Methodology

A structured survey of research articles and review of the literature was done in the electronic databases of Google Scholar, PubMed, Springer, Elsevier, and Google Scholar from January 1995 until April 2024 using the keywords “cancer in Jammu and Kashmir”, “genotyping of cancer in Jammu”, “genotyping of cancer in Kashmir”, “association study of cancer in Jammu and Kashmir”, Breast cancer in J&K population”, “gene polymorphism *OR* gene variant and risk of cancer, gene association with cancer”, “environmental factors and cancer risk in J&K”, “Epigenetics and cancer association in J&K population” etc. The review focused exclusively on primary research articles published in English, utilizing linguistic filters for publication selection. Secondary research, incomplete data, and non-English publications were excluded to ensure data integrity.

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). In addition, Network of enriched terms: colored by cluster ID, where nodes that share the same cluster ID are typically close to each other were creted using Metascape.

Table 1: Top 20 clusters with their representative enriched terms (one per cluster). "Count" is the number of genes in the user-provided lists with membership in the given ontology term. "%" is the percentage of all of the user-provided genes that are found in the given ontology term (only input genes with at least one ontology term annotation are included in the calculation). "Log10(P)" is the p-value in log base 10. "Log10 (q)" is the multi-test adjusted p-value in log base 10.

Category	Description	Count	%	Log10(P)	Log10(q)
hsa01524	KEGG Pathway - Platinum drug resistance	12	22.64	-20.44	-16.09
WP4673	WikiPathways - Male infertility	12	22.64	-16.69	-12.64
GO:0009410	GO Biological Processes - response to xenobiotic stimulus	15	28.30	-15.27	-11.40
GO:0006289	GO Biological Processes - nucleotide-excision repair	7	13.21	-11.14	-7.70
GO:0048732	GO Biological Processes - gland development	10	18.87	-8.51	-5.64
GO:0006302	GO Biological Processes - double-strand break repair	8	15.09	-8.39	-5.55
GO:1901987	GO Biological Processes - regulation of cell cycle phase transition	10	18.87	-8.24	-5.44
GO:0010225	GO Biological Processes - response to UV-C	4	7.55	-8.23	-5.44
WP254	WikiPathways - Apoptosis	6	11.32	-7.98	-5.22
GO:0006979	GO Biological Processes - response to oxidative stress	9	16.98	-7.86	-5.11
GO:0070198	GO Biological Processes - protein localization to chromosome, telomeric region	4	7.55	-7.71	-4.98
GO:0007548	GO Biological Processes - sex differentiation	8	15.09	-7.51	-4.82
M256	Canonical Pathways - PID TAP63 PATHWAY	5	9.43	-7.40	-4.73
WP3891	WikiPathways - Benzene metabolism	3	5.66	-7.00	-4.42
WP176	WikiPathways - Folate metabolism	5	9.43	-6.86	-4.32
WP1601	WikiPathways - Fluoropyrimidine activity	4	7.55	-6.43	-4.00
GO:0048147	GO Biological Processes - negative regulation of fibroblast proliferation	4	7.55	-6.38	-3.97
GO:0033144	GO Biological Processes - negative regulation of intracellular steroid hormone receptor signaling pathway	4	7.55	-6.28	-3.91
GO:0035239	GO Biological Processes - tube morphogenesis	9	16.98	-5.59	-3.32
R-HSA-3700989	Reactome Gene Sets - Transcriptional Regulation by TP53	7	13.21	-5.50	-3.26

Table 2: Details of the studies included in the present study

S.No	References	Year of Pub.	Gene	Variant	Cancer Type	Studied Region	Study Conclusion
1	**Nagpal et al., 2020**	2020	OGG1	rs1052133	BC	Jammu	Overall, the hOGG1-Ser326Cys polymorphism may be associated with an increased risk of breast cancer in the J&K population.
2	**Verma et al., 2020**	2020	DNAH11	rs2285947	BC	Jammu	The data suggest that the DNAH11 gene variant rs2285947 is a potential risk factor for ovarian and breast cancers in the studied population.
3	**Bakshi et al., 2020**	2020	TCF21	rs12190287	BC	Jammu	This is the first study providing preliminary data for the J&K population, highlighting the role of 15 variants in breast cancer development. Notably, four variants—rs1051266, rs12190287, rs2229080, and rs2298881—showed significant associations with breast cancer.
			SLC19A1	rs1051266	BC		
			ERCC1	rs2298881	BC		
			SLC19A1	rs1051266	BC		
			PALB2	rs249954	BC		
			ATM	rs664677	BC		
			FGFR2	rs2981582	BC		
			SLC4A7	rs4973768	BC		
			ANKLE1	rs2363956	BC		
			CYP19A1	rs10046	BC		
			TERT	rs2736100	BC		
			TERT	rs2735940	BC		
			TERF1	rs2975843	BC		
			BRIP1	rs4986764	BC		
			REV1	rs3792152	BC		
4	**Mir et al., 2008**	2008	MTHFR	rs1801133	BC	Kashmir	This pilot study suggests that the MTHFR 677T-variant allele, in combination with MTRR 66G-variant or GCP II 1561 T-variant alleles, may reduce breast cancer susceptibility. Additionally, we note a potentially protective effect of the GCPII variant
			FOLH1	rs61886492	BC		
			MTRR	rs1801394	BC		
5	**Syeed et al., 2010**	2010	TP53	rs1800372	BC	Kashmir	Our findings suggest that the TP53 R72P polymorphism is a risk factor for breast cancer. Specifically, the Pro72 allele and the PP genotype are associated with a higher risk of developing breast cancer.
6	**Iqbal et al., 2016**	2016	NME1	NG	BC	Kashmir	The study showed a strong association between the NME1 heterozygous genotype and breast cancer when classified by lymph node involvement.
			MKK4	NG	BC		
7	**Sharma et al., 2018**	2018	MTHFR	rs1801133	BC	Jammu	The study concludes MTHFR gene to be a potential candidate for breast tumorigenesis
8	**Rasool et al., 2018**	2018	Survivin/BIRC5	rs9904341	BC	Kashmir	The results suggest the association of -31G/C survivin polymorphism at a genotypic and allelic level in breast cancer.

