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To investigate the affiliation of XRCC-1 Gene Arg194Trp polymorphism in alcohol and tobacco substance users and loco-regionally progressed Laryngeal squamous cell carcinoma

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A B S T R A C T

Objectives: The correlation of XRCC-1 Gene Arg194Trp polymorphism with alcohol and tobacco substance user and with loco-regionally progressed squamous cell cancer of the larynx (LSCC) was assessed in this research study. The result of this research study is described herein.

Material and methods: A tertiary hospital-based observational case-control research was carried out. DNA segregation and Genotype examination were done from the blood sample of the control group and cases to know the correlation between XRCC-1 gene polymorphism with loco-regionally progressed LSCC and with hazard factors tobacco and alcohol.

Results: In the cases, the existence of DNA repair XRCC-1 gene polymorphic variants (Hetero CT and Mutant TT) was recognizable in contrary to the control group arm. The XRCC-1 gene polymorphic hetero (CT) genotype (O.R-1.96; 95% C.I: 1.23–3.13; P < 0.004) and mutant (TT) genotype variants (O.R-1.95; 95% C.I: 0.59–6.44; P = 0.27) was correlated with access hazard of loco-regionally progressed LSCC, and its statistically convincing for polymorphic hetero (CT) variant. The data were adapted for the age of the patients and control group, circadian alcohol intake, tobacco chewing habits, and the tobacco smoking habits during application of multivariate logistic regression. Its apparent that the hazard is amalgamated with hetero (CT) genotype variant (O.R- 1.67; 95% C.I: 0.98–2.82; P = 0.05) and mutant (TT) genotype variant (O.R- 1.62; 95% C.I: 0.88–2.78; P = 0.11) and its statistically convincing for polymorphic hetero (CT) genotype variant. Cases with the record of substance use (alcohol and tobacco) have an abundance of XRCC-1 hetero (CT) and mutant (TT) genotype variants in allegory to control group. Increased hazard is related with XRCC-1 hetero (CT) variant in smokers (O.R 3.28; 95% C.I: 1.45–7.41; P = 0.004), in tobacco chewers (O.R-3.79; 95% C.I: 1.87–7.71; P = 0.0002), and in alcohol consumers (O.R- 4.24; 95% C.I: 2.21–8.15; P= < 0.0001) which is statistically significant.

Conclusion: This research investigation demonstrates the correlation of XRCC-1 polymorphic hetero genotype (CT) & mutant genotype (TT) variants as hazard factor in loco-regionally progressed LSCC. Cases with the record of alcohol intake habits, tobacco smoking and chewing habits and XRCC-1 hetero genotype (CT) variant have statistically increased the hazard of loco-regionally progressed LSCC, which demonstrate the role of gene-ecological interconnection in modifying the vulnerability of loco-regionally progressed LSCC.

1. Introduction

Worldwide approximately about five lacs individuals have diagnosed annually with squamous cell cancer of head and neck region (HNSCC).[1] In HNSCC, Laryngeal cancer is most commonly diagnosed subtype.[2] Increase hazard of LSCC is seen with ecological factors like alcohol intake and tobacco consuming habits. Metabolites produce by consumption of alcohol and tobacco usage leads to an increase in the oxidative stress and DNA Strand interruption. Three most important process of DNA repair is base excision repair (BER) pathway, nucleotide excision repair (NER) pathway, and double-strand break (DSB) repair. XRCC-1 DNA repair gene plays an important role in BER pathway. DNA repair gene single nucleotide polymorphism (SNPs) can lead to changes in individual accountability to larynx cancer.[3] In the XRCC-1 DNA repair gene, three different types of Single nucleotide polymorphisms (SNPs) have been observed. 1st SNP is observed in the 6th exon at codon 194 which lead to change in Arginine amino acid to Tryptophan amino acid (Arginine194Trpytophan polymorphism), 2nd SNP is observed in 9th exon at codon 280 which lead to change in arginine amino acid to Histidine amino acid (Argine280Histidine polymorphism), the

