RESEARCH ARTICLE

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# North India Cancer Risk: A Detailed Review with Focus on Jammu and Kashmir Demographics

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## Abstract

**Background:** Cancer is a global medical challenge, and research is at its peak to understand the unique mechanisms of cancer cells. The expanding field of epidemiology, including molecular and environmental studies, helps us better understand the distribution of molecular changes and environmental risk factors in the population. Aim: In the present review, we aimed to find out the different genes and environmental factors that are associated with different cancers in the Jammu and Kashmir (J&K) region of the North Indian population. **Method:** A Systematic approach of literature survey was used to curate research data based on genetic and environmental epidemiology specifying the J&K region. **Result:** Of 640 articles found initially and screening of 490 records, 97 studies were included for the final review. It was observed that numerous genes that are strongly linked to various cancer types have been discovered as a result of the rising genotyping trend, which has grown in the demography exponentially over the last few decades. The majority of these genes are related to cell cycle regulation, cell growth signaling, and apoptosis regulation. Additionally, high promoter hypermethylation of various genes which were found to be attributed to the presence of distinct dietary patterns. The most important environmental risk attributes were salt tea consumption and dried pickles. **Discussion and Conclusion:** In conclusion, the J&K population possesses many common polymorphisms in various genes with a small effect size that makes individuals more prone to different forms of cancers interacting with different environmental factors. What we can't do is, change the gene sequence or molecular changes which are the main changes for determining the susceptibility of any altered condition but what we can do is lower/ limit the exposure to the environmental factors which is a key element playing with the susceptibility's threshold. Therefore, limiting exposure to environmental factors could be a major step in lowering the risk of disease.

**Keywords:** North-Indian population- Jammu- Kashmir- Cancers

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## Introduction

Cancer, a term we're all familiar with, is often thought of as a modern disease. However, its history predates humans, with evidence of malignancies found in animals during paleontological excavations [1]. The first documented case of human cancer dates back to 3000 BC, with Hippocrates later introducing the terms "carcinos" and "carcinoma" to differentiate between tumors with and without ulcers [2]. Modern understanding of cancer is based on six biological "cancer hallmarks" [3]. Cancer, which encompasses a variety of types including carcinomas, lymphomas, leukemias, melanomas, and sarcomas, is influenced by both environmental factors such as diet, alcohol, smoking, and obesity [4], and genetic factors involving multiple inherited variants [5]. A critical distinction in cancer terminology includes the difference between a "tumor," a collection of abnormal cells, and "malignant neoplasms or cancer," which are capable of metastasizing and recurring, highlighting the disease's severity and complexity [6].

In the diverse and beautiful landscapes of Jammu & Kashmir (J&K), cancer, once considered rare, is becoming increasingly prevalent, raising significant concern among researchers. The causes of cancer in J&K differ from those in other parts of India, making this region a critical

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area for study [7]. Over the past few decades, significant progress has been made in understanding cancer genetics and environmental factors within J&K [8-13]. This review compiles the genetic and environmental cancer risk factors identified in the J&K population, providing valuable insights into disease causation, susceptibility, and prevention.

## Materials and Methods

Refer to the supplementary file for detailed methodology information (Methodology: Supplementary file).

## Results

After a critical review of literature from online databases, initially, approximately 640 articles were found. Following the screening of 490 records, 97 studies (78 genetic association studies and 19 epigenetic analyses) (Figure 1) were included in the final review (Supplementary file: Table 2 & 3). Our investigation revealed that various forms of cancer have been explored in the region of J&K, including breast cancer, leukemia, colorectal cancer, gastric cancer, thyroid cancer, lung cancer, and esophageal cancer. Multiple genetic studies have identified a range of genetic variants associated with the risk of these cancers, with more than 75 genes studied for associations with different forms of cancer. Additionally, authors from the region have examined epigenetic changes, which are closely associated with region-specific environmental factors. The extensive research conducted by various researchers has provided a wealth of knowledge regarding the genetics of cancer in this region, detailed are provided in the following paragraphs.

*Review of Literature*

Cancer is considered a complex disorder due to the involvement of many environmental factors and many genes (polygenic). Regarding the genetics of the disease, it involves the accumulation of inherited mutations, particularly single nucleotide polymorphisms (SNPs) which are considered the most common type of genetic variation, involving changes in a single DNA nucleotide, and they are frequently observed across populations. These genetic variations contribute significantly to an individual's susceptibility to various types of cancer [14, 15]. Cancer research groups in J&K have shown an intense interest in studying such genetic variants (SNPs) using advanced genotyping technologies, generating enormous data over the past decade. To utilize this data, various types of cancers and their associated SNPs in the north Indian population of J&K have been investigated and are detailed below.

*Breast Cancer*

Independent research have shed light on the prevalence of breast cancer in the area under study. Notably, Qurieshi and group conducted a study in the Kashmir division, revealing that breast cancer ranks as the second most

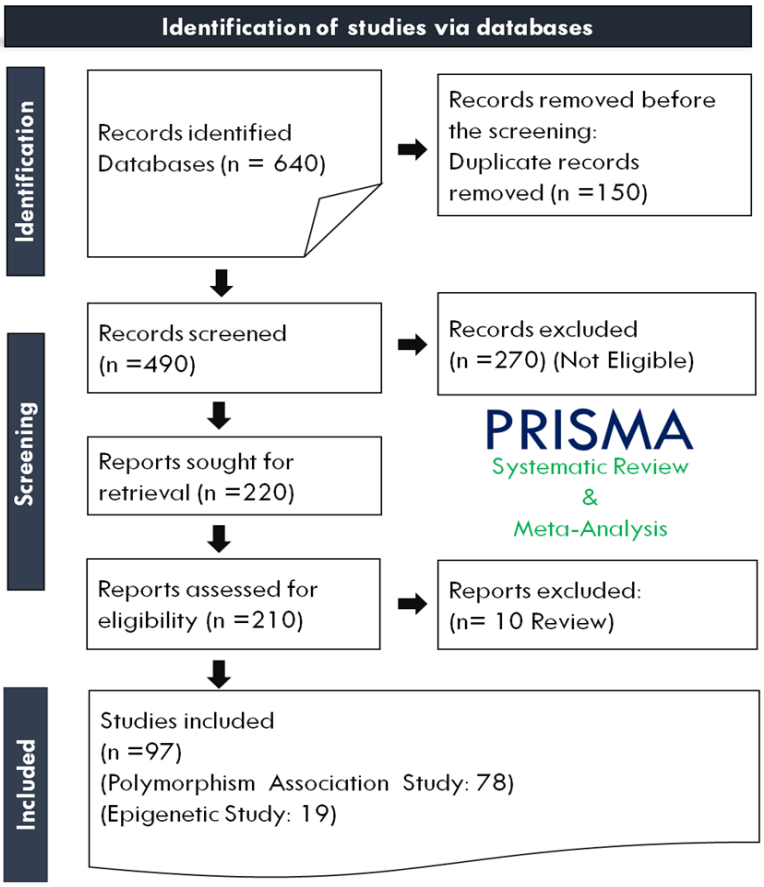


Figure 1. Schematic Representation of Literature Survey from Different Online Sources

prevalent malignancy in the Kashmir valley, accounting for an estimated frequency of 16.1% [16]. Further insights emerged from a hospital-based retrospective study led by Singh and group, which investigated the pattern of malignancies in the Jammu region [17]. The findings of this research reveal that breast cancer holds the highest estimated prevalence in Jammu, constituting a significant 35.7% of reported cases.