9	**Ayub et al., 2014**	2014	BRCA2	rs1799943	BC	Kashmir	These variations, along with other low-penetrance genes, may contribute to breast cancer susceptibility in this population cohort with sporadic types of breast cancer
10	**Khan et al., 2014**	2014	MDM2	NG	BC	Kashmir	Our data suggest that polymorphisms in the MDM2 gene may act synergistically to increase the risk of breast cancer.
11	**Verma et al., 2020**	2020	LRFN2	rs2494938	BC	Jammu	Not associated with the risk of BC in Jammu population
12	**Verma et al., 2023**	2023	TP63	rs10937405	BC	Jammu	Our results indicate that the TP63 gene variant rs10937405 does not increase the risk of breast and ovarian cancer in the J&K population.
13	**Sheikh et al., 2016**	2016	MnSOD	rs4880	BC	Kashmir	In conclusion, the MnSOD Ala-9Val polymorphism may modify the risk of developing breast cancer, particularly in individuals over 45 years old, those using oral contraceptives, and those with an urban lifestyle.
14	**Sharma et al., 2017**	2017	GSTT1	I/D	BC	Jammu	The present study supports the lack of association between the null GSTM1 genotype and breast cancer risk in the population of Jammu.
15	**Bhat et al., 2019**	2019	TERT	rs2853677	Leukemia	Jammu	This study suggests that rs2853677 of TERT is associated with multiple cancers and could serve as a potential marker for diagnosing non-small cell lung cancer and leukemia.
16	**Bhat et al., 2019**	2019	ARID5B	rs10740055	Leukemia	Jammu	The variants rs10740055 of ARID5B and rs6964823 of IKZF1 were found to act individually and additively as risk factors for leukemia in the populations of Jammu and Kashmir, Northern India.
			IKZF1	rs6964823	Leukemia	Jammu	
17	**Bhat et al., 2021**	2021	TP63	rs10937405	Leukemia	Jammu	The study concludes that the rs10937405 variant is a risk factor for leukemia in the Jammu and Kashmir population of North India.
18	**Shapoo et al., 2022**	2022	CYP2D6	rs35742686	Leukemia	Kashmir	The study concluded that the rs35742686 and rs3892097 SNPs are significantly associated with increased risk of ALL in Kashmiri children.
				rs3892097	Leukemia	Kashmir	
19	**Bhat et al., 2021**	2021	REV1	rs3792152	Leukemia	Jammu	Our study is the first to provide preliminary data on the association of these variants with leukemia in the Jammu and Kashmir region of North India. While both genetic and environmental factors contribute to leukemia risk, genetic factors have been underexplored in this population. Our findings suggest these genes could be potential biomarkers for evaluating leukemia outcomes, as they are involved in apoptosis, cell growth, proliferation, DNA repair, and chromatin remodeling. Although this study is a significant step, functional studies are needed to clarify the biological roles of these genes in leukemia, and larger cohort studies are necessary for validation.
			TERT	rs2736100	Leukemia		
				rs2735940	Leukemia		
			TERF1	rs2975843	Leukemia		
			TERT	rs10069690	Leukemia		
			FGFR2	rs2981582	Leukemia		
			GSTP1	rs1695	Leukemia		
			AKT1	rs2494752	Leukemia		
			TERF2	rs251796	Leukemia		
			BCL2	rs1801018	Leukemia		
			TCF21	rs12190287	Leukemia		
			TNKS	rs6990097	Leukemia		
			BRIP1	rs4986764	Leukemia		

			PSCA	rs2976392	Leukemia		
			CYP19A1	rs10046	Leukemia		
			ERCC5	rs751402	Leukemia		
			ERCC1	rs229881	Leukemia		
20	**Devi et al., 2023**	2023	MTHFR	rs1801133	Leukemia	Jammu	In conclusion, rs1801133 of MTHFR, rs4646903 of CYP1A1, and the GSTT1-null mutation increase disease susceptibility in the Jammu region of North India, unlike the GSTM1-null mutation.
			CYP1A1	rs4646903	Leukemia	Jammu	
			GSTT1	I/D	Leukemia	Jammu	
			GSTM1	I/D	Leukemia	Jammu	
21	**Bhat et al., 2020**	2020	HOXA7	rs2301721	Leukemia	Jammu	The present study concludes that the variant rs2301721 in the HOXA7 gene serves as a risk factor in the development of leukemia in the population of the Jammu region.
22	**Shaffi et al., 2009**	2009	CYP1A1	rs4646903	LC	Kashmir	Our findings support the conclusion that CYP1A1m1 and m2 polymorphisms are associated with an increased risk of smoking-related lung cancer in the Kashmiri population.
				rs1048943	LC		
23	**Bhat et al., 2019**	2019	TERT	rs2853677	LC	Kashmir	This study suggests that rs2853677 of TERT is associated with multiple cancers and could serve as a potential marker for diagnosing non-small cell lung cancer and leukemia.
24	**Bhat et al., 2020**	2020	LRFN2	rs2494938	LC	Kashmir	These results suggest that rs2494938 polymorphism of the LRFN2 gene is a risk factor in the North Indian populations to develop NSCLC
25	**Jamwal et al., 2021**	2021	REV3L	rs1002481	LC	Jammu	Our data supports a strong association between variants rs1002481, rs462779, rs465646, and NSCLC, suggesting a potential role of these REV3L variants in increasing the risk of developing NSCLC.
				rs462779	LC		
				rs465646	LC		
				rs11153292	LC		
26	**Bhat et al., 2021**	2021	TCF21	rs12190287	LC	Jammu	Among these six variants, TCF21 (rs12190287), ERCC1 (rs2298881, rs11615), ERCC5 (rs751402), ARNTL (rs4757151), and BRIP1 (rs4986764) demonstrated a significant association with NSCLC risk ($p \leq 0.003$) in the Jammu and Kashmir population.
			ERCC1	rs11615	LC		
			ERCC5	rs751402	LC		
			ARNTL/ BMAL1	rs4757151	LC		
			BRIP1	rs4986764	LC		
27	**Bhat et al., 2019**	2019	TP63	rs10937405	LC	Jammu	Our data support that the rs10937405 variant is also significantly associated with the NSCLC and is a risk factor.
28	**Bhat et al., 2023**	2023	TERT	rs10069690	LC	Jammu	Our findings suggest that variants in the TERT and POT1 genes, along with telomere length, may serve as potential biomarkers and therapeutic targets for NSCLC in this population.
				rs2242652	LC		
			POT1	rs10228682	LC		
			TERF2	rs251796	LC		
				rs2975843	LC		
29	**Verma et**	2019	hOGG1	rs1052133	OC	Jammu	Our results indicate that the G allele of rs1052133 imparts protection to the

