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Association Between PARP-1 Val762Ala Gene Polymorphism and Lung Cancer Risk: A Hospital-based Case-Control Study

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ABSTRACT:

Background: The gene polymorphisms in PARP can influence the effectiveness of DNA repair, increasing genomic instability and there by the risk of cancer. The decreased PARP-1 activity, impact base excision repair (BER) and single strand break (SSBR) repair, and promote the growth of DNA damage and carcinogenesis. Because of increased exposure to carcinogens like tobacco smoke and pollution, which cause oxidative DNA damage, it is crucial to look at PARP-1 polymorphisms in lung cancer. Finding these variations could enhance early detection, risk assessment, and individualized care. An increased risk of developing lung cancer is associated with the Val762Ala SNP in PARP-1. Along with its relationship to addictions and other environmental factors, the study investigates the association between the PARP-1 762 Val>Ala polymorphism with the incidence of lung cancer.

Materials and Methods: 45 histologically verified cases of lung cancer and 57 age-sex-matched healthy controls were included in our study. All subjects' demographic information was gathered through the use of standardized questionnaires. Blood samples were obtained, and DNA was extracted from them. The PARP-1 Val762Ala variant was amplified in PCR using specifically designed primers and examined using restriction fragment length polymorphism (RFLP) using BstUI enzyme. The digested products were electrophoresis on 3% agarose gel for allele distinction.

Results: Logistic regression analysis of our results indicated no significant association of mutated heterozygous genotype in PARP-1 Val762Ala polymorphism with the lung cancer risk. However, demographic variables also showed significantly increased susceptibility in subjects with smoking habit, ($\chi 2$=6.760, p=0.009). Similarly, the education also shows a significant risk in the population with low education levels ($\chi 2$=15.275, p=0.033), age group between 51-70 years ($\chi 2$=8.390, p=0.039).

Conclusion: The findings obtained from this study indicates that the polymorphic PARP-1 762 Val>Ala was not significantly associated with lung cancer risk in the studied population.

Keywords: Lung Cancer; PARP-1 [Poly (ADP Ribose) Polymerase 1]; Genetic Polymorphism; PCR-RFLP.

Introduction:

Globally lung cancer ranks among the most prevalent and fatal cancer. According to GLOBOCAN 2022 it has a rough estimate of about 2.5 million diagnosed cases and a total of 1.8 million deaths worldwide. In woman with 9.4% new cases, it is the second most common after breast with 23.8% [1]. Men have a 3.8% possibility of being diagnosed with this lesion, whereas women have a lower probability of 1.77%. The gender disparity in this disease incidence is primarily because men and more likely to smoke tobacco as compared to women. In developed countries, its incidence is decreasing among men but increasing among women because woman choose to adopt and quit smoking later than men do.[2] In 2022, East Asia recorded the highest occurrence rate (39.4 out of 100,000), with China accounting for 42.7% of global cases (1,060,584) and 40.3% of deaths (733,291). Other high-incidence regions included North America (31.9), Western Europe (31.2), and Eastern Europe (27.6) per 100,000, while Western Africa (2.1) and Middle Africa (2.3) had the lowest rates.[3] In India it's burden constitutes 5.9% of all cancer cases.[4] Although the specific cause of LC is not fully understood, it is generally recognized to result from a number of contributing factors such as genetics, family history, environmental and lifestyle factors. Tobacco usage is the primary cause, with susceptibility increasing with duration and intensity of exposure.[5] Gene polymorphism refers to variations in the sequence of DNA that occur in more than 1% of the population. These variations lead to gene diversity such as physical characteristics, diseases vulnerability and drug responses. Polymorphisms are common and can be advantageous, harmful or cause no effects. Whereas mutations are