Apart from the vital estimates, multiple molecular epidemiological studies employing a case-control design in the J&K region, have provided valuable insights into the genetic landscape of BC. Concentrating on the Kashmir region, Mir and colleagues delved into the intricate interplay of polymorphisms in folate metabolism genes and their collective impact on BC susceptibility among Kashmiri women. Their findings were striking, indicating that individuals carrying the *MTHFR* C677T and *GCP II* 1561CT genotypes exhibited a notable 3.5 and 7.7-fold decreased risk for breast cancer, respectively, in comparison to the wild types. Additionally, subjects with the *MTRR* 66 G-allele showcased a substantial 4.5-fold decreased risk compared to the wild type (*MTRR* 66A) [18]. The *TP53* with an R72P variant emerged as a significant risk, being associated with BC in the ethnic Kashmiri population, as highlighted by the study conducted by Syeed and group [19]. Building upon this, Iqbal and colleagues, with a sample size of approximately 130/200 case/control subjects, observed a significant association between the *NME1* gene and breast cancer within the Kashmiri population [20].

When we concentrated our research on the Jammu population, the *MTHFR* C677T variant which had been demonstrated to have a strongly protective link with breast cancer (BC) in the Kashmiri community was shown to have a significantly greater risk association with breast cancer [9]. Furthermore, the genetic repertoire associated with BC in J&K extends beyond these specific genes. Noteworthy associations include Survivin (rs9904341) reported by Rasool and group in 2018 [10], *ERCC1* (rs2298881), *SLC19A1* (rs1051266), *TCF21* (rs12190287) highlighted by Bakshi et al. in 2020 [21], and *DNAH11* (rs2285947) explored by Verma and group [22], along with *OGG1* (rs1052133) documented by Nagpal and group, among others [23]. Comprehensive details regarding the genes and variants linked to them that influence the risk of BC in the J&K region of the north Indian population (Table 1).

In addition to common BC risk variants i.e., SNPs (Table 1), various rare gene variants called mutations have been identified. Ayub and group reported a novel missense variation (rs11571654) in the *BRCA2* gene, along with silent mutations at positions 846 and 1131. Heterozygous polymorphic variants at codon positions 846 and 868 transitioned to homozygous genotypes in tumor samples [24]. Akhter and group found mutations in exon 2 of the p21 gene, including a G>T transition at codon 107 and an A>C transition at codon 146, potentially affecting p21's anti-proliferative function [25]. Syeed and group investigated Caveolin-1's clinical relevance in 130 malignant breast tissue specimens from the Kashmiri population, identifying a 29.2% mutational status, including ten novel mutations [26]. Additionally, Syeed and group revealed significant mutations (40.7%) in hot spot exons and *FHIT* promoter hypermethylation (45.3%) in the *FHIT* gene, suggesting a strong association between *FHIT* gene mutations and hypermethylation, leading to complete gene inactivation in breast cancer [27].

*Leukemia*

Leukemia, prevalent in the Jammu region at 8.3% of male cancer cases over five years [17], and higher in Kashmir at 9.9% between 2005-2010 [28], is intricately linked to multiple genetic risk factors per molecular epidemiological studies. Researchers, such as Bhat and colleagues, investigated the impact of *TERT* rs2853677 on leukemia susceptibility in the Jammu region. Their study, involving 203/400 case/control subjects, revealed a significant association between rs2853677 and the risk of leukemia, with the presence of this polymorphism increasing the risk by 2.9-fold [29]. TP63 polymorphism (rs10937405) emerged as a critical diagnostic marker for the J&K population in a study conducted by Bhat and collaborators in 2021[30]. Furthermore, in the Jammu region of the North Indian population, specific genetic variants, such as rs1801133 in *MTHFR*, rs4646903 in CYP1A, and the GSTT1-null mutation, are identified as critical risk factors for disease susceptibility, whereas the *GSTM1*-null mutation does not share this association [31].

In the Kashmir population, susceptibility to leukemia is associated with variations in the GSTP1 gene, which plays a crucial role in safeguarding cellular DNA from oxidative damage. Baba and colleagues observed that the A313G polymorphism (Ile105Val) in GSTP1, particularly the GG genotype, significantly heightens the risk of leukemia [32]. Additionally, the cytochrome gene family, notably CYP1A1 and CYP2D6, recognized for their role in metabolizing and eliminating xenobiotics, emerged as significant risk markers for leukemia, particularly acute lymphoblastic leukemia, in the region [11]. Moving to folate metabolism regulation, *MTHFR*, a crucial regulator, has been studied in the context of CML. Baba and group found that the 677 CT+TT genotype significantly increases the risk of CML by 2-fold [33]. In another observation concerning the IRF-1 gene and acute myeloid leukemia in the Kashmir population, Khan and group noted that different exon regions (2, 3, and 4) were prone to deletion, with exon 3 being the most affected. These deletions played a critical role in leukemogenesis, exhibiting higher frequency in adults and being associated with low hemoglobin, high total leukocyte count, and low platelet counts [12]. This comprehensive understanding sheds light on the intricate genetic determinants contributing to leukemia vulnerability in these populations. All the information is needed to understand the genes and variations associated with them that affect the leukemia risk in the J&K region of north India (Table 2).

Enclosing the section, it is evident that many genes have been observed serving as risk contributors to leukemia in our demography of interest and their related pathways. These pathways, including the telomerase pathway *(TERT), p53* signaling pathway (*TP63*), folate metabolism pathway (*MTHFR*), interferon signaling

