ala^{499}Val* were significantly associated with better overall survival (adjusted HR = 0.45, 95% CI = 0.25–0.82, $p = 0.0096$), compared with the CC genotype. Thus this could be considered as an independent prognostic factor forADCCpatients receiving chemotherapy.Other clinical features were all seen to have no apparent effect in influencing the prognostic outcomes of lung cancer patients receiving chemotherapy except ECOG status(Table 8). There might be potential association of ECOG status with the prognosis of ADCC patients (HR = 1.43, 95%CI = 1.06–1.93; $p = 0.01$). In case of the *XPC* Lys^{939}Gln both the univariate and multivariate cox regression models did not show any significant association between the variant genotypes and overall survival (Table 7,Fig. 2a-d).

Association between XPC Polymorphisms and Clinical Benefit

XPC gene polymorphisms and chemotherapy response in lung cancer patients treated with first-line platinum-based drug along with taxol based drug or combination chemotherapy for ≥6 cycles are shown in Table 9. The association between responders (platinum-sensitive) and non-responders

Table 5 Combination of genotypes of XPC polymorphic variants and their relationship with the risk of lung cancer

Genotypes	Cases, n (%) $N = 141$	Controls, n(%) $N = 156$	Adjusted OR (95% CI)[b]	p-value[a]
XPC Lys^{939}Gln & XPCAla^{499}Val				
0 (AA + CC)	56	64	1.00 (Reference)	
1(AC + CT)	85	91	1.90 (0.918–3.94)	0.446
2(CC + TT)	-	1	-	-
1–2	85	92	1.29(0.823–2.049)	0.260

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

[b] Adjusted Odds ratios, 95% confidence intervals and their corresponding p-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status.

0 wild genotype, 1 heterozygote genotype, 2 mutant genotype, 3 combined hetero and mutant genotype

Table 6 Relationship of clinicopathologial features with XPC Lys[939]Gln and XPC Ala[499]Val genotypes in lung cancer patients

Variable	Clinical stage		AOR[b] (95% CI)	p^a value	TNM stage		AOR[b] (95% CI)	p^a value	Metastasis		AOR[b] (95% CI)	p^a value
	III	*IV*			*T3 + T4*	*T2 + T1 + T0*			*Positive*	*Negative*		
XPCLys[939]Gln	175	163			276	50			188	189		
AA	59	64	Reference		96	30	Reference		74	67	Reference	
AC	82	75	0.80 (0.48–1.15)	0.39	131	12	3.54(1.71–7.35)	0.0006	81	87	0.79 (0.50–1.27)	0.34
CC	34	25	0.60 (0.30–1.17)	0.13	49	9	1.71(0.74–3.93)	0.20	33	35	0.59 (0.10–3.29)	0.48
AC + CC	141	139	0.75 (0.47–1.19)	0.23	180	21	1.93(1.08–3.43)	0.02	114	122	1.12 (0.71–1.75)	0.61
XPCAla[499]Val												
CC	82	73	Reference		125	36	Reference		69	86	Reference	
CT	91	86	0.91 (0.53–1.57)	0.74	147	29	0.91 (0.53–1.57)	0.74	84	99	1.13 (0.72–1.77)	0.58
TT	2	4	0.59 (0.10–3.29)	0.55	5	2	0.59 (0.10–3.29)	0.55	3	4	1.07 (0.22–5.01)	0.92
CT + TT	93	90	0.85 (0.49–1.44)	0.58	152	31	0.85 (0.49–1.44)	0.55	87	103	1.13 (0.72–1.77)	0.05

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls.0: wild genotype

[b] Adjusted Odds ratios, 95% confidence intervals and their corresponding *p*-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status

1 heterozygote genotype, 2 mutant genotype, 3 combined hetero and mutant genotype

Table 7 Overall survival analysis using in genotypes of XPC polymorphic variants and their association with lung cancer risk