rare and often cause diseases.[6] Poly (ADP ribose) polymerases (PARPs), are key players in cancer biology, influencing tumorigenesis, its progression, and treatment response.[7] PARPs are classified as poly-ADP-ribosyl transferases (pARTs). They facilitate the attachment of ADP-ribose polymers to specific target molecules.[8] They are crucial for restoring DNA due to damage in cancer especially in the base excision repair (BER) pathway. [9-10] PARP-1, are rapidly recruited to sites of nucleic acid damage enabling them to transfer ADP-ribose units to themselves and to other acceptor proteins.[11] Poly-ADP-ribosylation functions as a signaling mechanism that helps coordinate and carry out DNA damage response thereby maintaining the integrity and preventing the accumulation of mutations that can cause tumourgenisis. [12] Several studies have shown that a defect in the PARP-1 gene could lead to carcinogenesis, genomic instability, resistance to cell death signaling mechanisms, and altering gene transcription. [13-15] The PARP-1 gene in humans is situated on the long arm of chromosomal region 1q41–42, comprising of 23 exons and spanning roughly 47.3 kb. [16] Poly (ADP ribose) polymerases-1 is rich in single nucleotide polymorphisms (SNPs), out of which 17 are non-synonymous, among them, rs1136410, which causes a T→C substitution at codon 762 in exon 17, is thoroughly examined. It is a valine-to-alanine substitution within the sixth helix of the C-terminal nicotinamide adenine dinucleotide-binding domain, which is essential for the proper functioning of the enzyme. As a result, individuals carrying this variant allele are more vulnerable to developing malignancies and different carcinogens like tobacco smoke, diesel exhaust, Polycyclic Aromatic Hydrocarbons (PAHs) and asbestos. [17-18] Molecular studies on Poly (ADP ribose) polymerase (PARPs)-1 Valine762Alanine a Single Nucleotide Polymorphism (SNP) have found a substantial correlation with heightened likelihood of different cancers like breast, stomach, lung, cervix, brain, and colorectum. [19-24] Extensive research has been conducted on The PARP-1 762 Val>Ala polymorphism across various ethnic groups. It has been found that this polymorphism is linked with various cancer and is especially higher among the Asians as compared to the Caucasians. [25] The Asians in particular the Chinese population have a strong relationship of cancer susceptibility with PARP-1 762 Val>Ala polymorphism. [26] Only a few studies have explored the PARP-1 762 Val>Ala polymorphism among the Indian population with risk to different cancers like gall bladder and oral squamous cell carcinoma. [27-28] Previous studies have identified a connection between rs1136410 polymorphism and LC susceptibility [29-30] However due to genetic diversity and environmental pollutants its contribution with lung carcinoma has been inconsistent across different ethnic groups and regions. This case-control research conducted in a healthcare setting explores the link with PARP-1 Val762Ala and risk of LC, especially on its interaction with addictions such as smoking, consumption of alcohol, and other environmental exposures like radon gas, lead, arsenic, asbestos and fuel exhaust. This gene-environment interaction can help in evaluation, different preventive measures, and potential therapeutic interventions using PARP inhibitors.

Methodology:

Ethical Clearance

Ethical clearance for the study was granted by Institutional Ethics Committee under protocol no. MDC/JNMCIEC/371 of KLE's Academy of Higher Education and Research, Belagavi.

Study design

Type of study

This was a case–control study.

Study population

In the present study, all cases willing to take part and who satisfied the inclusive criteria of the study were recruited from the Oncology Department of KLE's Dr. Prabhakar Kore Hospital & Medical Research Centre.

Controls

Age and sex-matched cancer-free individuals who were willing to take part and who satisfied the inclusive criteria of the study were selected from the General OPD of the same hospital.

Sample size

A total of 102 participants (45 lung cancer cases and 57 healthy controls) were recruited for the study. The sample size was estimated using previous prevalence data ($P_1 = 0.389$, $P_2 = 0.279$), assuming 95% confidence interval and 20% allowable error, yielding approximately 45 samples per group.

Duration of study

The duration of the study was from May 1, 2024, to March 31, 2025.