Table 1. Breast Cancer and Associated Genes and Their Associated Variants

| S.NO | Gene | Chr. Loc | Protein | Variant | Nucleotide Change | VT | Studied Region | Case/ Control | Res | References |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *OGG1* | 3p25.3 | 8-Oxoguanine DNA Glycosylase | rs1052133 | C>G/T | MV | Jammu | 165/200 | √ | Nagpal et al. [23] |
| 2 | *DNAH11* | 7p15.3 | Dynein Axonemal Heavy Chain 11 | rs2285947 | G>A | IV | Jammu | 135/330 | √ | Verma et al. [22] |
| 3 | *TCF21* | 6q23.2 | Transcription Factor 21 | rs12190287 | C>G | 3' UTR-V | Jammu | 150/400 | √ | Bakshi et al.[21] |
| 4 | *SLC19A1* | 21q22.3 | Solute Carrier Family 19 Member 1 | rs1051266 | T>C | MV | | | √ | |
| 5 | *ERCC1* | 19q13.32 | ERCC Excision Repair 1 | rs2298881 | C>A | IV | | | √ | |
| 6 | *DCC* | 18q21.2 | DCC netrin 1 receptor | rs2229080 | C>A | MV | | | X | |
| 7 | *PALB2* | 16p12.2 | Partner And Localizer Of BRCA2 | rs249954 | G>A | IV | | | X | |
| 8 | *ATM* | 11q22.3 | ATM Serine/Threonine Kinase | rs664677 | C>A/T | IV | | | X | |
| 9 | *FGFR2* | 10q26.13 | Fibroblast Growth Factor Receptor 2 | rs2981582 | A>G | IV | | | X | |
| 10 | *SLC4A7* | 3p24.1 | Solute Carrier Family 4 Member 7 | rs4973768 | C>T | UTRV | | | X | |
| 11 | *ANKLE1* | 19p13.11 | Ankyrin Repeat And LEM Domain Containing 1 | rs2363956 | T>G | MV | | | X | |
| 12 | *CYP19A1* | 15q21.2 | Cytochrome P450 Family 19 Subfamily A Member 1 | rs10046 | G>A | IV | | | X | |
| 13 | *TERT* | 5p15.33 | Telomerase Reverse Transcriptase | rs2736100 | C>A | 5UTRV | | | X | |
| | | | | rs2735940 | A>G | UTV | | | X | |
| 14 | *TERF1* | 8q21.11 | Telomeric Repeat Binding Factor 1 | rs2975843 | A>G | UTV | | | X | |
| 15 | *BRIP1* | 17q23.2 | BRCA1 Interacting Helicase 1 | rs4986764 | A>G | MV | | | X | |
| 16 | *REV1* | 2q11.2 | REV1 DNA Directed Polymerase | rs3792152 | A>G | IV | | | X | |
| 17 | *MTHFR* | 1p36.22 | Methylenetetrahydrofolate Reductase | rs1801133 | G>A | MV | Kashmir | 35/33 | P | Mir et al.[18] |
| 18 | *FOLH1* | 11p11.12 | Folate Hydrolase 1 | rs61886492 | C>T | MV | | | P | |
| 19 | *MTRR* | 5p15. 31 | Methyltetrahydrofolate-homocysteine methyltransferase reductase | rs1801394 | A>G | MV | | | P | |
| 20 | *TP53* | 17p13.1 | Tumor Protein P53 | rs1800372 | T>C | SV | Kashmir | 130/220 | √ | Syeed et al.[19] |
| 21 | *NME1* | 17q21.33 | NME/NM23 Nucleoside Diphosphate Kinase 1 | NG | NG | NG | Kashmir | 130/200 | √ | Iqbal et al.[20] |
| 22 | *MKK4* | 17p12 | MAP kinase kinase 4 | NG | NG | NG | | | X | |
| 23 | *MTHFR* | 1p36.22 | Methylenetetrahydrofolate Reductase | rs1801133 | C>T | MV | Jammu | 106/128 | √ | Sharma et al [9] |
| 24 | *Survivin/ BIRC5* | 17q25.3 | Baculoviral IAP Repeat Containing 5 | rs9904341 | G>A | 5' UTR V | Kashmir | 190/200 | √ | Rasool et al.[10] |
| 25 | *BRCA2* | 13q13.1 | BRCA2 DNA Repair Associated | rs1799943 | G>C | 5' UTR V | Kashmir | NG | √ | Ayub et al.[24] |
| 26 | *MDM2* | 12q15 | MDM2 Proto-Oncogene | NG | NG | NG | Kashmir | 30/20 | √ | Khan et al.[119] |
| 27 | *LRFN2* | 6p21.2-p21.1 | Leucine Rich Repeat And Fibronectin Type III Domain Containing 2 | rs2494938 | G>A | IV | Jammu | 135/330 | X | Verma et al. [22] |
| 28 | *TP63* | 3q28 | Tumor Protein P63 | rs10937405 | C>T | IV | Jammu | 150/210 | X | Verma et al. [120] |
| 29 | *MnSOD* | 6q25.3 | Superoxide Dismutase 2 | rs4880 | A>G | MV | Kashmir | 255/267 | √ | Sheikh et al. [121] |
| 30 | *GSTT1* | 22q11.23 | Glutathione S-Transferase Theta 1 | I/D | I.D | I/D | Jammu | 60/90 | X | Sharma et al. [122] |

MV, Missense Variant; IV, Intronic Variant; 3' UTR-V, Un Translated Region Variant; SV, Synonymous Variant; 5' UTR V, 5' Un Translated Region Variant; Res, Result; I/D, Insertion/Deletion; NG, Not Given

Table 2. Leukemia and Associated Genes and Their Associated Variants

| S.NO | Gene | Chr. Loc | Protein | Variant | Nucleotide Change | VT | Studied Region | Case/ Control | Res | References |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *TERT* | 5p15.33 | Telomerase Reverse Transcriptase | rs2853677 | G>A | IV | Jammu | 203/400 | √ | Bhat et al. [123] |
| 2 | *ARID5B* | 10q21.2 | AT-Rich Interaction Domain 5B | rs10740055 | C>A | IV | Jammu | 210/406 | √ | Bhat et al. [123] |
| 3 | *IKZF1* | 7p12.2 | IKAROS Family Zinc Finger 1 | rs6964823 | G>A | 3UTR | Jammu | 210/406 | √ | |
| 4 | *TP63* | 3q28 | Tumor Protein P63 | rs10937405 | C>T | IV | Jammu | 188/400 | √ | Bhat et al. [124] |
| 5 | *CYP2D6* | 22q13.2 | Cytochrome P450 Family 2 Subfamily D Member 6 | rs35742686 | | MV | Kashmir | 300/600 | √ | Shapoo et al. [125] |
| | | | | rs3892097 | G>A | SSV | Kashmir | 300/600 | √ | |
| 6 | *REV1* | 2q11.2 | REV1 DNA Directed Polymerase | rs3792152 | A>G | IV | Jammu | 166/592 | X | Bhat et al. [124] |
| 7 | *TERT* | 5p15.33 | Telomerase Reverse Transcriptase | rs2736100 | C>A | IV | | | X | |
| | | | | rs2735940 | A>G | UTV | | | X | |
| 8 | *TERF1* | 8q21.11 | Telomeric Repeat Binding Factor 1 | rs2975843 | A>G | UTV | | | X | |
| | *TERT* | 5p15.33 | Telomerase Reverse Transcriptase | rs10069690 | C>T | IV | | | √ | |
| 9 | *FGFR2* | 10q26.13 | Fibroblast Growth Factor Receptor 2 | rs2981582 | A>G | UTV | | | X | |
| 10 | *GSTP1* | 11q13.2 | Glutathione S-Transferase Pi 1 | rs1695 | A>G | MV | | | X | |
| 11 | *AKT1* | 14q32.33 | AKT Serine/Threonine Kinase 1 | rs2494752 | A>G | UTV | | | X | |
| 12 | *TERF2* | 16q22.1 | Telomeric Repeat Binding Factor 2 | rs251796 | A>G | IV | | | X | |
| 13 | *BCL2* | 18q21.33 | BCL2 Apoptosis Regulator | rs1801018 | T>C | SV | | | X | |
| 14 | *TCF21* | 6q23.2 | Transcription Factor 21 | rs12190287 | C>G | 3UTR | | | √ | |
| 15 | *TNKS* | 8p23.1 | Tankyrase | rs6990097 | T>C | 5UTR | | | √ | |
| 16 | *BRIP1* | 17q23.2 | BRCA1 Interacting Helicase 1 | rs4986764 | A>C | MV | | | √ | |
| 17 | *PSCA* | 8q24.3 | Prostate Stem Cell Antigen | rs2976392 | G>A | IV | | | √ | |
| 18 | *CYP19A1* | 15q21.2 | Cytochrome P450 Family 19 Subfamily A Member 1 | rs10046 | G>A | 3'-UTRV | | | X | |
| 19 | *ERCC5* | 13q33.1 | ERCC Excision Repair 5, Endonuclease | rs751402 | A>G | 5UTR-V | | | X | |
| 20 | *ERCC1* | 19q13.32 | ERCC Excision Repair 1, Endonuclease Non-Catalytic Subunit | rs229881 | A>G/T | IV | | | X | |
| 21 | *MTHFR* | 1p36.22 | Methylenetetrahydrofolate Reductase | rs1801133 | C>T | MV | Jammu | 111/161 | √ | Devi et al. [31] |
| 22 | *CYP1A1* | 15q24.1 | Cytochrome P450 Family 1 Subfamily A Member 1 | rs4646903 | A>G/T | DTV | Jammu | 111/161 | √ | |
| 23 | *GSTT1* | 22q11.23 | Glutathione S-Transferase Theta 1 | I/D | I/D | I/D | Jammu | 111/161 | √ | |
| 24 | *GSTM1* | 1p13.3 | Glutathione S-Transferase Mu 1 | I/D | I/D | I/D | Jammu | 111/161 | X | |
| 25 | *HOXA7* | 7p15.2 | Homeobox A7 | rs2301721 | C>T | MV | Jammu | 90/90 | √ | Bhat et al. [126] |

SSV, Splice Site variant; DTV, Downstream Transcript Variants; VT, Variant Type

pathway (IRF-1), glutathione metabolism pathway (*GSTP1*), and cytochrome P450 metabolism pathway (*CYP1A1* and *CYP2D6*), are important for cancer-related pathways.