Genotype	No.	Censored (Alive)	Uncensored (Dead)	Median overall survival MST(months)	Crude HR[a](95%CI)	Adjusted HR[b] (95%CI)	Log rank P	p[3]
Lys[939]Gln								
Lys/Lys	86	61	25	7.20	1.00(Reference)	1.00(Reference)		
Lys/Gln	123	90	33	5.93	1.00(0.73–1.39)	1.06(0.76–1.49)	0.79	0.70
Gln/Gln	41	32	9	6.23	1.14(0.74–1.78)	1.01(0.85–1.32)	0.79	0.93
Ala[499]Val								
Ala/Ala	108	82	26	6.40	1.00(Reference)	1.00(Reference)		
Ala/Val + Val/Val	142	101	41	6.73	0.89(0.66–1.19)	0.84(0.63–1.10)	0.44	0.26
ADCC								
Lys[939]Gln								
Lys/Lys	24	18	6	8.53	1.00(Reference)	1.00(Reference)		
Lys/Gln	45	32	13	7.56	1.13(0.64–2.01)	1.01(0.54–1.91)	0.90	0.95
Gln/Gln	13	9	4	9.30	1.06(0.48–2.34)	1.07(0.71–1.60)	0.90	0.72
Ala[499]Val								
Ala/Ala	39	32	7	6.70	1.00(Reference)	1.00(Reference)		
Ala/Val + Val/Val	43	27	16	10.33	0.58(1.02–2.88)	0.45 (0.25–0.82)	0.03	0.0096
SCLC								
Lys[939]Gln								
Lys/Lys	30	22	8	6.73	1.00(Reference)	1.00(Reference)		
Lys/Gln	31	22	9	8.26	0.99 (0.55–1.79)	0.99(0.52–1.87)	0.99	0.97
Gln/Gln	8	7	1	3.43	1.05(0.44–2.50)	1.24(0.43–3.56)	0.99	0.68
Ala[499]Val								
Ala/Ala	26	18	8	4.46	1.00(Reference)	1.00(Reference)		
Ala/Val + Val/Val	43	33	10	7.23	0.95(0.53–1.69)	0.85(0.45–1.57)	0.85	0.60
SQCC								
Lys[939]Gln								
Lys/Lys	31	21	10	7.20	1.00(Reference)	1.00(Reference)		
Lys/Gln	47	36	11	5.43	0.97(0.56–1.65)	1.09(0.61–1.97)	0.91	0.75
Gln/Gln	19	15	4	6.86	1.09 (0.55–2.10)	0.85(0.38–1.87)	0.91	0.69
Ala[499]Val								
Ala/Ala	42	31	11	6.86	1.00(Reference)	1.00(Reference)		
Ala/Val + Val/Val	55	41	14	5.26	1.18 (0.53–1.34	0.99(0.62–1.60)	0.47	0.99

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

[b] Hazard ratios, 95% confidence intervals and their corresponding *p*-values were calculated by Kaplan Meier survival analysis after adjusting for remission and survival in months and [b] Adjusted hazard ratios, 95% confidence intervals and their corresponding *p*-values were calculated by Cox regression models adjusted for age, sex, smoking status, stage, kps and ecog

0: wild genotype, 1: heterozygote genotype, 2: mutant genotype, 1: combined hetero and mutant genotype