Collection of Blood sample and genomic DNA isolation

Whole blood samples about 2-3ml were collected from all participants in a sterile EDTA containing tubes after obtaining written informed consent and were transported to the laboratory in cold condition. Extraction was carried out using the HiPurA® Blood DNA Miniprep Purification Kit (Make: HiMedia Laboratories). Following the protocol provided by the manufacture genomic Deoxyribose Nucleic acid was isolated from the whole blood. The samples were treated with Proteinase K (200µg/µl) to digest the proteins and subsequently RNase A (200µg/µl) to make it RNA free. The obtained pellet of DNA was then resuspended in elution buffer and 1% agarose gel was used to evaluate its concentration and quality. The concentration of extracted nucleic acid was quantified on a NanoDrop (Make: Implen N60) based on absorbance ratios at A260/A230 and A260/A280. After purification polymerase chain reaction followed by restriction fragment Length Polymorphism (PCR- RFLP) was employed for further genotyping.

Genotyping tests

PCR-RFLP assay was performed for genotyping using appropriate forward and reverse primer set designed to amplify the regions of DNA from PARP-1 gene that contain polymorphic sites of study interest. PARP-1 Val762Ala variation was detected through polymerase chain reaction. A 20 µL reaction mixture containing purified genomic deoxyribose nucleic acid template of 100 ng and nuclease-free water (15 µL) was used for each reaction. Taq buffer 2.0 µL, (GeNei, Merck Biosciences), dNTPs 0.5 µL, (GeNei, Merck Biosciences), Taq polymerase enzyme 0.5 µL, (GeNei, Merck Biosciences), Primers 0.5 µL (Make: Integrated DNA Technologies) Forward (5'-TTT GCT CCT CCA GGC CAA CG-3'), Reverse (5'-TGG AAG TTT GGG ACC GCT GC-3'). Applied Biosystems ProFlex Polymerase Chain Reaction System (Make: Thermo Fisher Scientific) was employed for amplification. Under the following thermal cycling conditions, initial denaturation at 94°C for 5 min, 35 repeated cycles of denaturation at 94°C for 30 sec, annealing at 56°C for 20 sec, initial extension at 72°C for 20 sec, final extension at 72°C for 5 min the amplification was carried out. Until further analysis the reactions were maintained at 4°C. Gel electrophoresis with a percentage of 1.5 agarose was used to confirm the expected band size of 210 bp. PCR amplicon each of 10µl of sample was digested with 1 U i.e. 0.2 µL of *BstUI* restriction enzyme (NEB) following verification of the amplified fragment of expected size. Incubation was followed for 6–8 hours at 60°C. Digested products were then separated on 2-3% of agarose gel (Make: Sigma) at 100 volts for 30 mins. After the run, ethidium bromide-stained gels were observed under ultraviolet transilluminator (Make: Vilber), and documented with a gel imaging system (Make: BioVision).

Criteria for Inclusion and Exclusion-Cases

Inclusion

1. Newly diagnosed & histologically confirmed lung cancer patients.
2. No prior history of other malignancies.
3. All patients in the study willing to provide written consent for participation.

Exclusion

1. A history of any previous malignancy in patients.
2. Patients with metastasized cancer from other organs.

Criteria for Inclusion and Exclusion for controls

Inclusion

1. Age and gender-matched cancer-free individuals as controls.
2. Healthy patients with no prior history of any type of malignancy.

Exclusion

1. Patients with a history of any previous malignancy.
2. Unwilling to participate in the study.
3. Aged 18 and below years.

Statistical analysis

By making use of the Odds ratio (OR) we examined the relationship between polyadenosine diphosphate-ribose polymerase genotype and the possible risk of respiratory cancer. To ascertain the vulnerability of LC linked to genotypes, the logistic regression framework was employed to estimate Odds Ratio (OR) and a confidence interval (CI) of 95 per cent along with variable adjustment. Difference was considered statistically significant for $p \leq 0.05$ and all p values were two-sided. All statistical analyses were performed with SPSS (IBM Version 11.0) software.