	al., 2019		XRCC1	rs25487	OC		population whereas variant rs25487 was not associated with OC.
30	**Verma et al., 2020**	2020	PIK3CA	rs2699887	OC	Jammu	The interactive analysis also reveals that variants of PIK3CA, GSTP1, and ERCC1 carry a relatively high risk of ovarian cancer.
			GSTP1	rs1695	OC		
			CYP19A1	rs10046	OC		
			FGFR2	rs2981582	OC		
			ERCC5	rs751404	OC		
			ERCC1	rs2298881	OC		
31	**Verma et al., 2020**	2020	DNAH11	rs2285947	OC	Jammu	The collected data proposed that the variant rs2285947 of DNAH11 gene is a potential risk factor for ovarian and breast cancers in the studied population.
			of LRFN2	rs2494938			
32	**Verma et al., 2023**	2023	TP63	rs10937405	OC	Jammu	Our results indicate that the TP63 gene variant rs10937405 does not increase the risk of breast and ovarian cancer in the J&K population.
33	**Sharma et al., 2024**	2024	ADGRG4	rs5930932	OC	Jammu	According to the findings of the current investigation, the ADGRG4 gene variant rs5930932 increases the risk of OC
34	**Sharma et al., 2021**	2021	ARID5B	rs10740055	CRC	Jammu	Our results indicate that the A allele of rs10740055 imparts risk to the population and also that a larger sample size is needed for further statistical validation.
35	**Sharma et al., 2021**	2021	IKZF1	rs6964823	CRC	Jammu	It was found that the variant rs6964823 of the IKZF1 gene is associated with a higher risk of CRC within the population of J&K
36	**Sharma et al., 2021**	2021	WT1	rs2234593	CRC	Jammu	This study is the first to link genetic variants to colorectal cancer in the studied population using high-throughput MassARRAY™ technology. Further evaluation of these variants in other populations is needed to understand genetic complexity and address missing heritability
			BRCA1	rs1799966	CRC		
			DCC	rs2229080	CRC		
			HYKK	rs8034191	CRC		
			TP53	rs1042522	CRC		
			MTHFR	rs1801133	CRC		
			CYP19A1	Rs10046	CRC		
37	**Sameer et al., 2010-a**	2010	TP53	rs1800371	CRC	Kashmir	We conclude that Arg72Pro SNP is associated with susceptibility to developing CRC in this ethnic Kashmiri population.
				rs1042522	CRC	Kashmir	
38	**Banday & Sameer, 2019**	2019	TIMP2	rs8179090	CRC	Kashmir	The present study demonstrates that there is a strong and highly significant association between the TIMP2-418G/C and TIMP3-1296T/C promoter SNPs and the risk of developing CRC in ethnic Kashmiri population
			TIMP3	rs9619311	CRC		
39	**Sameer et al., 2012**	2012	GSTP1	Null	CRC	Kashmir	There was no significant association between GSTP1 I105V genotypes and the disease.
40	**Sameer et al., 2011**	2011	CYP2E1	rs2031920	CRC	Kashmir	We suggest that CYP2E1 polymorphisms are involved in the susceptibility to developing CRC in the ethnic Kashmiri population.
				I/D	CRC		
41	**Nissar et al., 2016-a**	2016	GSTT1	I/D	CRC	Kashmir	Our results suggest that GSTM1 and GSTT1 gene deletion/null gene polymorphisms are not a key modulators of the risk of developing CRC in Kashmiri population
			GSTM1	I/D	CRC		