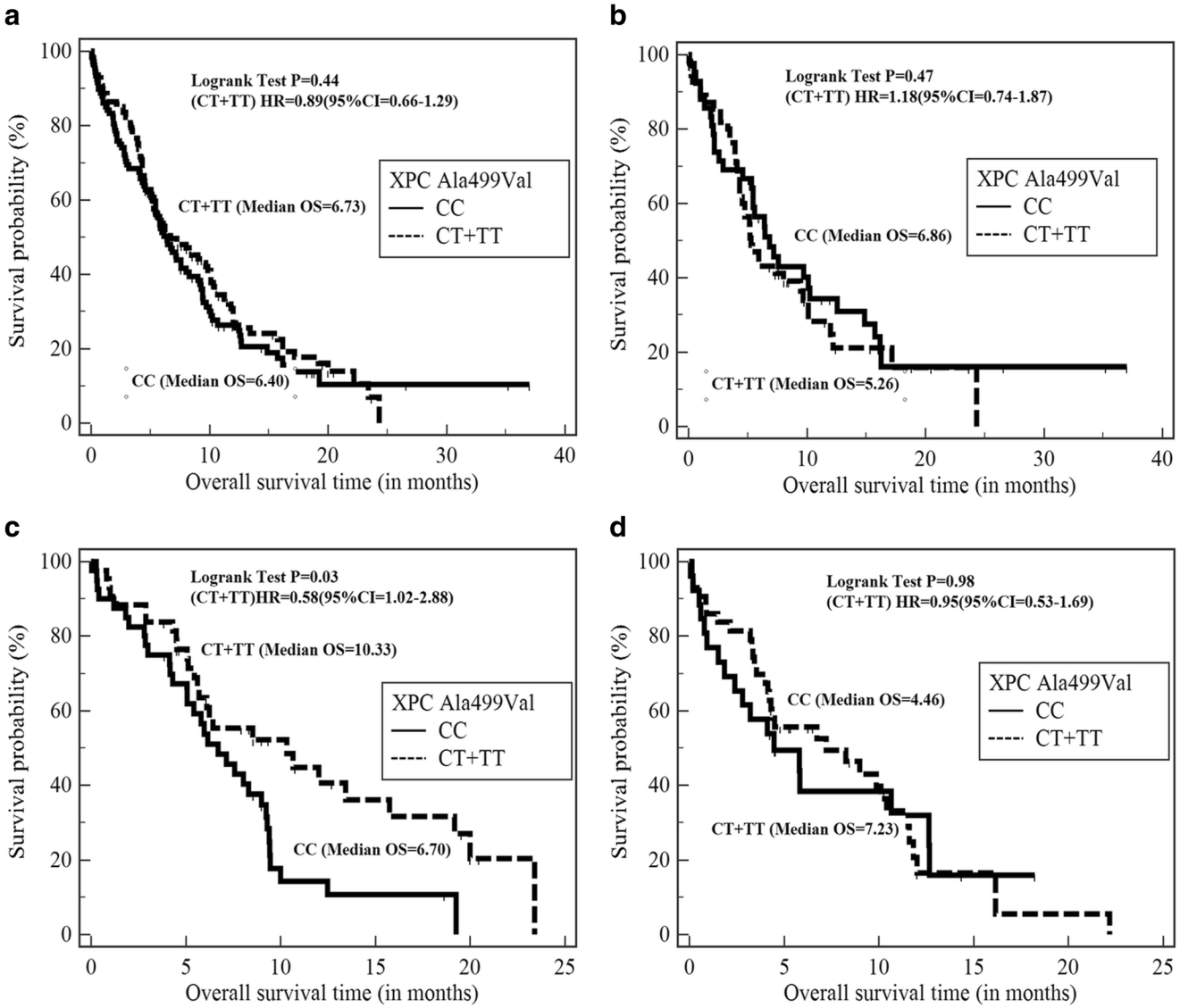

Fig. 1 The overall survival in lung cancer patients is represented in form of Kaplan Meier survival curve. The survival probability of different genotypes present in the sample population has been compared with the overall survival time in months for *XPC* Ala^{499}Val Polymorphism. **(a)** showed overall survival in XPC Ala^{499}Val, the dotted line represents the survival of the CT + TT (double genotype) with the median survival time of 6.73 months while the dark black line shows the overall survival of the wild genotype with median survival time of 6.49 months with log rank test value $P = 0.44$. **(b)** shows the Kaplan Meier survival curve for the patients diagnosed with Squamous cell cancer for XPC Ala499Val polymorphism. The dotted line depicts the survival of the CT + TT (Mean survival time = 5.26 months) genotype while black line depicts the survival of wild genotype (6.86 months). **(c)** shows the Kaplan Meier survival curve for the patients diagnosed with Adenocarcinoma for XPC Ala499 Val polymorphism. The figure showed a better survival for CT + TT genotype depicting Mean survival time of 10.33 months. **(d)** showed the Kaplan Meier curve for patients diagnosed with Small cell lung cancer for XPC Ala499Val polymorphism.

(platinum-resistant) and the panel of *XPC* polymorphisms was assessed by a multivariate logistic regression model adjusted for age, stage, smoking, stage and histology. Each genotype was compared with the wild genotypes. The sample population having total 167 lung cancer patients were divided into two groups: good responders (CR + PR) and poor responders (SD + PD). There was no statistically significant difference between responders and non-responders and the XP genotypes. The lack of statistical significance can be accounted towards the low sample size.