Objective:

1. To study the gene polymorphism between PARP-1 Val762Ala polymorphism and lung cancer risk.
2. To study the association between the PARP-1 Val762Ala polymorphism with addictions and exposed environmental factors

Results

Characteristics of the Study Population

During this study a total of 45 clinically confirmed cases and 57 healthy disease-free controls were selected from the rural population of northwestern Karnataka. The mean (Mean±SD) age in years was found to be 61.16±12.9 for cases and 55.51±14.84 for healthy controls. The interactions between the demographic data such as tobacco chewing, smoking habit, alcohol consumption and their genotype frequency distribution between cases and sex-matched controls were investigated. The clinical and demographic data of the research participants are displayed in Table 1.

After performing Chi Square test, the male and female distributions were similar (p=0.153) in both groups for gender.

This suggests that gender does not have any correlation with the probability of developing the disease and there was no conclusive evidence linking its susceptibility to a family history of the disease (p=0.945). However, no correlation was found between economic status (p = 0.127) and alcohol consumption (p = 0.100). Although there were more cases (41.2%) with a habit of chewing tobacco, there was no statistical difference (p = 0.181).

Smokers in the patient group had a percentage of 37.8 which was relatively higher while 62.2 per cent was of the controls group. Non-smokers were mostly in the healthy individual group (70%). This strongly suggests that smoking is a significant factor ($\chi 2$=6.760 p = 0.009).

Cases aged ≥71 had the largest proportion approximately 66.7%. The p-value (0.039) suggests that age is significantly associated with this carcinoma in the studied population.

Another major factor that increased chance of developing respiratory cancer was illiteracy ($\chi 2$=15.275, p=0.033). Less frequently associated factor was higher education levels (HSC and above). Notably, the healthy individual group consisted solely of higher educated, but the patients were more prevalent among those with lower educational attainment. Vegetarians were significantly more likely to be in the control group (70.6%). Mixed diet individuals were more frequent in the case group (p= 0.034) (51.5%). This suggests that a vegetarian diet may safeguard against the occurrence of lung cancer.

Table 1: Comparative data of demographic data among individuals with LC cases and healthy controls.

Parameters		**LC Cases**	**Controls**	**Chi Square**	**Probability-value (χ^2)**
Mean age (in years) ± SD		61.16±12.9	55.51±14.84	-	-
Age	<=50 yrs	7(25.9%)	20(74.1%)	8.390	0.039*
	51-60yrs	14(56.0%)	11(44.0%)		
	61-70yrs	14(40.0%)	21(60.0%)		
	>=71 yrs	10(66.7%)	5(33.3%)		
Gender	Male	30(50%)	30(50%)	2.045	0.153
	Female	15(35.7%)	27(64.3%)		
Family History of Cancer	Yes	3(42.9%)	4(57.1%)	0.005	0.945
	No	42(44.2%)	53(55.8%)		
Education	Illiterate	19(46.3%)	22(53.7%)	15.275	0.033*
	SSC	11(44.0%)	14(56.0%)		
	HSC	8(66.7%)	4(33.3%)		
	Graduate	6 (42.9%)	8(57.1%)		
	Diploma	0(0.0%)	2(100.0%)		
	Post Graduate	1(100%)	0(0.0%)		
	PhD	0(0.0%)	7(100.0%)		
Economic Status	Lower Income	22(53.7%)	19(46.3%)	4.132	0.127
	Middle Income	23(36.7%)	38(63.3%)		
	Higher Income	0(0.0%)	0(0.0%)		
Tobacco Habit	Yes	35(41.2%)	50(58.8%)	1.789	0.181
	No	10(58.8%)	7(41.2%)		
Alcohol Consumption	Yes	4(36.4%)	7(63.6%)	1.9	0.1
	No	53(58.2%)	38(41.8%)		
Diet	Vegetarian	10(29.4%%)	24(70.6%)	4.474	0.034*

	Mixed	35(51.5%%)	33(48.5%%)		
Smoking habit	Yes	31 (37.8%)	51 (62.2%)	6.760	0.009*
	No	14 (70.0%)	6 (30.0%)		

Evaluation of PARP-1 Val762Ala Gene Variation on predisposition to LC

To assess the relationship of PARP genotypes with respiratory cancer a logistic regression model was used.