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3rd SNP occurs in 10th exon at codon 399 which lead to change in Arginine amino acid to Glutamine amino acid (Arginine399Glutamine polymorphism).[4] Hindrance to the platinum-based concurrent chemoradiation (CCRT) can occur in patients with higher DNA damage resolution capacity. The XRCC-1 gene plays a crucial part in DNA damage resolution following the platinum-based CCRT. Variation in responsiveness of tumor cells toward CCRT is seen, when there is an alteration in XRCC-1 DNA resolution gene and its protein expression.[5–7]

2. Material and technique

2.1. Study plan

A tertiary hospital-based prospective case-control research study was performed. Between August 2013 and July 2016, 150 male patients were incorporated into the study group with pathologically diagnosed LSCC. The admittance basis for patients (cases) were the age of the patient ≥18 years, the performance score (Kernofsky Performance score) of ≥80, adequate Complete blood count test (C.B.C) and Differential count (D.C) test with neutrophils $> 1.5 \times 10^9$ cells per liter, Platelets $> 100 \times 10^9$ cells per liter, adequate kidney function test (K.F.T) with Creatinine Clearance (C.C) of ≥50 ml per minute, loco-regionally progressed LSCC (Stage III & IV), and with no distant metastasis to lung or liver. The control group comprises an equal number of healthy males. The following information was taken from the cases, chief complaints, history of presenting illness, followed by the general and systemic examination, local examination of oral cavity and neck and direct laryngoscopy. Data were collected regarding the family history of carcinoma, personal history of substance use (alcohol consumption, tobacco smoking, and tobacco chewing habits). Investigations to know the general health and organ function was done which include Complete blood count (C.B.C), Liver function test (L.F.T), Kidney function test (K.F.T), pre-treatment dental check-up. To know the local and regional disease status, investigations like Head and neck Computed Tomography (C.T) scan and Magnetic resonance imaging (M.R.I) was done. Chest roentgenogram (Posterior anterior view) and Ultrasonography (U.S.G) whole Abdomen of the cases was done to rule out the lung metastasis, and liver metastasis. In this research, the American Joint Committee on cancer (A.J.C.C 2010) manual was used for the staging of larynx cancer patients.[8] The Fine needle aspiration cytology (F.N.A.C) from the lymph node basin and the biopsy from laryngeal lesion was done by the E.N.T (Ear Nose and Throat) specialists. The cytology and histopathological examination (HPE) examination were done by the pathologist for confirmation of LSCC in patients. From multiple health camps, 150 healthy male individuals were enrolled in the control group arm. 2 ml (milliliters) of whole blood was taken in two EDTA (Ethylenediaminetetraacetic acid) tube from all the control group and patients. DNA segregation from the whole blood samples of control and cases was done using Polymerase chain reaction (PCR), and the XRCC-1 Gene analysis was done using Restriction fragment length polymorphism (RFLP)