*Lung Cancer*

Multiple researchers have found many different gene variations in the population under study. For example, Shaffi and his team found two specific changes in the *CYP1A1* gene, known as m1 (T6235C) and $m^2$ (A4889G). These changes were linked to a higher risk of lung cancer in people from Kashmir [34]. Bhat and colleagues investigated *TERT* (rs2853677) and *LRFN2* (rs2494938) in the Jammu population. Their findings revealed that the rs2494938 variation in the *LRFN2* gene is associated with an increased risk of non-small cell lung cancer in North Indians [35] . Another important gene is the *REV3L* gene which helps to make a DNA part called polymerase zeta. Changes in this gene, like rs1002481, rs462779, and rs465646, can make lung cancer more likely in people from Jammu, increasing the risk by 3.5, 3.7, and 2.2 times respectively [13]. The genetic narrative continues with Bhat and colleagues, revealing a collection of genetic factors associated with lung cancer in the Jammu population, including *TCF21* (rs12190287), *ERCC1* (rs11615), *ERCC5* (rs751402), *ARNTL* (rs4757151), and *BRIP1* (rs4986764) [36]. Table 3 provides detailed information on the genes and variations associated with them that affect the risk of lung cancer in the J&K region of the north Indian population.

*Ovarian Cancer*

In 2019, Verma and group, while investigating the disease-susceptible variants rs1052133 of hOGG1 (human 8-oxoguanine glycosylase 1) and rs25487 of *XRCC1* (X-ray repair cross-complementing 1) with OC in the population of Jammu, India, reported that the G allele of rs1052133 protects whereas the variant rs25487 was not associated with OC in the studied population [37]. In another study, *PIK3CA* (rs2699887), *GSTP1* (rs1695), *ERCC1* (rs2298881), and *DNAH11* (rs2285947) were found in the patients of OC belonging to the population of the Jammu region. It was found that *PIK3CA* (rs2699887), *GSTP1* (rs1695), *ERCC1* (rs2298881), and *DNAH11* (rs2285947) increase the risk of ovarian cancer by 1.72, 1.87, 0.66, and 1.7 times, respectively [38]. Supplementary file Table 4 provides complete information on the genes and variations associated with them that affect the risk of ovarian cancer in the J&K region of the northern Indian population.

*Colon rectal cancer*

Population geneticists have extensively investigated the genetic basis of CRC within the Kashmiri population. Through a series of comprehensive studies conducted by Sameer and colleagues, several genes, including *TP53* (Pro47Ser and *TP53* Arg72Pro), *CYP2E1* (RsaI), *TIMP2, NQO1* (Pro187Ser), *GSTP1,* and, have been identified as contributing factors to an elevated risk of CRC [39-42]. Furthermore, research into the 8-Oxoguanine DNA glycosylase (OGG1) gene revealed that while the Ser326Cys variation may not directly increase overall CRC susceptibility in Kashmiris, it may influence colon cancer risk through interactions with dietary factors [42]. Furthermore, investigations into the Vitamin D receptor gene (VDR) have revealed associations between its polymorphisms (Fok-I, Bsm-I, and Apa-I) and CRC risk, particularly the VDR-Fok-I polymorphism [43, 44]. Similarly, studies on DNA repair-associated genes such as *XRCC1*, *XRCC3*, LT-α+252A/G, and RAD51 have demonstrated significant CRC susceptibility linked to specific polymorphisms (Arg399Gln, Arg194Trp, Thr241Met in *XRCC1*, and G135C in RAD51) [45-51]. MMPs are proteolytic enzymes that play a pivotal role in the transformation and progression of tumors at all stages, especially during invasion and metastasis. Different MMPs such as MMP2-1306C/T, *MMP7*-181A/G, and MMP9-1562C/T SNPs were explored to observe the association by Banday and group and suggested that all polymorphism play a role as one of the key modulators of the risk of developing colorectal cancer in Kashmiri population [52]. Detailed information on the genes and variations associated with them that affect the risk of CRC in the J&K region of the northern Indian population is provided in Supplementary file Table 5.

*Esophageal Cancer*

The Kashmir population has been explored extensively in contrast to the Jammu population concerning esophageal cancer. Numerous research groups in Kashmir have explored diverse genetic risk attributes which exposure can increase the risk of EC. Malik and group have explored the GSTP (rs1695), and CYP2 (rs2031920) in the population of Kashmir using a case/control study design and have found that both variant significantly increases the risk of EC [53]. NAT2 [54], CASP8 (rs3834129) [55], DCC (rs714) [56], *GSTM1* (null genotype) [57], found out the significant association of these genetic variants with the EC and significantly increases the susceptibility of the diseases in the individuals of Kashmiri population. NQO1 and NQO2 with the two-transition polymorphism such as 609 C>T and -3423 G>A respectively were found to significantly increase the risk of diseases identified by Malik and group.

Qasim and his colleagues identify the association of two downstream variants formed due to transitions namely +405C/G & +936C/T in the VEGF gene in the population of Kashmir population. Their result shows a significant association of these downstream variants with the susceptibility of EC in the Kashmir population [58]. In 2016 and 2020 Shah and their group explore the *CYPA1*[59] and *LRFN2* (rs2494938) [60], *TCF21* (rs12190287), *CYP19A1* (rs10046) [61] to find out the association with the risk of EC and found out theses variation significantly increases the susceptibility of EC in the Kashmiri population. Supplementary file Table 6 provides insights into genes and variations affecting EC risk in the J&K region of the north Indian population.

*Gastric Cancer*

Malik and group have explored GC concerning genetic variants that increase the risk of diseases. *P16*

Table 3. Lung Cancer and Associated Genes and Their Associated Variants

| S.No | Gene | Chr | Protein | Variant | Nucleotide Change | Variant type | Studied Region | Case/ Control | Res | References |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *CYP1A1* | 15q24.1 | Cytochrome P450 Family 1 Subfamily A Member 1 | rs4646903 | T>C | DTV | Kashmir | 109/163 | √ | Shaffi et al. [34] |
| | | | | rs1048943 | A>G | MV | | | √ | |
| 2 | *TERT* | 5p15.33 | Telomerase Reverse Transcriptase | rs2853677 | G>A | IV | Kashmir | 178/400 | √ | Bhat et al. [127] |
| 3 | *LRFN2* | 6p21.2-p21.1 | Leucine Rich Repeat And Fibronectin Type III Domain Containing 2 | rs2494938 | G>A | IV | Kashmir | 189/430 | √ | Bhat et al. [126] |
| 4 | *REV3L* | 6q21 | REV3 Like, DNA Directed Polymerase Zeta Catalytic Subunit | rs1002481 | T>A | IV | Jammu | 200/300 | √ | Jamwal et al. [13] |
| | | | | rs462779 | G>A | MV | Jammu | 200/300 | √ | |
| | | | | rs465646 | G>A | 3' UTR V | Jammu | 200/300 | √ | |
| | | | | rs11153292 | G>A | IV | Jammu | 200/300 | X | |
| 5 | *TCF21* | 6q23.2 | Transcription Factor 21 | rs12190287 | C>G/T | 3' UTR V | Jammu | 162/592 | √ | Bhat et al. [124] |
| 6 | *ERCC1* | 19q13.32 | ERCC Excision Repair 1 | rs11615 | A>G | SV | | | √ | |
| 7 | *ERCC5* | 13q33.1 | ERCC Excision Repair 5 | rs751402 | A>G | 5' UTR V | | | √ | |
| 8 | *ARNTL/ BMAL1* | 11p15.3 | Basic Helix-Loop-Helix ARNT Like 1 | rs4757151 | A>G | IV | | | √ | |
| 9 | *BRIP1* | 17q23.2 | BRCA1 Interacting Helicase 1 | rs4986764 | A>C | MV | | | √ | |
| 10 | *TP63* | 3q28 | Tumor Protein P63 | rs10937405 | T>C | IV | Jammu | 190/400 | √ | Bhat et al. [29] |
| 11 | *TERT* | 5p15.33 | Telomerase Reverse Transcriptase | rs10069690 | C/T | IV | Jammu | 162/561 | √ | Bhat et al. [128] |
| 12 | | | | rs2242652 | A/G | IV | | | √ | |
| | *POT1* | 7q31.33 | Protection Of Telomeres 1 | rs10228682 | C/T | IV | | | √ | |
| 13 | *TERF2* | 16q22.1 | Telomeric Repeat Binding Factor 2 | rs251796 | A/G | IV | | | X | |
| | | | | rs2975843 | A/G | UTV | | | X | |