42	**Banday et al., 2017-a**	2017	IL-10	rs1800872	CRC	Kashmir	This study has shown that there is a significant association between the IL-10 −592C/A promoter SNP and a decreased risk of CRC in an ethnic Kashmiri population, but the association between IL-10 −1082A/G SNP and the risk of CRC in the population under study is not significant.
			IL-10	rs1800896	CRC		
43	**Banday, & Aga, 2021**	2021	LTA	rs909253	CRC	Kashmir	This study demonstrated a significant association between the LT-α+252A/G SNP and CRC risk in the ethnic Kashmiri population
44	**Nissar et al., 2019**	2019	GSTP1	I105V	CRC	Kashmir	The homozygous Val/Val genotype was associated with a modestly elevated risk for CRC but not reach at significance
45	**Banday et al., 2017-b**	2017	IL-6	rs1800795	CRC	Kashmir	This study demonstrates that there is a strong and highly significant association between the IL-6 -174G/C promoter single nucleotide polymorphism and a decreased risk of colorectal cancer in ethnic Kashmiri population
46	**Sameer et al., 2012**	2012	OGG1	rs1052133	CRC	Kashmir	This study suggests that the OGG1 polymorphism is not associated with the risk of development of CRC in the Kashmiri population
47	**Nissar et al., 2015**	2015	XRCC1	Arg194Trp	CRC	Kashmir	Our results suggest that the XRCC1 Arg194Trp polymorphism increases CRC risk, indicating that the BER repair pathway influences colorectal cancer development in the Kashmiri population.
48	**Nissar et al., 2014-b**	2014	XRCC3	Thr241Met	CRC	Kashmir	This study found that individuals with the XRCC3 Thr/Met and Met/Met genotypes have a significantly elevated CRC risk, about 2.5 times higher than those with the Thr/Thr genotype.
49	**Nissar et al., 2014-a**	2014	RAD51	G135C	CRC	Kashmir	Our results suggest that the G135C polymorphism of the RAD51 gene is associated with an increased risk of CRC in our population.
50	**Nissar et al., 2013**	2013	XRCC1	Arg399Gln	CRC	Kashmir	This study suggests that the XRCC1 polymorphism is associated with an increased risk of CRC.
51	**Rasool et al., 2013 & 14**	2013	VDR	ApaI	CRC	Kashmir	BsmI was found to be significantly associated with the risk of CRC in contrast to ApaI and Fok I
				Fok I	CRC	Kashmir	
				Bsm I	CRC	Kashmir	
52	**Sameer et al., 2012**	2012	NQO1	Pro189Ser	CRC	Kashmir	Not significantly associated with the risk of CRC in Kashmiri ethnic group
53	**Nissar et al., 2017**	2017	Il-1B	-31C/T & -511T/C	CRC	Kashmir	This study has demonstrated that the association between the IL1β-31C/T and IL1β-511T/C promoter SNPs and risk of CRC in ethnic Kashmiri population is not significant
54	**Khan et al., 2013**	2013	XRCC1	Arg399Gln	CRC	Kashmir	No significant result
55	**Shah et al., 2020**	2020	TCF21	rs12190287	EC	Jammu	We explored 12 SNPs that were found to be associated with multiple cancers in literature with esophageal cancer within the population of J&K. This is the first study to find the relation of these SNPs with ESCC within the studied population. This study explores the relation of genetic and environmental factors with the ESCC
			CYP19A1	rs10046	EC		
			TERT	rs2735940	EC		
				rs10069690	EC		

			ERCC5	rs751402	EC		susceptibility.
			PIK3CA	rs2699887	EC		
			REV1	rs3792152	EC		
			FGFR2	rs2981582	EC		
			GSTP1	rs1695	EC		
			TERF2	rs251796	EC		
			DCC	rs2229080	EC		
			BCL2	rs1801018	EC		
56	**Malik et al., 2010**	2010	GSTP	rs1695	EC	Kashmir	In conclusion, GSTP1val/val and CYP2E1c1c2 genotypes/c2 allele increased the risk of ESCC and EADC, respectively, in the Kashmiri population; whereas GSTM3AB genotype imparted lower risk for both ESCC and EADC.
			GSTM1	Null			
			CYP2E1	rs2031920			
			GSTT1	Null			
			GSTM3	rs1799735			
			CYP1A1	rs4646903			
57	**Malik et al., 2011-b**	2011	CASP8	rs3834129	EC	Kashmir	Polymorphism in CASP8 -652 6N ins/del polymorphism modulates the risk of EC and GC in Kashmir valley.
58	**Malik et al., 2013**	2013	DCC	rs714	EC	Kashmir	In conclusion, genetic variations in DCC rs714 (A>G) modulate risk of EC and GC in high-risk Kashmir population.
59	**Makhdoomi et al., 2015**	2015	GSTM1	Null	EC	Kashmir	We found a significant interaction between the GSTT1 and GSTM1 genotypes with regard to ESCC risk
60			GSTT1	Null	EC	Kashmir	
61	**Shah et al., 2018**	2018	CYPA1	rs762551	EC	Kashmir	The study indicates that CYP1A2*1F polymorphism is associated with ESCC risk and the risk is modified in salt drinkers.
62	**Malik et al., 2014**	2014	PLCE1	rs2274223	EC	Kashmir	Genetic variations in PLCE1 modulate risk of EC in the high risk Kashmiri population
				rs3765524	EC		
				rs7922612	EC		
63	**Qasim et al., 2015**	2015	VGEF	rs2010963	EC	Kashmir	From the results of the present study a significant association of +936C>T and +405C>G polymorphisms with increased esophageal cancer risk exists in the Kashmiri population
				rs3025039	EC		
64	**Malik et al., 2009**	2009	NAT2	rs1799929	EC	Kashmir	NAT2 slow acetylator genotype may increase susceptibility to ESCC, and NAT2 haplotypes (C(481)A(590)G(857) and T(481)A(590)G(857)) may predict susceptibility to EC and GC in the Kashmir Valley.
				rs1799930	EC		
				rs1799931	EC		
65	**Shah et al., 2020**	2020	LRFN2	rs2494938	EC	Kashmir	The study highlights LRFN2 as a candidate gene for esophageal cancer susceptibility in the population of J&K and calls for a detailed study with a large sample size and involving more ethnic groups of India.
66	**Malik et al.,**	2011	NQO1	rs1800566	EC	Kashmir	The NQO1 609C>T TT genotype and T allele were significantly associated with