2.2. Genotype testing

To detect the DNA repair XRCC-1 gene Arg194Trp polymorphism, the technique described by Sturgis et al. was used.[9] RP 5′- TACCCTC AGACCCACGAGT-3′ and FP 5′- GCCAGGGCCCCTCCTTCAA-3′ were the two primers sequence used for knowing the XRCC-1 (Arg194Trp) polymorphism. The reaction blend (25 μl) contained 9 buffers {10 mM (Millimolar) of Tris-Hydrochloric acid puffer pH 8.3, 25 mM (Millimolar) of Potassium Chloride (KCl), 1.5 mM (Millimolar) of Magnesium Chloride (MgCl2), 200 μM (Micromolar) of each Nucleotide, 100 ng (Nanogram) of DNA, 200 nM (Nanomolar) of both the primers, 1.5 Unit of highly thermostable Taq polymerase enzyme, and milli-Q water}. Warm cycler with accompanying protocol was used for the process of amplification: To initiate the process of denaturation 94^0 Celsius of heat was applied for five minutes followed by 35 rotation of 94^0 Celsius for forty-five seconds, 62^0 Celsius for thirty-five seconds, 72^0 Celsius for sixty seconds, and 72^0 C for ten minutes for the last step of elongation process. PCR process leads to the production of 485 base pair (bp). Different genotype variants of XRCC-1 polymorphism is differentiated using RFLP. 10 μl (Microliter) of the mixture produced by PCR is processed with One Unit of Pvu II restriction enzyme. This processed blend was then incubated at 37^0 Celsius for the whole night. Ethidium bromide containing 3% agarose gel was used for electrophoresis and was inspected on Imaging System (VERSA DOC Model 1000, Bio-Rad). The gain of the Pyu II restriction site in the polymorphic allele is used to recognize the polymorphism (Arg194Trp) of the 6th exon. The genotype polymorphism was differentiated as wild (CC) type variant, and polymorphic variants (hetero CT and mutant TT). A solitary band of 485 base pair (bp) is seen in wild-type allele (C), while two segments of 89 base pair (bp) and 396 base pair (bp) are seen in polymorphic allele (T), and three segments of 485 base pair (bp), 396 base pair (bp) and 89 base pair (bp) are recognized in heterozygous allele (CT).

This research study convention was accepted by the human ethics committee. For enrollment in this research study group and before initiating the whole blood sample (2 milliliters) collection from cases and control, assent was taken. A questionnaire sheet was filled up by all the enrolled cases and controls regarding their medical history, tobacco smoking and chewing habits, family history of cancer, alcohol intake. Cases and controls were categorized as tobacco smokers who had regular tobacco smoking habits and with smoking index (S.I) ≥ 730 (S.I = cigarettes smoked/day x 365 days). Cases and control were categorized as tobacco chewers who had the chewing year (C.Y) ≥ 365 (C.Y is defined as the frequency of tobacco chewed day for a time span of 3 years).[10] Cases and controls with the habit of either tobacco smoking or chewing were categorized as tobacco substance users. Cases and controls with approximately total consumption of alcohol of ≥90 liters/year were categorized as alcohol substance users.[11]

2.3. Statistical Analysis

The χ^2 (chi-square) test were used to know the recurrence of XRCC-1 genotype variants among the control group. Crude Odds proportions (O.R) and 95% Confidence Interval (C.I) were computed to know the correlation between genotype variants and hazard of loco-regionally progressed LSCC. To calculate the adjusted Odds ratio ($O.R^a$) for the variables like age in years, tobacco smoking habits, tobacco chewing habits, and alcohol intake, multiple logistic regression was used. To know the relationship between the ecological factors and genotypes variants or between the genotype variants, conditional logistic regression was used. The described herein P-value is two-tailed, and the P-value < 0.05 was regarded as statistically cogent. To execute all the statistical analysis, statistical package for social science (SPSS) software (Version 11.0 windows; SPSS Chicago, IL) was used.

3. Observation and results

A hospital-based prospective case-control research was conducted between July 2013 and July 2016. The results herein are discussed in reference to the study group (cases and control) age in years, the subsite of laryngeal cancer in cases, stage of LSCC at presentation in cases, presence of Arg194Trp polymorphism genotype variants in cases and control group, correlation between Arg194Trp polymorphism with loco-regionally progressed LSCC, correlation between alcohol and tobacco intake with loco-regionally advanced LSCC, and correlation between genotype variants of Arg194Trp polymorphism with alcohol and tobacco substance users. The average age in years of the patients and the control group were 46 ± 10 and 46 ± 11. The smoking habits were observed to be higher in the patients (cases) in contrast with the control group. In cases and control group arm, the tobacco chewing habits and alcohol intake habits were almost similar. In the cases group,

Table 1
Distribution of age in years and the risk factors for loco-regionally progressed LSCC cases and controls.