The PARP-1 Valine 762 Alanine gene variation was assessed in 45 respiratory cancer patients and a comparable number of healthy individuals (57). It was found that the frequency distribution showed no strong correlation among the cases and control participants for the wild type genotype (WT) with p value 0.084 in the study population. Similarly, we did not observe any statistical difference (P=0.718) in the mutated heterozygous genotype among the studied subjects with patients meaning a lower odd of the outcome compared to WT, but with a wide confidence interval (0.250 to 2.066), indicating uncertainty. Individuals who carried the mutated variant genotype 7.875 had a higher odd of the outcome compared to WT. However, the confidence interval (0.788 to 78.671) is very wide, indicating variability and possible lack of precision in the rural population of northwestern region of Karnataka for the risk of this carcinoma. The genotype frequencies of PARP-1 762 Valine>Alanine polymorphic variants and their correlation with patients and healthy individuals are listed in Table 2.

Table 2. Distribution patterns of PARP-1 762 Val>Ala gene variation in LC patients and controls.

Genotype	**LC Cases**	**Controls**	**OR (CI 95%)**	***p*-value**
Wild type (WT)	30(39.0%)	47(61.0%)	1(Reference)	
				0.084
Heterozygous type (HT)	7(87.5%)	1(12.5%)	0.718 (0.25-2.06)	0.539
Variant type (VT)	8(47.1%)	9(52.19%)	7.875(0.78-78.67)	0.079

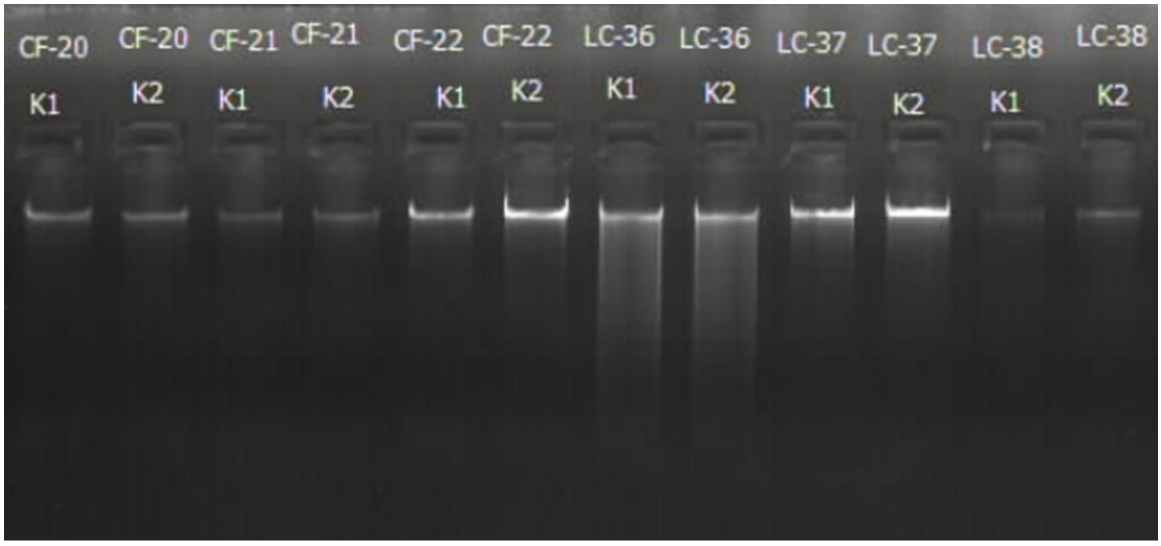

Figure 1. Agarose gel of isolated DNA showing yields for CF-20[K1- 100 ng, K2-100 ng], CF-21[K1-100 ng, K2-100 ng], CF-22[K1-200ng, K2-200ng], LC-[36(K1-200ng, K2-200ng), 37(K1-500ng, K2-500ng),38(K1-50ng, K2-100 ng)].