	2011		NQO2	rs2070999	EC		increased risk for GC, whereas NQO2 -3423G>A polymorphism did not show 67any association with GC. Also, NQO1 609C>T TT genotype showed significant association with gastric adenocarcinoma.
67	**Bashir et al., 2015**	2015	XRCC3	rs861539	GC	Kashmir	These findings suggest that polymorphisms of XRCC3 Thr241Met may not play a role in the etiology of gastric cancer.
68	**Malik et al., 2009**	2009	NAT2	rs1799929	GC	Kashmir	NAT2 slow acetylator genotype may increase susceptibility to ESCC, and NAT2 haplotypes (C(481)A(590)G(857) and T(481)A(590)G(857)) may predict susceptibility to EC and GC in the Kashmir Valley.
				rs1799930	GC		
				rs1799931	GC		
69	**Malik et al., 2011-b**	2011	CASP8	rs3834129	GC	Kashmir	Polymorphism in CASP8 -652 6N ins/del polymorphism modulates the risk of EC and GC in Kashmir valley.
70	**Malik et al., 2013**	2013	DCC	rs714	GC	Kashmir	In conclusion, genetic variations in DCC rs714 (A>G) modulate risk of EC and GC in high-risk Kashmir population.
71	**Malik et al., 2011-a**	2011	MMP-7	rs11568818	GC	Kashmir	In conclusion, results from present study suggest that a common MMP-7 (181A>G) genetic polymorphism may contribute to squamous cell gastric cancer susceptibility in the Kashmir valley.
72	**Qadir et al., 2021**	2021	VDR	rs1544410	GC	Kashmir	In conclusion, our study suggests that VDR BsmI SNP has a significant association with increased risk of GC
				rs7975232	GC		
73	**Malik et al., 2011**	2011	NQO1	rs1800566	GC	Kashmir	The NQO1 609C>T TT genotype and T allele were significantly associated with increased risk for GC, whereas NQO2 -3423G>A polymorphism did not show any association with GC.
			NQO2	rs2070999	GC		
74	**Ashraf et al., 2015**	2015	ERCC2	rs13181	GC	Kashmir	The magnitude and statistical significance of Asp312Asn polymorphism was smaller and weaker than the Lys751Gln polymorphism studied in the present study of GC cases vs controls.
				rs1799793	GC		
75	**Qadri et al., 2014**	2014	TLR4	rs4986790	GC	Kashmir	No correlation was found between the appearance of disease and HP infection or the presence of TLR4 and IL-8 gene polymorphisms and HP infection.
				rs4986791	GC	Kashmir	
			IL-8/ CXCL8	251 T>A	GC	Kashmir	
76	**Malik et al., 2009**	2009	GSTM1	I/D (null)	GC	Kashmir	In conclusion, GSTM1null and CYP2E1c1c2 genotype/c2 allele alter the risk for GC in the Kashmir population whereas GSTM3AB genotype seems to confer lower risk for GC
			GSTT1	I/D (null)			
			GSTP1	rs1695			
			GSTM3	rs1799753			
			CYP1A16	rs4646903			
			CYP2E1	rs2031920			
77	**Nissar ett al., 2018**	2018	XRCC1	Arg399Gln	GC	Kashmir	Polymorphic variants of XRCC1 Arg399Gln and XPD Lys751Gln are not associated with the risk of gastric cancer in the Kashmiri population.
			XPD	Lys751Gln			
78	**Khan et al., 2015**	2015	RET	rs1799939	THY	Kashmir	In conclusion, RET gene G691S/S904S polymorphisms were over-represented and L769L polymorphism was under-represented in PTC and FTC patients.
				rs1800861	THY	Kashmir	

				rs1800863	THY	Kashmir	

Table 3: Description of studies finding the epigenetic and risk of different form of cancer in J&K population

S.No	Author Name	Year	Gene	Type of cancer	Region	Conclusion
1	**Asiaf et al., 2014**	2014	CDH1	BC	Kashmir	Our preliminary findings suggest that abnormal CDH1 methylation occurs in high frequencies in infiltrating breast cancers associated with a decrease in E-cadherin expression.
2	**Akhter et al., 2014**	2014	P21	BC	Kashmir	we show for the first time that the significant association of p21 mutation and hypermethylation leads to the complete inactivation of p21 gene in Indian female breast cancer patients.
3	**Asiaf et al., 2019**	2011	DAPK1	BC	Kashmir	we consider DAPK1 inactivation by promoter hypermethylation likely plays a role in the development and progression of breast cancer.
4	**Perveez&Ajaz, 2015**	2015	KLOTHO	CRC	Kashmir	We conclude that KLOTHO promoter hypermethylation is an epigenetic inactivation in colorectal cancer, indicating its potential as a prognostic predictor in our population.
5	**Afshan et al., 2021**	2021	VDR	CRC	Kashmir	Our study, the first of its kind from Kashmir, indicates that VDR exhibits an aberrant methylation pattern in CRC, leading to a loss of expression.
6	**Wani et al., 2019 &13**	2019	P16 & MGMT	CRC	Kashmir	We also found a significant correlation between P16 and MGMT promoter hypermethylation and loss of protein expression in CRC.
7	**Dar et al., 2013**	2013	HMLH1	CRC	Kashmir	The results suggest that hMLH1 aberrant promoter methylation in the Kashmiri population contributes to colorectal cancer carcinogenesis and is one of the most common epigenetic changes in its development.
8	**Maqbool et al., 2021**	2021	LATS 1 & LATS 2	CRC	Kashmir	LATS1/2 hypermethylation is a key step in the development of colorectal cancer
9	**Guroo et al., 2018**	2018	UNC5C	CRC	Kashmir	We conclude that UNC5C hypermethylation is implicated in CRC which plays a role in its tumorigenesis and may predict the late stage disease.
10	**Sameer et al., 2011**	2011	APC	CRC	Kashmir	Although the number of mutations in the APC and β-catenin genes in our CRC cases was very low, the study confirms the role of epigenetic gene silencing of the pivotal molecular gladiator, APC, of the Wnt pathway in the development of CRC in the Kashmiri population.
11	**Hussain et al., 2011**	2011	SOCS-1	EC	Kashmir	Transcriptional inactivation of the SOCS-1 gene, primarily due to promoter hypermethylation and possibly HPV infection, may play an important role in esophageal carcinogenesis in Kashmir.
12	**Yousuf et al., 2014**	2014	MGMT	EC	Kashmir	MGMT promoter hypermethylation and concomitant loss of MGMT protein expression may play an important role in the development of gastric cancer
13	**Bhat et al., 2012**	2012	HMLH1,RASSF1A	EC	Kashmir	It was found that the frequency of promoter region hypermethylation of the mismatch repair gene hMLH1 was 56% in esophageal cancer cases and in histopathologically confirmed normals