Characteristics	Control N (%)	Cases N (%)
Enrolled	150	150
Age (Mean ± S.D)	46 ± 11	46 ± 10
Non-Smoker	111 (73%)	65 (43%)
Smoke	39 (27%)	85 (57%)
Tobacco chewers	75 (50%)	81(54%)
Non-Tobacco Chewers	75 (50%)	69(46%)
Alcohol Users	83(55%)	86(57%)
Non-alcohol Users	67(45%)	64(43%)

the supraglottic subtype of LSCC comprises about 82%, the glottic subtype of LSCC comprises about 17% and subglottic subtype comprises about 1%. 63% of cases presented with stage III LSCC and 37% cases presented with stage IV LSCC (Table 1). The Genotype variants of XRCC-1 gene in patients (cases) and control group. In cases, the presence of polymorphic XRCC-1 genotype variants (hetero CT and mutant TT) was apparent in contrast to the control arm. XRCC-1 polymorphic hetero (CT) genotype (O.R-1.96; 95% C.I: 1.23–3.13; P < 0.004) and mutant (TT) genotype variants (O.R-1.95; 95% C.I: 0.59–6.44; P = 0.27) was correlated with access risk of loco-regionally progressed LSCC, and its statistically cogent for polymorphic hetero (CT) variant. While applying the multivariate logistic regression analysis, the abstracts were adapted for age, circadian alcohol intake, tobacco chewing habits and tobacco smoking habits. Its apparent that the hazard is amalgamated with hetero (CT) genotype variant (O.R- 1.67; 95% C.I: 0.98–2.82; P = 0.05) and mutant (TT) genotype variant (O.R- 1.62; 95% C.I: 0.88–2.78; P = 0.11) and its statistically cogent for hetero (CT) genotype variant as displayed in Table 2. Cases with the record of substance use (alcohol and tobacco) have an abundance of XRCC-1 hetero (CT) and mutant (TT) genotype variants in allegory to control group. To know the information regarding a gene-ecological relationship, patients with tobacco chewing and smoking habits and alcohol intake habits were stratified. It was noticed that cases who were tobacco smokers have higher chances of XRCC-1 polymorphic (hetero CT and mutant TT) genotype variants in contrast with the control group. Increased hazard of loco-regionally progressed LSCC is correlated with XRCC-1 hetero (CT) variant in tobacco smokers (O.R 3.28; 95% C.I: 1.45–7.41; P= < 0.004), tobacco chewers (O.R-3.79; 95% C.I: 1.87–7.71; P = 0.0002), and alcohol consumers (O.R- 4.24; 95% C.I: 2.21–8.15; P= < 0.0001) which is statistically significant as displayed in Tables 3.1, 3.2 and 3.3.