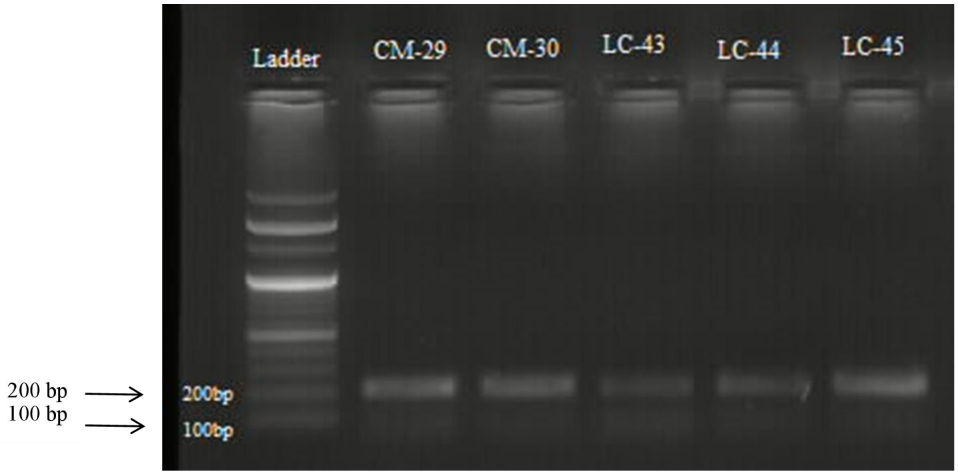

Figure 2. PCR products confirming a 200bp band, with a DNA ladder (100 bp), and samples CM-[29-30], LC-[43-45]

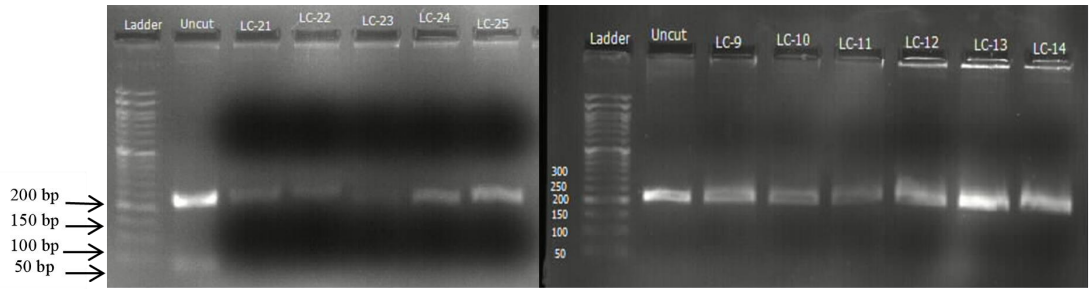

Figure 3. The analysis of f PARP-1 Val762Ala polymorphism using PCR-RFLP technique. LC-[21-22,25,9-12,14] were the Wild genotype. LC-[23-24] were the mutated Variant genotype (VT). LC-13 was a mutated Heterozygous genotype (HT).

DISCUSSION

PARP-1 a well-researched gene functions as a vital isomer within the PARP family. It was first identified by Chambon et al. in 1963. This enzyme catalyzes the synthesis of ADP-ribose polymers. [31] To prevent the accumulation of mutations which ultimately could lead to carcinogenesis it is essential to have effective repair mechanisms thereby preserving the genomic stability. [32] 90% of PARP cellular activity is due to PARP-1. It is a deoxyribose nucleic acid interacting protein capable of recognizing strand interruptions. This enzyme in combination with XRCC-1, POL β and ligase III repairs strand breaks in response to DNA lesion. It functions either as homodimers or heterodimers [33] as well as help in mitigating ionizing radiation and oxidative stress. [34] Hence an impairment or defect in the gene could lead to carcinogenesis. [35] There have been several studies conducted which have reported the gene to be associated with various tumors like breast, lung, and prostate. [36-38] The PARP-1 gene consists of several SNP's. The rs1136410 polymorphism is the best studied among them all and has been associated with an overall vulnerability to cancer. [39] This variation causes the amino acid to shift from valine to alanine in highly conserved catalytic domain (PARP signature motif), where nicotinamide adenine dinucleotide interacts with the enzyme. This change arises from a thymine to cytosine transition in exon 17 at codon 762. [40] This affects the enzymatic activity of the gene to effectively restore strand breaks causing malignant tumors to form. Studies have reported that this polymorphism reduces the activity of PARP-1 up to 30-40%. The extent of reduction depends on the number of variant alleles present, this in turn affects the BER pathway which is involved in repairing the damaged strand breaks. [41]