14	**Bhat et al., 2016**	2016		EC	Kashmir	These findings indicate that promoter hypermethylation at CpG island may be responsible for reduction of expression at protein level which may be an initial event in carcinogenesis and the progression of GC.
15	**Salam et al., 2009**	2009	P16	EC	Kashmir	Analysis of patients dietary habits revealed a strong association between promoter methylation and high consumption of hot salted tea ($P < 0.05$) which is a most favourite drink commonly consumed by Kashmiri people.
16	**Rah et al., 2021**	2021	p16;/CDKN2A, HMLH1,RASSF1A	PC	Kashmir	Methylation of the p16 gene could also modulate transcription of genes thereby increasing the predisposition and susceptibility towards PC.
17	**Nissar et al., 2021**	2021	XRCC1	EC	Kashmir	The present study indicates that XRCC1 undergoes aberrant promoter hypermethylation with subsequent loss of protein expression in gastric cancer.
18	**Baba et al., 2017**	2017	P15	Leukemia	Kashmir	Complete methylation and loss of p15 gene expression causes susceptibility to relapse and decreased survival in APL patients.
19	**Nikbakht et al., 2017**	2017	CASP8, TMS1, and DAPK	Leukemia	Kashmir	The present study indicated the impact of hypermethylation-mediated inactivation of CASP8, TMS1 and DAPK genes, which is associated with risk of childhood ALL.

Table 4: Ovarian Cancerand associated genes and their associated variants

S.NO	Gene	Chr	Protein	Variant	Nucleotide Change	Variant type	Studied Region	Case/ Control	Res	References
1	***hOGG1***	3p25.3	8-Oxoguanine DNA Glycosylase	rs1052133	C>G	MV	Jammu	130/150	**P**	**Verma et al. [37]**
2	***XRCC1***	19q13.31	X-ray repair cross-complementing 1	rs25487	A>G	MV			**X**	
3	***PIK3CA***	3q26.32	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	rs2699887	C>T	UTV	Jammu	200/400	✔	**Verma et al. [38]**
4	***GSTP1***	11q13.2	Glutathione S-Transferase Pi 1	rs1695	A>G	MV			✔	
5	***CYP19A1***	15q21.2	Cytochrome P450 Family 19 Subfamily A Member 1	rs10046	A>G	IV			**X**	
6	***FGFR2***	10q26.13	fibroblast growth factor receptor 2	rs2981582	T>C	IV			**X**	
7	***ERCC5***	13q33.1	ERCC Excision Repair 5, Endonuclease	rs751404	A>G	5UTRV			**X**	
8	***ERCC1***	19q13.32	ERCC Excision Repair 1, Endonuclease Non-Catalytic Subunit	rs2298881	C>A/T	UTV			**P**	
9	***DNAH11***	7p15.3	Dynein Axonemal Heavy Chain 11	rs2285947	G>A	IV	Jammu	219/330	✔	**Verma et al. [22]**
10	***LRFN2***	6p21.2-p21.1	Leucine Rich Repeat And Fibronectin Type III Domain Containing 2	rs2494938	G>A	IV			**X**	
11	***TP63***	3q28	Tumor Protein P63	rs10937405	C>T	IV	Jammu	150/210	**X**	**Verma et al. [120]**
12	***ADGRG4***	Xq26.3	Adhesion G protein-coupled receptor G4	rs5930932	T>A/C	MV	Jammu	115/120	✔	**Sharma et al. [129]**

P: Positive Association, **X:** Non-significant Association, ✔**:** Significant Association**, MV:** Missense Variant**, UTV:** Upstream Transcript Variant, **IV:** Intronic Variant, **5'UTRV:** 5'-Untranslated Region Variant