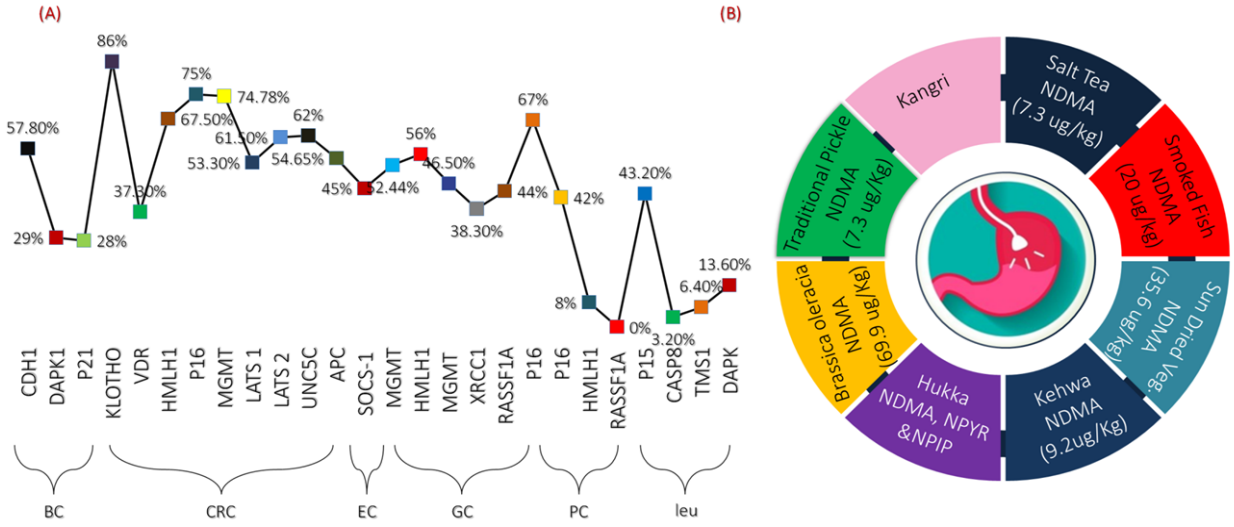


Figure 2. (A): Frequency of promoter methylation of different genes associated with different cancers such as CRC (Colon Rectal Cancer), EC (Esophageal cancer), GC (Gastric Cancer), Leu (Leukemia), PC (Pancreatic Cancer), BC (Breast Cancer) in Jammu & Kashmir population. (B): Environmental factors associated with Gastric cancer in Kashmir demography.

gene, *GSTM1* null variant, *CYP2E1* (rs2031920), *NAT2,* and *GSTM3* (rs1799735) have been found significantly associated with the diseases in the population of Kashmir. *GSTM3* (rs1799735) significantly increases the risk by about 8.98 times in the individuals of the Kashmir population [54]. In 2011, Malik and colleagues further explored *MMP7* and its variant (181A>G) which is formed by the transition of Adenine to Guanine (181A>G) and NQO1 (609 C>T) to find out the association with gastric cancer. They found that the *MMP7* gene increases the risk by 2.13 times along with the *NAO1* gene of gastric cancer in the population of Kashmir [62, 63]. In 2013, Malik and group again found a significant association between the *DCC* gene and its variant (rs714) [56]. Another research group namely, Bashir and group in 2015 provided nonsignificant evidence of rs861539 of *XRCC3* using 80/70 case/ control with the association with Gastric cancer [64]. BsmI variant of the VDR gene was found to significantly increase the risk of stomach cancer [65]. Polymorphic variants of *XRCC1* Arg399Gln and XPD Lys751Gln are not associated with the risk of gastric cancer in the Kashmiri population [49]. Detailed information on the genes and polymorphisms associated with them that affect the J&K region of the north Indian population's risk of GC (Supplementary file Table 7).

Moreover, in our comprehensive analysis of various cancer types, we have observed a singular genetic association with thyroid cancer risk, represented by the RET gene. This significant discovery, outlined in Supplementary file Table 8, underscores the importance of understanding the genetic underpinnings of thyroid cancer within our study.

*Epigenetics and Risk Of Cancer*

Epigenetics, which includes histone modifications and CpG island hypermethylation [66], plays crucial

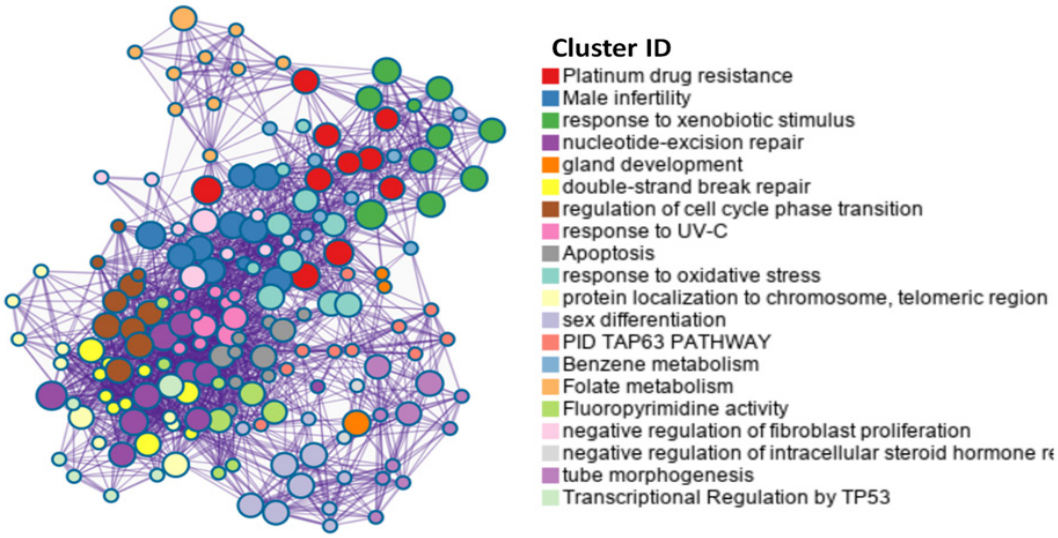


Figure 3. Network of Enriched Terms: colored by cluster ID, where nodes that share the same cluster ID are typically close to each other (Metascape).

roles in cancer progression, particularly in the diverse cancer landscape of J&K, notably Kashmir, revealing unique epigenetic alterations across various genes and cancer types. The landscape of BC risk is multifaceted, involving a multitude of genetic variants intricately linked to diverse cellular regulation pathways (Table 1). Beyond genetic variations, epigenetic changes, such as CDH1 hypermethylation, have emerged as crucial players in BC development. This epigenetic alteration correlates with diminished E-cadherin protein levels, underscoring its pivotal role in tumorigenesis. Additionally, CDH1 methylation patterns exhibit correlations with tumor characteristics, hinting at its potential as a diagnostic and prognostic biomarker for BC [67]. Moreover, DAPK1 promoter hypermethylation has shown significant associations with the loss of DAPK1 protein expression, aligning with estrogen receptor negativity, triple-negative breast cancer, and advanced tumor stages [68, 69]. Another study delving into epigenetic alterations in the p21 gene revealed substantial promoter hypermethylation in a considerable percentage of patients, suggesting complete gene inactivation in breast cancer. These findings underscore the intricate interplay of both genetic and epigenetic modifications in silencing the p21 gene in this population [25].