Discussion

In NER pathway, *XPC* is one of the major gene which is related to recognition of damage, forms an open complex and takes part in DNA repair [15]. The NER pathway primarily involved in removal of large lesions and thus considered as the important defense mechanism for the structurally unrelated lesions [16]. Many past studies have emphasized on the relation of DNA adduct levels with the development of lung cancer [17]. Functional SNPs which are basically present in

Table 8 Cox regression survival analysis adjusted for $Ala^{499}Val$ variant in ADCC patients

$N = 80$ Censored = 23 Uncensored = 60 Covariates	b	SE	Wald	P^a-value	Adjusted OR[b] (Exp b)	95% CI[b] of Exp (b)
Age	0.013	0.015	0.797	0.371	1.013	0.983to1.044
Sex	−0.240	0.445	0.291	0.589	0.786	0.328to1.881
Smoking	0.389	0.393	0.980	0.322	1.475	0.682to3.190
Stage	0.110	0.214	0.266	0.605	1.117	0.733to1.700
KPS	-0.442	0.305	2.103	0.146	0.642	0.353to1.168
ECOG	0.361	0.153	5.545	**0.0185**	1.435	1.062to1.938
XPC $Ala^{499}Val$	−0.785	0.303	6.715	**0.096**	0.455	0.251to0.825

The values in bold represented significant p-values. Whereas non-significant values are not represented in bold

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

[b] Adjusted hazard ratios, 95% confidence intervals and their corresponding *p*-values were calculated by Cox regression models adjusted for age, sex, smoking status, stage, kps and ecog

0 wild genotype, 1 heterozygote genotype, 2 mutant genotype, 1 combined hetero and mutant genotype

protein coding region alter the amino acid sequence which leads to the alteration of protein function. The *XPC* $Lys^{939}Gln$ and $Ala^{499}Val$ polymorphism cause amino acid substitution in the functional domain which alter the DNA repair capacity and its susceptibility towards the lung cancer.

In this hospital-based case-control study, we investigated the association of two polymorphisms within the *XPC* gene i.e. $C^{499}T$ and $A^{939}C$ towards risk for the lung cancer and also evaluated the clinical outcomes in a North Indian population. When we analyzed each variant of *XPC* gene separately, an increased risk of lung cancer was found in patients with *XPC* $A^{939}C$ mutant genotype (***p* = 0.0007**), similarly when theresults were analyzed for histological subgroups, the variant genotype was found to be significantly associated with all the histology's of lung cancer. On the contrary the variant genotype of *XPC* $C^{499}T$ was found to be less represented in lung cancer patients thus suggesting a strong protective effect (***p* = 0.003**). Furthermore, we analyzed the combined effect of both the polymorphic variants, no significant association was observed towards risk for lung cancer.

The investigations in the present study have shown two fold higher risk for the homozygous variant of *XPC* $Lys^{939}Gln$ gene in North Indian population which agreed with the results of Jinet al. [18]who also assessed a higher risk of developing lung cancer in Asian subjects carrying variant allele of *XPC* $Lys^{939}Gln$ polymorphism. The above study was further supported by Nielson et al. [16] who also emphasized on an increased risk of lung cancer in variant genotype of $A^{939}C$ in Caucasian population. It can be suggested that the variant form of *XPC* $A^{939}C$might be closely related towards increased susceptibility towards the development of lung cancer. This may be because *XPC* protein binds with the HR23B to form a heterodimeric complex which is considered as the crucial step for the detection of wide variety of lesions [16] and hence recruit the whole repair machinery to the damaged site [19, 20]. It has also been suggested that polymorphisms in *XPC* might lead to the alteration in the repair capacity of an individual which causesgenetic instability and may ultimately results into carcinogenesis [21].

Further, the present study suggested a strong protective effect for the lung cancer in *XPC* $C^{499}T$, particularly in the mutant (TT) genotype(OR:0.25). The results suggested that the genetic alteration in *XPC*, interaction with environmental factors, ethnic background, host characteristics or prolonged exposure to the carcinogen may be the possible reasons for this protective effect. Our results were consistent with the studies conducted by Shen et al. [22] suggesting a protective effect of *XPC*$C^{499}T$ towards the risk of lung cancer in Asian population. However, studies reported by Vodicka et al. [23] and Jin et al. [18]differ from the present study suggesting no functional significance of *XPC* $Ala^{499}Val$towards risk of lung cancer in European and Korean population. However, the difference in findings may be due to ethnic differences or low sample size with limited statistical power.