Table 5: CRC and associated genes and their associated variants

S.NO	Gene	Chr	Protein	Variant	Nucleotide Change	VT	Studied Region	Case/ Control	Res	References
1	***ARID5B***	10q21.2	AT-Rich Interaction Domain 5B	rs10740055	C>A	IV	Jammu	180/ 390	✔	**Sharma et al. [130]**
2	***IKZF1***	7p12.2	IKAROS Family Zinc Finger 1	rs6964823	G>A	3' UTR V	Jammu	182/396	✔	**Sharma et al. [131]**
3	***WT1***	11p13	WT1 Transcription Factor	rs2234593	G>T	IV	Jammu	100/392	✔	**Sharma et al. [132]**
4	***BRCA1***	17q21.31	BRCA1 DNA Repair Associated	rs1799966	T>A	MV			✔	
5	***DCC***	18q21.2	DCC Netrin 1 Receptor	rs2229080	C>A	MV			✔	
6	***HYKK***	15q25.1	Hydroxylysine Kinase	rs8034191	T>C	IV			✔	
7	***TP53***	17p13.1	Tumor Protein P53	rs1042522	G>C	MV			✔	
8	***MTHFR***	1p36.22	Methylenetetrahydrofolate Reductase	rs1801133	C>T	MV			X	
9	***CYP19A1***	15q21.2	Cytochrome P450 Family 19 Subfamily A Member 1	rs10046	G>A	3'UTR			X	
10	***TP53***	17p13.1	Tumor Protein P53	rs1800371	C>T	MV	Kashmir	86/160	✔	**Sameer et al. [39]**
				rs1042522	C>G	MV	Kashmir	86/160	✔	
11	***TIMP2***	17q25.3	TIMP Metallopeptidase Inhibitor 2	rs8179090	G>C	UTV	Kashmir	142/184	✔	**Banday & Sameer, [133]**
12	***TIMP3***	22q12.3	TIMP Metallopeptidase Inhibitor 3	rs9619311	T>C	UTV			✔	
13	***GSTP1***	11q13.2	Glutathione S-Transferase Pi 1	Null	A>G		Kashmir	86/160	X	**Sameer et al. [134]**
14	***CYP2E1***	10q26.3	Cytochrome P450 Family 2 Subfamily E Member 1	rs2031920	C>T	UTV	Kashmir	86/160	✔	**Sameer et al. [41]**
				I/D	I/D	I/D			✔	
15	***GSTT1***	22q11.23	Glutathione S-Transferase Theta 1	I/D	I/D	I/D	Kashmir	160/200	X	**Nissar et al. [135]**
16	***GSTM1***	1p13.3	Glutathione S-Transferase Mu 1	I/D	I/D	I/D			X	
17	***IL-10***	1q32.1	Interleukin 10	rs1800872	T>G	IV	Kashmir	142/184	P	**Banday et al. [136]**
18	***IL-10***	1q32.1	Interleukin 10	rs1800896	A>G	-			X	
19	***LTA***	6p21.33	Lymphotoxin Alpha	rs909253	A>G	IV	Kashmir	141/184	✔	**Banday and Aga, [51]**
20	***GSTP1***	11q13.2	Glutathione S-Transferase Pi 1	I105V			Kashmir	160/200	X	**Nissar et al. [137]**
21	***IL-6***	7p15.3	Interleukin 6	rs1800795	G>C	UTV	Kashmir	142/184	P	**Banday et al. [138]**
22	***OGG1***	3p25.3	8-Oxoguanine DNA Glycosylase	rs1052133	C>G	MV	Kashmir	114/200	X	**Sameer et al. [42]**
23	***NQO1***	16q22.1	NAD(P)H:quinone Oxidoreductase 1	Pro189Ser	C>T	MV	Kashmir	86/160	X	**Sameer et al. [134]**
24	***XRCC1***	19q13.31	X-Ray Repair Cross Complementing 1	rs1799782	C>T	MV	Kashmir	100/100	✔	**Nissar et al. [48]**
25	***XRCC3***	14q32.33	X-Ray Repair Cross Complementing 3	rs861539	C>T	MV	Kashmir	120/150	✔	**Nissar et al. [47]**
26	***RAD51***	15q15.1	RAD51 recombinase	rs1801320	G>C	3'UTR	Kashmir	100/120	✔	**Nissar et al. [46]**
27	***XRCC1***	19q13.31	X-Ray Repair Cross Complementing 1	rs25487	T>C	MV	Kashmir	130/150	✔	**Nissar et al. [45]**

28	***VDR***	12q13.11	Vitamin D Receptor	ApaI			Kashmir	180/188	**X**	**Rasool et al. [44]**
				Bsm I					✔	
29	***VDR***	12q13.11	Vitamin D Receptor	Fok I			Kashmir	312/305	**X**	**Rasool et al. [43]**
30	***XRCC1***	19q13.31	X-Ray Repair Cross Complementing 1	Arg399Gln	G>A		Kashmir	120/146	**X**	**Khan et al. [50]**
31	***IL-1B***	2q14.1	Interleukin-1Beta	-31C/T	C>T		Kashmir	142/184	**X**	**Banday et al. [139]**
				-511T/C	T>C		Kashmir		**X**	