In colorectal cancer (CRC), muttiple factors are involved [70] and one such example is epigenetic modifications of genes that are involved in various pathways, including tumor suppression and DNA mismatch repair, have been observed. Significant research has been reported from the region of Kashmir. KLOTHO, a unique candidate gene associated mostly with senescence suppression, has been shown to contribute to cancer through inadequate function. In the Kashmir valley, KLOTHO promoter hypermethylation (86%) has recently been related to colorectal cancer [71]. To investigate the impact of promoter methylation in the VDR gene, a transcription factor with several biological roles, in connection to its expression and clinicopathological characteristics in CRC patients. Afshan and colleagues discovered that the hypermethylated state of the VDR promoter (37.33%) was significantly inversely related to its expression [72]. *P16* and *MGMT* promoter hypermethylation and loss of protein expression in CRC [8, 73, 74]. Dar and colleagues also studied the methylation pattern of the *HMLH1*gene in colon rectal cancer and found a higher frequency of methylation in cases (67.5%) compared to controls (15%). Additionally, they also found promoter methylation was found to be certainly higher in Stage III/IV (85.71%) compared to Stage I/ II (57.69%) but they did not find it significant [75]. In 52.3% and 61.5%, respectively, of the CRC patients, the promoter regions of the LATS 1&LATS 2 genes which play a critical role in tumor suppression were found to be hyper-methylated, which substantially corresponds with Lymph node metastasis. This increased frequency was observed by Maqbool and colleagues using methylation-specific PCR (MS-PCR) [76]. Epigenetic alterations in the netrin-1 receptors are related to the malignant potential of CRC. Promoter hypermethylation of the UNC5C gene (one of the netrin-1 receptors) has been found significantly found to be associated with colorectal cancer cases where the frequency was 62% (31

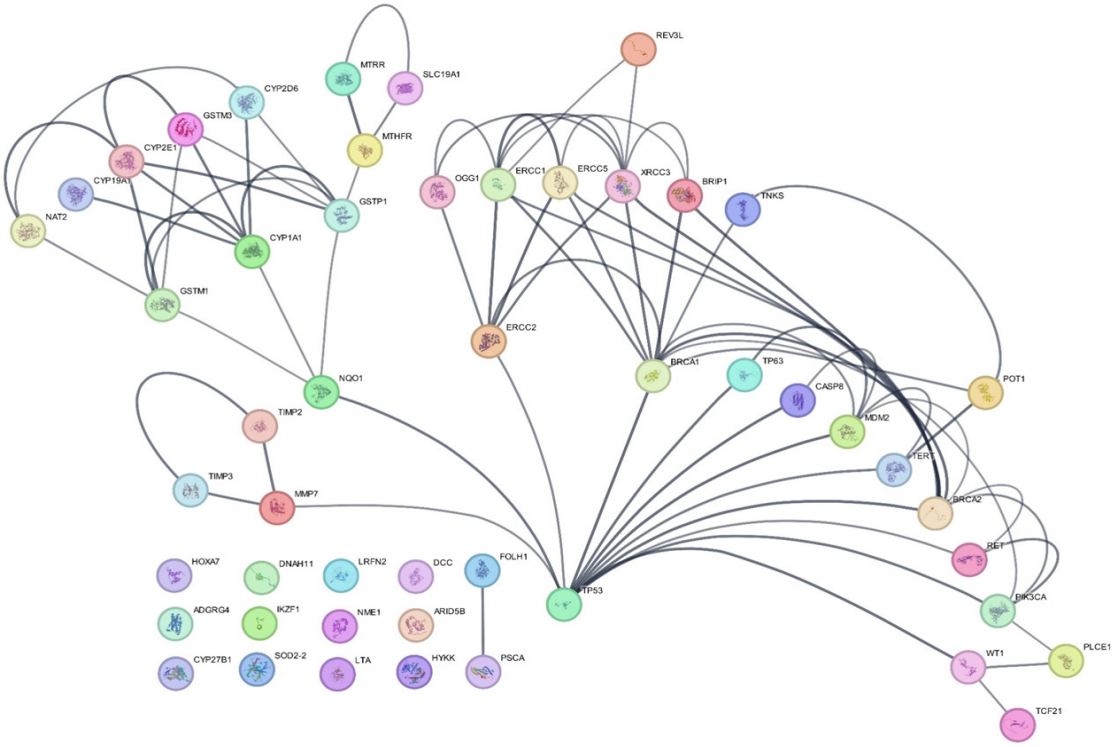


Figure 4. Protein-Protein Interaction Network (PPI) Analysis of Different Cancer-Associated Genes was Done by String Database (STRING: functional protein association networks (string-db.org) and Cytoscape V3.9.1 was utilized for network visualization and analysis (Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization). The network comprises 50 nodes and 78 edges, with an average of 4.27 neighbors per node. It has a diameter of 7 and a density of 0.122