4. Discussion

This investigational study objective intends to evaluate the interrelationship of XRCC-1 gene Arg194Trp polymorphism in alcohol and tobacco substance users and in influencing the hazard of loco-regionally progressed LSCC. Higher risk of HNSCC was observed in two RFLP at 6th and 10th exon of DNA repair XRCC-1 gene of the Caucasian population. Patient (cases) with records of contemporaneous alcohol intake habits and tobacco smoking and chewing habits was observed to have the higher recurrence of polymorphic genotype variants.[9] The wild-type variant of Arg194Arg genotype was observed in the higher number of cases, whereas wild-type variant of Arg399Arg genotype was observed to be higher in the control group.[12] The Variant allele (T) was observed in 59% of the population existing in the northern region of India, the recurrence of genotype variants was 20% CC (homozygous allele) subtype, 47% CT (polymorphic heterozygous allele) subtype, and 33% TT (polymorphic homozygous allele) subtype. The recurrence of an allele in the population existing in the southern region of India was distinct from the entire populaces excluding the population existing in the northern region of India.[13] In Indian populace, the two genotypes Arg194Trp (O.R: 2.27; 95% C.I = 1.01–5.08; P < 0.001) and Arg280His (O.R: 4.95; 95% C.I = 2.48–9.89; P < 0.001) was correlated with increased risk of hepatocellular cancer (H.C.C). The risk for H.C.C was elevated by 35.96 times in Arg194Trp (O.R: 35.96; 95% C.I: 11.64–110.91; P-value < 0.001) and it was elevated by 5.28 times in Arg399Gln (O.R: 5.28; 95% C.I: 2.81–9.09; P value < 0.001) when found in association with genotype Arg280His.[14] Our investigational study suggests that in cases, the presence of polymorphic XRCC-1 genotype variants (Hetero CT and Mutant TT) was noticeable in contrast to the control group arm. The XRCC-1 gene polymorphic hetero (CT) genotype (O.R-1.96; 95% C.I: 1.23–3.13; P < 0.004) and mutant (TT) genotype variants (O.R-1.95; 95% C.I: 0.59–6.44; P = 0.27) was correlated with access hazard of loco-regionally progressed LSCC, and its statistically convincing for polymorphic hetero (CT) variant. The data were adapted for the age of the patients and control group, circadian alcohol intake, tobacco chewing habits, and the tobacco smoking habits during application of multivariate logistic regression. Its apparent that the hazard is amalgamated with hetero (CT) genotype variant (O.R- 1.67; 95% C.I: 0.98–2.82; P = 0.05) and mutant (TT) genotype variant (O.R- 1.62; 95% C.I: 0.88–2.78; P = 0.11) and its statistically convincing for polymorphic hetero (CT) genotype variant. The above-mentioned results are naturally conceivable. The polymorphism causing the change in amino acid location in DNA repair gene and leads to debilitation of DNA resolution process and hence these polymorphisms can theoretically lead to malignancy in a person with the history of alcohol and tobacco substance use. Changes in DNA repair capacity which is caused by the modification in the amino acid (A.A) type and amino acid location in the gene are confirmed by this investigational study and a few validating points are displayed herein. First is the higher number of the XRCC-1 gene polymorphic genotype (hetero CT and mutant TT) variants in the patients (cases) in contrast to control group arm. The quantity of exposure of these risk factors (alcohol and tobacco substance use) and its effect on these polymorphic (hetero CT and mutant TT) genotype variants underpins an adjoin influence of these polymorphic genotype variants. The patients (case) and controls who had present alcohol intake habits and tobacco smoking and chewing habits were correlated with the increased frequency of XRCC-1 gene polymorphic genotype variants indicate a gene–ecological relationship. Having these XRCC-1 gene polymorphic genotype (hetero CT and mutant TT) genotype variant is not a hazard for loco-regionally progressed LSCC except in the presence of alcohol intake habits, tobacco smoking habits and tobacco chewing habits. As investigated by the Lunn et al., population with the XRCC-1 gene Arg399Gln polymorphism there is larger amounts of Glycophorin-A variant and the DNA adducts of Aflatoxin B1.[15] The meta-analysis comprising of

Table 2
XRCC-1 Arg194Trp polymorphisms Genotype distribution in Controls and Cases.

Genotype variant	Control (N = 150)	Case (N = 150)	O.R (C.I 95%)	P- value	O.R[a] (C.I 95%)	P- value
XRCC1(wt/wt CC)	88	63	1 Ref			
XRCC1(Hetero CT)	57	80	**1.96 (1.23–3.13)**	**< 0.004**	**1.67 (0.98–2.82)**	**0.05**
XRCC1(Mutant TT)	5	7	1.95 (0.59–6.44)	0.27	1.62 (0.88–2.78)	0.11

O.R: Odds ratio; 95% C.I: 95% Confidence Interval; **P-value: < 0.05 is regarded as statistically notable**, O.R[a]: Adjusted Odds ratio in multivariate logistic regression models (Data is adapted for tobacco smoking habits, age in years, tobacco chewing habits, daily consumption of alcohol and genotype variants).

Table 3
Gene-ecological correlation.