The present investigation was undertaken to ascertain if the rs1136410 polymorphism is linked with enhanced vulnerability to LC in rural population. Our finding suggested no significant association with LC risk and the polymorphism. The statistical analysis revealed that all of the p-values were higher than 0.05, indicating that none of the factors achieved statistical significance. In particular, the p-values for the wild-genotype (WT), heterozygous (HT), and variant (VT) genotypes were 0.084, 0.539, and 0.079, respectively. While these values were close to significance, they did not meet the threshold. With a significance of 0.718, the HT genotype had a lower odds ratio than the WT genotype, indicating a decreased probability of the result. Its wide confidence interval (0.250–2.066), however, suggested that the estimate was highly uncertain. On the other hand, the VT genotype showed a value of 7.875, which indicates that the probabilities of the outcome were much higher than those of WT. However, the large confidence interval (0.788–78.671) points to significant unpredictability and lack of precision. In support to our finding of no association, a study conducted on Koren population also states that there is no relationship with the risk of lung cancer among the three variant haplotypes at position 81, 284, and 762 in poly (ADP-ribose) polymerase gene. [42] On the contrary a study conducted on the Turkish population the rs1136410 polymorphism was found to significantly increase the likelihood of lung cancer. [43] However few studies reported the polymorphism does not significantly affect susceptibility to

lung cancer. [44] A study conducted by Kim et al. the rs1136410 was shown to have better survival outcome to the disease. [45] In broader context it has been shown that this particular polymorphism decreases the efficiency of the enzyme in response to strand interruptions and impair the recruitment of repair factors like XRCC-1 thereby causing the accumulation of mutations which could lead to carcinogenesis. [46] The Val762Ala SNP may impair the activity of PARP-1 besides the non-repair function like transcriptional regulation. A defect in the PARP-1 gene like polymorphims can alter its ability to interact with transcriptional factors and regulate gene expression.[47] PARP-1 functions in remodelling of chromatin structure, an alteration or defect could potentially modify the histones thereby impacting the regulation of gene expression. [48] Polymorphisms in PARP gene may affect key repair pathways like base excision repair (BER), single-strand break repair (SSBR), nucleotide excision repair (NER) and homologous recombination (HR). [49] To our knowledge till today there are very few Indian studies in which PARP-1 762 Val>Ala polymorphism has been reported to be associated with susceptibility to lung cancer and ours is the first to report this association from the unexplored pool of north western Karnataka region. The discrepancy between these studies and ours might be due to the small sample size which is insufficient for conducting a molecular epidemiological investigation because of which, some subgroup analyses may have poor statistical power. Secondly, both overall comparisons and several subgroup analyses showed clear heterogeneity among studies, which may have been caused by variations in cancer types and races.

Conclusion

In conclusion, the present study provides evidence that the PARP-1 Val 762 Ala polymorphism does not have any significant association with the incidence of LC in the population of northwestern Karnataka. While the odds ratio for VT suggested a strong effect, its wide confidence interval reduced its precision. While gender, family history, economic status, alcohol consumption, and tobacco use showed no significant effect. Smoking, education levels, a mixed diet, and age were significantly associated with the contributing factors. Higher education and a vegetarian diet appeared protective against the risk of LC. Both genetic predispositions and environmental factors may contribute to the disease hence findings of present study should be further validated with large sample sizes across different ethnic backgrounds and geographical regions.

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