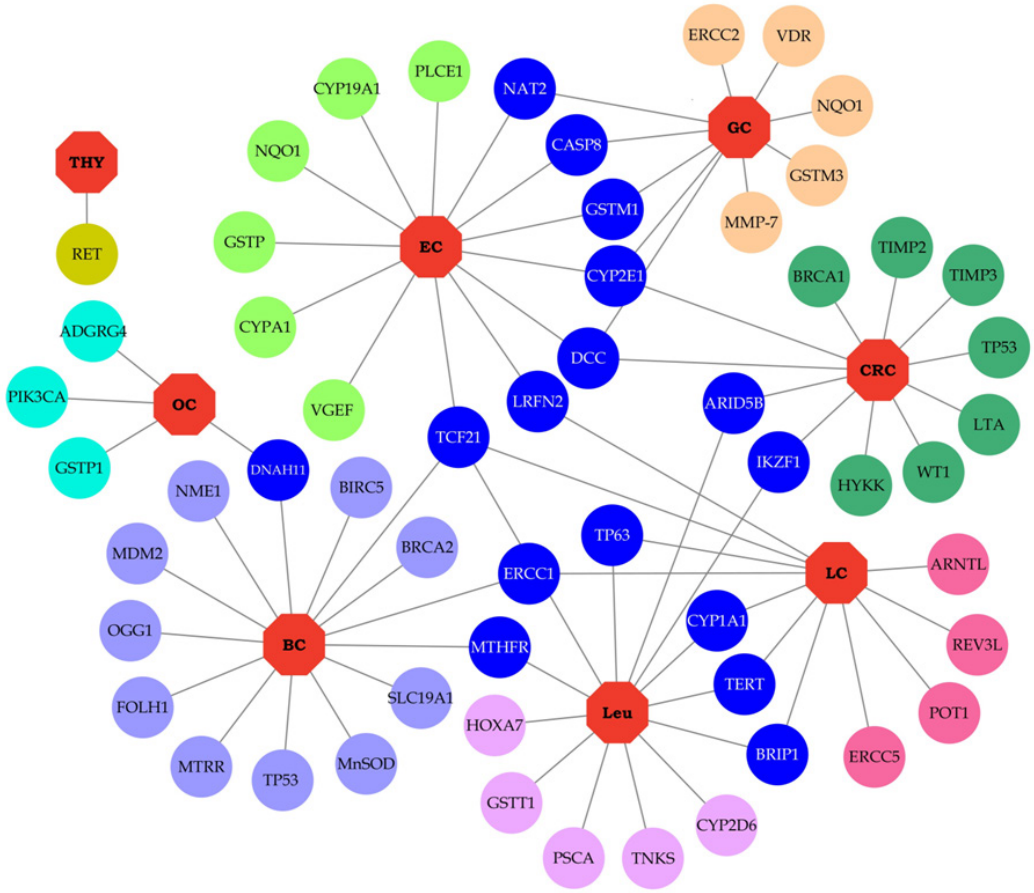


Figure 5. Diseases and Gene Interaction among North Indian of Jammu and Kashmir Population Created by Cytoscape V3.9.1 (Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization). (Legends: Red node= Disease Node, Blue=Shared genes by different cancers)

of 50) and 38% (19 of 50) patients were unmethylated ($p<0.0001$). Such a higher was also significantly observed in stage III/IV as compared to stage I/II with a frequency of 75.8% and 42.8% respectively($p>0.05$) [77]. Promoter hypermethylation of APC was observed in 54.65 percent (47 of 86) of CRC cases [41].Promoter hypermethylation of CpG islands of the p16 gene in male/female colorectal cancer patients of Kashmiri origin [74].

Hussain and group observed that 45% of esophageal tumor tissues contained aberrant promoter methylation of the *SOCS-1* gene, which is a key negative regulator of the JAK/STAT system. *SOCS-1* was also shown to be substantially related to advanced stages of esophageal carcinoma [78]. *MGMT* (O6-methylguanine-DNA methyltransferase) is a critical DNA repair enzyme that removes methyl groups as well as larger adducts at the O6 position of guanine. Loss of function due to promoter hypermethylation resulting in G: C to A>T transitions. Yousuf and group found such hypermethylation in 52.44 % of gastric tumor samples which resulted in a significant loss of protein function [79]. Bhat and group tried to test the hypothesis that promoter hypermethylation of *HMLH1*, *RASSF1A*, and *MGMT* genes could influence susceptibility to GC in the Kashmir population. Therefore, after using methylation-specific polymerase chain reaction and Western blotting technique, they found a significant increase in promoter hypermethylation of *HMLH1* (56%), *MGMT* gene (46.5% cases), and RASSF1A gene (44% cases) which were predominated in the male population causes a significant loss of expression [80, 81]. Salam and group have found that the increased loss of p16 expression (67%) in ESCC cases was majorly due to promoter methylation. Such increased methylation significantly correlated with the increasing severity of histological grades of cancer ($P = 0.0001$) [82]. Rah and colleagues examined the CpG islands of the cyclin-dependent kinase inhibitor 2A (p16; CDKN2A), MutL homolog 1 (*HMLH1*), and RASSF1A genes (Ras association domain-containing protein 1) after analyzing 50 pancreatic cancer cases observed a significant CpG methylation in the promoter regions of the *P16* and *HMLH1* genes [83]. Nissar and colleagues indicate that *XRCC1* undergoes aberrant promoter hypermethylation (38.3%) with subsequent loss of protein expression in gastric cancer [84].

In an attempt to better understand the prognostic value of *P15* gene promoter hypermethylation and its expression in APL patients in Kashmir, Baba and colleagues discovered that 43.2% of cases had methylated *P15* genes, which substantially corresponds with a lower survival rate for APL patients (acute promyelocytic leukemia). Hypermethylation of the 5′CpG islands of the *CASP8, TMS1*, and *DAPK* gene promoters was found in 3.2, 6.4, and 13.6% of 125 childhood ALL (Acute Lymphoblastic Leukemia) samples from the north Indian population, respectively which significantly correlates with the mRNA downregulation [85].

Enclosing the section, epigenetic alterations, particularly promoter hypermethylation, play a significant role in various cancers prevalent in the Kashmiri population. Studies have revealed hypermethylation of genes like *CDH1, DAPK1, KLOTHO, VDR, P16, MGMT, HMLH1, LATS1, LATS2, UNC5C, APC, SOCS-1,* and *XRCC1* across different cancer types (Supplementary file: Table 3) with different frequency (Figure 2A). These epigenetic changes correlate with loss of gene expression and tumor progression. Understanding the interplay between genetic and environmental factors contributing to these epigenetic modifications is crucial for cancer prevention and treatment in this region. Such hypermethylation might be due to dietary patterns (See section: Environmental factors).

*Environmental factors*

Over the past few decades, researchers have delved into a range of environmental factors, uncovering various risk elements. Common risk factors like tobacco, alcohol, red meat, and smoking are universal and not tied to any specific group of people. However, when we explored the literature, we discovered unique environmental risk factors that are quite specific to the Kashmir region. These distinctive factors include sun-dried veggies, the famous "namkeen chai" or salt tea, smoked fish (sun-dried fish), kangri (a traditional firepot), and traditional pickles (Figure 2B). The specificity of these factors stems from the diverse lifestyle in Kashmir, influenced by the region's seasonal and environmental variations, setting it apart from other parts of India. Kashmir has a pleasant environment, but winters bring a significant drop in temperature [86]. To cope with the harsh weather, the people of Kashmir have adapted by using kangri, relying on sun-dried vegetables as winter food, sipping hot salt tea, and adopting other practices (Figure 2B). The unique adaptations of the Kashmiri population to survive the cold also pose risks for various cancers, notably the digestive tract cancer such as gastric cancer, earning them the designation of endemic risk factors [74]. The things that make life in Kashmir special are unfortunately turning out to be risky.

Research found that sun-dried veggies can get infected by fungi and harmful aflatoxins due to too much UV radiation [87]. Also, when we try to keep food for a long time, it ends up containing dangerous stuff called N-Nitroso compounds, which can cause cancer. Many studies have shown how these cancer-causing compounds can harm our bodies [88]. The salt tea that Kashmiri people love to sip on isn't as simple as it seems. It packs a punch of carcinogenic compounds like methylamine, diethylamine, pyrrolidine, and methylbenzylamine [89] and is responsible for increasing the risk of esophageal cancer [90]. Methylamine is responsible for causing irritation to the mucosal membrane and showing its toxic side to the pancreas, hinting at the early signs of gastric cancer [91]. Diethylamine, when mixed with nitrites and other amines in the stomach's acidic environment, cooks up a potent troublemaker called Nitrosamine a real carcinogenic threat [92]. Pyrrolidine joins forces with sodium to create N-nitrosopyrrolidine, another potent carcinogenic compound that can wreak havoc on the liver and kidneys, paving the way for multiple tumors. Lastly, methylbenzylamine, a potent carcinogenic compound, fuels the growth of cells, ultimately leading to the formation of esophageal tumors.