However, when the sample population was stratified into different histological subtypes: ADCC,SQCC and SCLC, our results suggested a significant risk of occurrence of disease in patients with mutant genotype observed for all the three histological subtypes for *XPC* $Lys^{939}Gln$ which included ADCC(OR:4.72), SQCC(OR:3.06) and SCLC(OR:2.30).Although the reasons behind such histology dependent difference which is conferred by these polymorphism is unknown, but as suggested it may be related with the difference in carcinogenesis pathway among the histological subtypes of lung cancer. Many previous studies suggested that the determination of histological subtype is related with the individual's exposure to the specific initiation agent [24, 25]. Therefore, various genetic factors may be responsible for the susceptibility in histological subtypes of lung cancer [26, 27].

We also evaluated the role of gene-gene of the SNPs of the *XPC* genetowardsmodulating the risk for lung cancer [28]. A study by Letkova et al. [29] reported that when the genotypes of

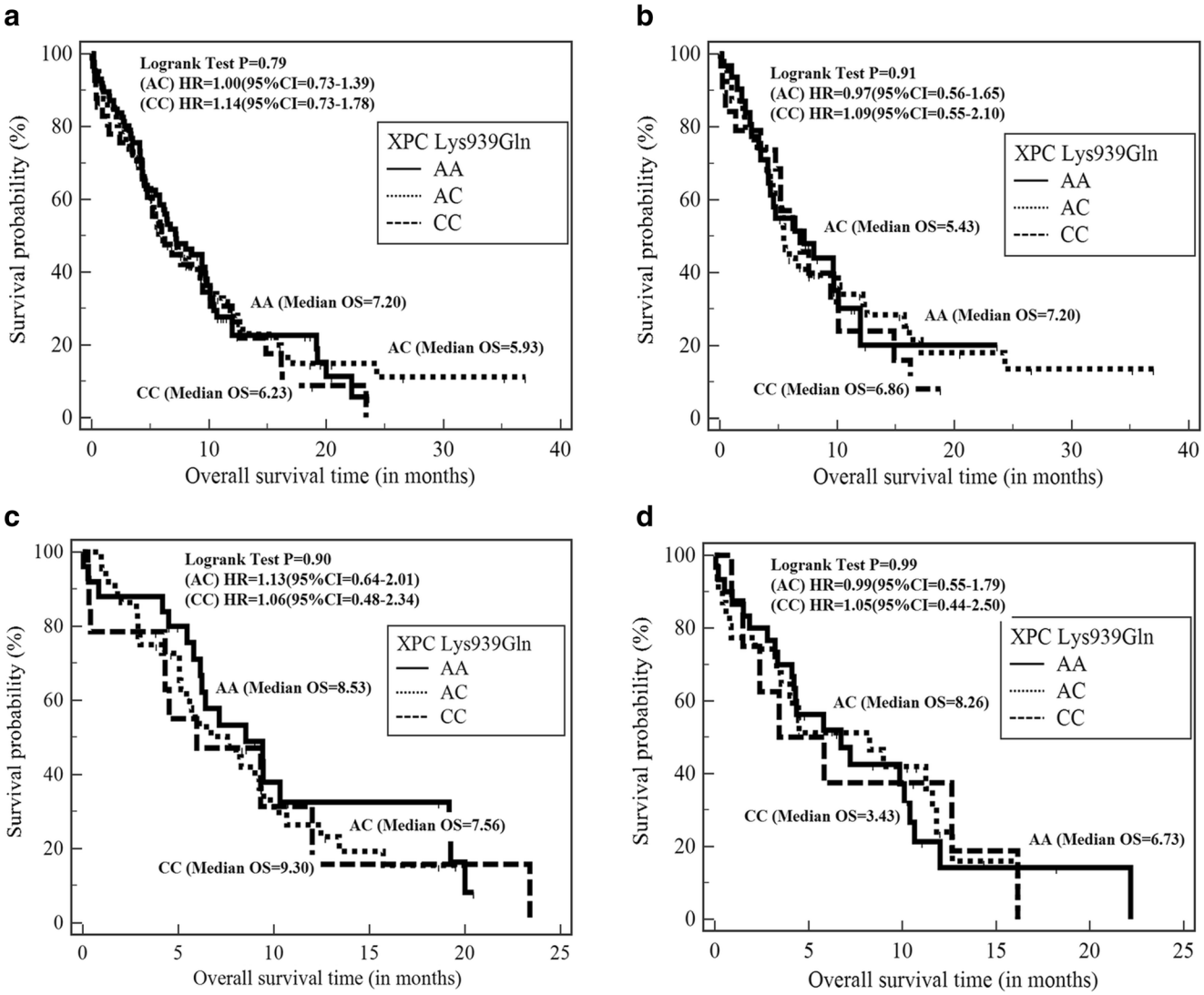

Fig. 2 The overall survival in lung cancer patients is represented in form of Kaplan Meier survival curve. The survival probability of different genotypes present in the sample population has been compared with the overall survival time in months for XPC Lys^{939}Gln polymorphism. **(a)** showed the overall survival of *XPC* Lys^{939}Gln, the dotted line represents the survival of the AC genotype (Median survival time = 5.93 months), wedged line shows the survival of CC genotype (Mean survival time = 6.23 months) while the dark black line shows the overall survival of the wild genotype(Mean survival time = 7.20 months) with median survival time of 6.49 months with log rank test value $P = 0.79$. **(b)** shows the Kaplan Meier survival curve for the patients diagnosed with Squamous cell cancer for *XPC* Lys^{939}Gln polymorphism. **(c)** shows the Kaplan Meier survival curve for the patients diagnosed with Adenocarcinoma for *XPC* Lys^{939}Gln polymorphism. **(d)** showed the Kaplan Meier curve for patients diagnosed with Small cell lung cancer for *XPC* Lys^{939}Gln polymorphism