3.1: Correlation Between XRCC-1 Arg194Trp Genotype variants with tobacco Smoking and Risk Of Loco-regionally progressed LSCC

Non-Smoker					Smoker				
Genotype variant	Control N = 110	Case N = 63	O.R (95% C.I)	P- value	Genotype variant	Control N = 40	Case N = 87	O.R (95% C.I)	P- value
XRCC1(wt/wt CC)	63	30	1 Ref		XRCC1(wt/wt CC)	25	33	1 Ref	
XRCC1(hetero CT)	45	32	1.49 (0.79–2.79)	0.20	XRCC1(hetero CT)	12	52	**3.28 (1.45–7.41)**	**< 0.004**
XRCC1(Mutant TT)	2	1	1.05 (0.09–12.0)	0.96	XRCC1Mutant TT	3	2	0.50 (0.07–3.25)	0.46

3.2: Correlation Between the XRCC-1 Arg194Trp Genotype variants with Tobacco Chewing and Risk Of Loco-regionally progressed LSCC

Non-Tobacco Chewer					**Tobacco Chewer**				
Genotype variant	**Control N = 67**	**Case N = 69**	**O.R (95% C.I)**	**P-value**	**Genotype variant**	**Control N = 75**	**Case N = 81**	**O.R (95% C.I)**	**P- value**
XRCC1(wt/wt CC)	33	25	1 Ref		XRCC1(wt/wt CC)	55	38	1 Ref	
XRCC1(hetero CT)	41	42	1.35 (0.68–2.65)	0.38	XRCC1(hetero CT)	16	42	**3.79 (1.87–7.71)**	**0.0002**
XRCC1(Mutant TT)	1	2	2.64 (0.22–30.7)	0.43	XRCC1(Mutant TT)	4	1	0.36 (0.03–3.36)	0.37

3.3: Correlation Between the XRCC-1 Arg194Trp Genotype variants with Alcohol consumption and Risk of Loco-regionally progressed LSCC

Non-Alcohol user					**Alcohol user**				
Genotype variants	**Control N = 67**	**Case N = 64**	**O.R (95% C.I)**	**P- value**	**Genotype variants**	**Control N = 83**	**Case N = 86**	**O.R (95% C.I)**	**P-value**
XRCC1(wt/wt CC)	33	34	1 Ref		XRCC1(wt/wt CC)	55	29	1 Ref	
XRCC1(hetero CT)	32	28	0.84 (0.42–1.70)	0.64	XRCC1(hetero CT)	25	56	**4.24 (2.21–8.15)**	**< 0.0001**
XRCC1(Mutant TT)	2	2	0.9 (0.12–7.29)	0.97	XRCC1(Mutant TT)	3	1	0.63 (0.06–6.35)	0.69

O.R: Odds Ratio; 95% C.I: 95% Confidence Interval; Ref: The reference category, **P-value: < 0.05 is regarded as statistically notable.**

twenty-nine studies reported no noteworthy correlation between the XRCC-1 gene Arg194Trp polymorphic genotypes, XRCC-1 gene Arg280His polymorphic genotypes, and XRCC-1 gene Arg399Gln polymorphic genotypes and with the hazard of HNSCC. The subdivision examination as suggested by patient race, cancer or disease subsite, and the genotyping strategy reported no outstanding relationship in any subdivision, besides in the latent class model oral cavity squamous cell cancer was affiliated with the Arg194Trp genotype variant. A correlation between the effect of XRCC-1 Arg194Trp polymorphism, smoking, and HNSCC was identified in polymorphic homozygote (TT) genotype (O.R: 2.53; 95% C.I: 1.16–5.53, P = 0.02).[16] The main limitation of this investigational research was the small number of patients, and hence this data has a constraint to be summarized to all the loco-regionally progressed LSCC patients. The additional investigational study is needed to exactly estimate and endorses the outcome of our investigational research which proposes that XRCC-1 gene Arg194Trp genotype variants have impinged the hazard in alcohol and tobacco substance users and in the patients with loco-regionally progressed LSCC.

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