Interestingly, the statistical association between salt tea and hypermethylation has been established by different research groups in the Kashmir population. Analysis of the patient's dietary habits revealed a strong association between promoter methylation and high consumption of hot salted tea [82]. This was later explored by Mir and colleagues who observed the close association between the aberrant methylation of *P16*, E-cadherin, and *HMLH1* promoters and the intake of local hot salted tea and sun-dried foods in the Kashmiri population [93]. In addition, *MGMT* hypermethylation and loss of protein expression were found to be significantly associated with high salt tea consumption which may play an important role in the development of gastric cancer in the Kashmiri population [79]. Subjects who drank >1250 ml of salt tea daily and harbored a mutant genotype of *CYP1A2*1F* were found to be more susceptible to ESCC. Such gene-environmental interaction modified the risk substantially [59]. Beautifully conceptualization of risks has been demonstrated by Khaliq and group as they added that more awareness about risk factors is needed to provide a clear picture of the role of risk factors in the development and treatment of CRC [94].

To this end, dependence on such factors contributes to the high risk of different cancers but majorly alimentary canal cancer including esophageal, stomach, and colon cancer. It has been well established that if the risk attributes could be avoided there is a decreased and increased likelihood of developing diseases and healthy life respectively.

## Discussion

In cancer, there are six distinct hallmarks that result from the disruption of specific genes responsible for regulating the cell cycle, apoptosis, DNA repair, and the metabolism of carcinogens. Various genetic alterations, including SNPs, deletions, and translocations, can lead to this dysregulation. The role of epigenetics in cancer development is also quite significant [3, 95] which encompasses histone methylation, acetylation, CpG island methylation, RNA interference, and more. Beyond genetics, environmental and lifestyle factors significantly influence cancer risk. Understanding how multiple susceptibility alleles interact with these factors is crucial in molecular and environmental epidemiology.

Upon reviewing the literature on cancer in the J&K population, we found numerous genes with SNPs significantly increasing cancer risk. Additionally, hypermethylation of CpG islands in gene promoter regions was noted as a crucial event in the development of various cancer types, leading to the aberrant silencing of tumor suppressor genes such as those associated with breast, pancreatic, gastric, colon, and leukemia. We analyzed associated genes for Pathway and Process Enrichment Analysis, identifying various clusters. These

clusters encompassed a wide range of pathways, including platinum drug resistance, response to xenobiotic stimuli, nucleotide excision repair mechanisms, and several other pathways significant for cancer-related hallmark features (Figure 3) (Supplementary file: Table 1). Furthermore, we used to String database (STRING: functional protein association networks (string-db.org) to create protein-protein interaction (PPI) for associated genes with different cancers after utilizing a specific setting (high confidence: 0.70). The interactions were then visualized and analyzed using Cytoscape V3.9.1 (Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization) (Figure 4). The main motivation for the creation of such interesting PPI was to find out the complexity of interaction between the different tumor proteins and thus establish high-risk genes for different cancers in the respective demography. The complexity seems to be very complex with 50 genes/ nodes, and 78 edges, and after utilizing the radial layout for the presentation of the PPI network, it was observed that *TP53* which is known as the guardian of the genome with the highest number of edges and are thus placed in the center of PPI network (Figure 4). Concerning the diseases and gene interaction, different cancers with their associated gene were observed where several genes were found to be shared by different cancers (Figure 5).

The present analysis found that several genes and their variants are associated with the risk of different cancers in the demography under study. In comparing our observed associations related to BC with studies conducted on other states of the Indian population and other populations, several noteworthy disparities emerge. For instance, regarding the *MTHFR* C677T polymorphism, Waseem and group demonstrated a significant association [96], whereas contrary findings were also reported [97-99]. Similarly, for the *TP53 R72P* variant, there is an inline [100] and contradictory result [101]. Moreover, variations in associations were noted for other genetic variants such as Survivin rs9904341 [102], *ERCC1* rs2298881 [103], *TCF21* rs12190287 [104], and *hOGG1* rs1052133 [105], underscoring the complexity and potential population-specific nature of genetic associations.

Studies such as the one conducted by Yan and colleagues have supported our association, particularly regarding *MTHFR* C677T and the risk of leukemia [106]. Similarly, research by Al-Adl and group has reinforced our hypothesis across different genetic variants, specifically *CYP1A1* rs4646903 [107]. Furthermore, investigations by Chen and group and Zhao and group have provided complementary evidence through their exploration of the *GSTT1* null mutation and *GSTM1* null mutation, respectively [108, 109]. Conversely, studies like those conducted by Ibrahim and colleagues in 2012 have presented contrasting results, particularly concerning the *GSTP1* A313G gene variant [110]. A similar trend was observed for ovarian cancer such as hOGG1 (rs1052133) [111], *XRCC1* (rs25487) [112] in contrast to *ERCC1* (rs2298881) [113]. In the investigation of CRC susceptibility within the Kashmiri population, various genes and their variants have been extensively studied, with different studies supporting the involvement of *TP53* Pro47Ser [114], *CYP2E1* [115], NQO1 variant Pro187Ser [116], VDR variants Fok-I, Bsm-I, and Apa-I [117], and *XRCC1* [118].

As we get closer to the end of this study, we have noticed that a significant amount of research has been conducted on the Kashmiri population. More than 55 studies originated from the Kashmir region, while approximately 35 came from the Jammu region. The increased focus on research might be linked to the higher occurrence of cancer cases in the valley, or perhaps it's a result of the growing interest in cancer epidemiology. Regardless of the driving force, one undeniable fact emerges cancer stands as a prevalent challenge in the population of Kashmir, especially when compared to the neighboring Jammu region. This observation is not rooted in detailed epidemiological studies but rather in the sheer number of cancer-focused studies emerging from the valley. Now, the important question for any curious researcher is: what spurred such an extensive exploration into the frequency of risk alleles in the Kashmiri population, covering various types of cancer? Is it the burgeoning interest of geneticists eager to unravel the gene and allele distribution in this unique community, or is it simply a matter of time unfolding? However, amid the ongoing research, crucial aspects remain unexplored, such as determining whether cancer mutations are spontaneous or inherited. Surprisingly, family-based study designs seeking out rare mutations and subsequent population scans for these variants are noticeably absent.

*Strengths and limitations & future perspective*

The study's strength lies in its comprehensive approach to gathering relevant literature on cancer research in Jammu and Kashmir. Conducting a structured survey and systematically reviewing articles from reputable electronic databases ensures a thorough examination. Specific keywords tailored to the region and cancer types enhance relevance. Focusing on primary research articles in English and applying linguistic filters demonstrate a commitment to data quality. Exclusion criteria, such as secondary research and non-English publications, enhance rigor.

Apart from the strengths identified in the present review, a notable limitation we observed is the absence of a cancer registry in Jammu and Kashmir. This absence underscores the critical necessity of establishing one. A comprehensive registry would bridge information gaps, facilitating targeted interventions like early detection programs and tailored treatment plans. In looking ahead, the establishment of such a registry is imperative. It would empower healthcare professionals and policymakers to devise effective prevention and control strategies by enhancing their understanding of cancer epidemiology. The elevated cancer prevalence in Kashmir highlights the urgency for research into region-specific determinants, which would, in turn, facilitate targeted interventions and optimize resource allocation.

In conclusion, Cancer research has uncovered numerous gene variations and environmental factors, revealing that cancer is complex, especially in North India. These risk factors hinder treatment and worsen patient

outcomes. While we can't change our genetic makeup, which determines susceptibility, we can reduce exposure to environmental factors, which are crucial for altering the susceptibility thresholds. Therefore, raising awareness about risk factors is essential for understanding cancer development and improving treatment.

## Author Contribution Statement

A.S. & P.K. conceptualized and contributed to the study design, S.B, S.S, M.B., S.B (5th)., I.B. & A.S. P.K., downloaded the literature, and A.S. drafted the manuscript and edited the pictures and table. R.K.P & P.K. (8th), edited the manuscript and P.K. finalized the manuscript.

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*Conflict of Interest Statement*

The authors declare that they have no conflict of interest.

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