both the polymorphic variants were combined as a single genotype, they did not show any significant association towards the risk of lung cancer. Our results were in concordance with the above study suggesting no significant risk associated with double variant genotype of both *XPC* variants for lung cancer.

In the present study, the analysis based on the haplotypes showed that when compared to the most abundant A-C haplotype, the A-T haplotype which consist of variant T-allele, conferred a significantly decreased risk of lung cancer. Our results were in accordance with the Zhu et al. [28]who observed decreased risk of bladder cancer (OR:0.64) in subjects carrying one variant T allele of *XPC Ala^{499}Val* genotype and one wild A allele of *Lys^{939}Gln*. They further suggested the correlation of the variant T-allele of *Ala^{499}Val* with the efficient DRC [28, 30]. Therefore, the favorable allele which consisted of A-T haplotype has been found to be associated with the favorable DRC status and hence confer a decreased risk towards the lung cancer risk. Our data also showed a protective effect for A-T and C-T haplotype while C-C haplotype which consist of the adverse allele showed a slight increased effect towards the lung cancer. The possible reason behind such effect in case of adverse allele is due to their less efficient DRC which it may or may not lead to a apoptotic effect [31, 32].

Table 9 Genotypic Response of XPC polymorphism to platinum based chemotherapy and their association with lung cancer risk

Genotype	Good responders (CR + PR)(N = 89)	Poor responders (SD + PD)(N = 78)	AOR[b] (95% CI)	P[a]-value
XPC lys^{939}Gln				
AA	30(33.70%)	26(29.21%)	(Reference)	
AC	43(48.31%)	36(46.15%)	1.15(0.55–2.38)	0.40
CC	16(17.97%)	16(20.51%)	0.97(0.61–1.50)	0.29
AC + CC	59(66.2%)	52(66.67%)	1.11(0.56–2.19)	0.40
XPC Ala^{499}Val			0.89(0.48–1.66)	0.73
CC	35(39.32%)	30(38.46%)	(Reference)	
CT	52(58.42%)	47(60.25%)	0.84(0.43–1.62)	0.44
TT	2(2.24%)	1(1.28%)	1.31(0.35–4.87)	0.31
CT + TT	54(60.67%)	48(61.5%)	0.85(0.44–1.69)	0.42

[a] Two-sided χ^2 test for either genotype distribution or allelic frequencies between the cases and controls

[b] Adjusted Odds ratios, 95% confidence intervals and their corresponding p-values were calculated by unconditional logistic analysis after adjusting for age, gender, smoking status, histology, stage, kps and ecog

0 wild genotype, 1 heterozygote genotype, 2 mutant genotype, 3 combined hetero and mutant genotype

We then analyzed the effect of *XPC* polymorphism on smoking. Smoking is the widely known predominant risk factor for lung cancer. Our results suggested a two fold increase in the risk of lung cancer in the homozygous variant of *Lys^{939}Gln* for both smokers (OR:2.55) and non-smokers. A more pronounced risk was observed in mutant (CC) genotype of heavy smokers (OR:3.71) for *XPC Lys^{939}Gln*. As a strong risk for lung cancer was observed in both smokers and non-smokers, it can be concluded that cigarette smoking may not be the major component associated with the initiation of lung cancer but many other unidentified carcinogens may have played the major role in development of the disease. The above study showed its consistence with the study carried out by Hu et al. [33]which showed more prominent risk in individuals carrying mutant genotype amongst smokers for *Lys^{939}Gln* polymorphism. Whereas the present study further showed a strong protective effect in individuals with *TT* and *CT* genotypes for *Ala^{499}Val* polymorphism amongst smokers. These genotypes may have showed their protective effect due to their modulating response towards the carcinogenic exposure. As per the 'greater apoptosis hypothesis' as stated by Zhu et al. [28] the apoptosis is usually triggered by exposure to a carcinogen, therefore, a increased protective effect may be observed amongst smokers [31, 32].

The survival analysis of 250 patients was carried out using Kaplan-Meier survival analysis and Cox regression analysis. The investigations in the present study suggested no significant association of *Lys^{939}Gln* variant in both univariate Kaplan Meier survival analysis and multivariate Cox regression analysis. Our results were in concordance with the study conducted by Matakideu et al. [34], as they suggested no significant association of *Lys^{939}Gln* variant between histology and stage of diagnosis in lung cancer patients. They further emphasized on an increased mean survival for mutant genotype in *XPC^{939}Gln* variant,which differs from the findings of the present study. These limitations may be due to small sample size, inadequate statistical power, different ethnic background and lack of evaluation of the effects of multiple related genes in same pathways.

As reported in previous studies that platinum based chemotherapeutics are the most common regimens used for the treatment of lung cancer patients and genetic factors are recognized as the important parameters for the efficacy of individuals towards the drugs [35, 36]. Many population based studies supported a relationship between polymorphism involved in DNA repair and decreased chemotherapy response. A poor survival has been observed in NSCLC patients which is partly due to resistance shown by the drugs.It has been suggested that the genetic variants as well as protein expression might affect the response to platinum based chemotherapy as well as its prognosis [37, 38]. Platinum based chemotherapy shows its anti-cancer activity by formation of bulky platinum-DNA adducts which result in the destabilization of the DNA helix leading to the blockage of replication which further results in inhibition of transcription process. These adducts are repaired by the NER-BER pathways and plays an important role in evaluating the sensitivity of the tumor cells to the platinum based treatment [39].

The polymorphism in the DNA repair pathway genes such as *XPC* alters the DNA repair activities and may influence response in patients towards the drug which may affect patient's survival and disease outcomes [40–42]. DNA repair mechanism is a complex process and understanding it along with the heterogeneity of tumor cells makes it more complicated for us to evaluate the effect of genetic polymorphism on the repair mechanism of DNA as well as response of patients to chemotherapy due to these repair mechanism. The present study does not show any significant association of the *XPC* genetic variants with the

patients treated with the platinum based chemotherapy. This means our results does not support the possibility that *XPC* genetic polymorphism involved in DNA repair capacity may affect treatment and do not have any influence on patients survival. Our results were in agreement with the findings of Matakideu et al. [34]as they suggested no significant association between the lung cancer patients with platinum based chemotherapy and both the *XPC* genetic variants. The possible reason behind such results may be the low sample size of the study or the ethnic background of the population.

In Conclusion, our study suggested that 2 exonic variants of *XPC* gene particularly *XPC* $A^{939}C$ modulates the risk of lung cancer in North Indian population.The survival analysis conducted in present study suggests no significant association between the *XPC* variants and survival of lung cancer patients. The study further reveals that *XPC* $Lys^{939}Gln$ and genotypic *XPC* $Ala^{499}Val$ are not associated with an effective response to platinum based chemotherapy.

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Compliance with Ethical Standards

Conflict of Interest None.

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