Table 6: **E**sophageal 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	***TCF21***	6q23.2	Transcription Factor 21	rs12190287	C>G/T	3' UTR V	Jammu	166/592	✔	**Shah et al. [60]**
2	***CYP19A1***	15q21.2	Cytochrome P450 Family 19 Subfamily A Member 1	rs10046	G>A	3' UTR V			✔	
3	***TERT***	5p15.33	Telomerase Reverse Transcriptase	rs2735940	A>G	UTV			X	
				rs10069690	C>T	IV			X	
4	***ERCC5***	13q33.1	ERCC Excision Repair 5, Endonuclease	rs751402	A>G	5UTR-V			X	
5	***PIK3CA***	3q26.32	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	rs2699887	C>T	UTV			X	
6	***REV1***	2q11.2	REV1 DNA Directed Polymerase	rs3792152	A>G	IV			X	
8	***FGFR2***	10q26.13	Fibroblast Growth Factor Receptor 2	rs2981582	A>G	UTV			X	
9	***GSTP1***	11q13.2	Glutathione S-Transferase Pi 1	rs1695	A>G	MV			X	
10	***TERF2***	16q22.1	Telomeric Repeat Binding Factor 2	rs251796	A>G	IV			X	
11	***DCC***	18q21.2	DCC Netrin 1 Receptor	rs2229080	C>A/G	MV			X	
12	*BCL2*	18q21.33	BCL2 Apoptosis Regulator	rs1801018	T>C	SV			x	
13	***GSTP1***	11q13.2	Glutathione S-Transferase Pi 1	rs1695	A>G	MV	Kashmir	135/195	✔	**Malik et al. [53]**
15	***GSTM1***	1p13.3	Glutathione S-Transferase Mu 1	Null	I/D	I/D			X	
16	***GSTT1***	22q11.23	Glutathione S-Transferase Theta 1	Null	I/D	I/D			X	
17	***GSTM3***	1p13.3	Glutathione S-Transferase Mu 3	rs1799735	I/D	I/D			X	
18	***CYP1A1***	5q24.1	Cytochrome P450 Family 1 Subfamily A Member 1	rs4646903	T>C	DTV			X	
19	***CYP2E1***	10q26.3	Cytochrome P450 Family 2 Subfamily E Member 1	rs2031920	C>T	TV			✔	
20	***CASP8***	2q33.1	Caspase 8	rs3834129	AGTAAG	UTV	Kashmir	135/195	✔	**Malik et al. [55]**
21	***DCC***	18q21.2	DCC Netrin 1 Receptor	rs714	A>G	IV	Kashmir	135/195	✔	**Malik et al. [56]**
22	***GSTM1***	1p13.3	Glutathione S-Transferase Mu 1	Null	I/D	I/D	Kashmir	492/492	✔	**Makhdoomi et al. [57]**
23	***GSTT1***	22q11.23	Glutathione S-Transferase Theta 1	Null	I/D	I/D			✔	
24	***CYPA1***	15q24.1	Cytochrome P450 Family 1 Subfamily A Member 1	rs762551	C>A	IV	Kashmir	404/404	✔	**Shah et al. [59]**
25	***PLCE1***	10q23.33	Phospholipase C Epsilon 1	rs2274223	A>G	MV	Kashmir	195/195	✔	**Malik et al. [140]**

				rs3765524	C>T	MV			✔	
				rs7922612	C>T	IV			✔	
26	***VGEF***	6p21.1	Vascular Endothelial Growth Factor A	rs2010963	C>G	UTV	Kashmir	150/150	✔	**Qasim et al. [58]**
				rs3025039	C>T	3' UTR V			✔	
27	***NAT2***	8p22	N-Acetyltransferase 2	rs1799929	C>T	SV	Kashmir	182/123	✔	**Malik et al. [141]**
				rs1799930	G>A	MV			✔	
				rs1799931	G>A	MV			✔	
28	***LRFN2***	6p21.2-p21.1	Leucine Rich Repeat And Fibronectin Type III Domain Containing 2	rs2494938	G>A	IV	Kashmir		✔	**Shah et al. [61]**
29	***NQO1***	16q22.1	NAD(P)H Quinone Dehydrogenase 1	rs1800566	C>T	MV	Kashmir	108/195	✔	**Malik et al. [63]**
30	***NQO2***	6p25.2	N-Ribosyldihydronicotinamide:Quinone Dehydrogenase 2	rs2070999	G>A	UTV			X	

Table 7: Gastric Cancerand associated genes and their associated variants

S.NO	Gene	Chr	Protein	Variant	Nucleotide Change	Variant type	Studied Region	Case/ Control	Res	References
1	***XRCC3***	14q32.33	X-Ray Repair Cross Complementing 3	rs861539	G>A	MV	Kashmir	80/70	X	**Bashir et al. [64]**
2	***GSTM1***	GSTM1	Glutathione S-Transferase Mu 1	Null	I/D	I/D	Kashmir	108/195	✔	**Malik et al. [141]**
3	***CYP2E1***	10q26.3	Cytochrome P450 Family 2 Subfamily E Member 1	rs2031920	C>T	UTV			✔	
4	***GSTM3***	1p13.3	Glutathione S-Transferase Mu 3	rs1799735	del/AGG	I/D			✔	
5	***GSTT1***	22q11.23	Glutathione S-Transferase Theta 1	Null	I/D	I/D			X	
6	***CYP1A1***	5q24.1	Cytochrome P450 Family 1 Subfamily A Member 1	rs4646903	T>C				X	
7	***NAT2***	8p22	N-Acetyltransferase 2	rs1799929	C>T	SV	Kashmir	182/123	✔	**Malik et al. [54]**
				rs1799930	G>A	MV			✔	
				rs1799931	G>A	MV			✔	
8	***CASP8***	2q33.1	Caspase 8	rs3834129	AGTAAG	UTV	Kashmir	108/195	✔	**Malik et al. [55]**
9	***DCC***	18q21.2	DCC Netrin 1 Receptor	rs714	A>G	IV	Kashmir	108/195	✔	**Malik et al. [56]**
10	***MMP-7***	11q22.2	Matrix Metallopeptidase 7	rs11568818	A>G	UTV	Kashmir	108/195	✔	**Malik et al. [63]**
11	***VDR***	12q13.11	Vitamin D Receptor	rs1544410	G>A	IV	Kashmir	143/150	✔	**Qadir et al. [65]**
				rs7975232	G>T	IV			X	
12	***NQO1***	16q22.1	NAD(P)H Quinone Dehydrogenase 1	rs1800566	C>T	MV	Kashmir	108/195	✔	**Malik et al. [55]**
13	***NQO2***			rs2070999	G>A	UTV			X	
14	***ERCC2***	19q13.32	ERCC Excision Repair 2	rs13181	A>C	MV	Kashmir	100/100	✔	**Ashraf et al. [142]**
				rs1799793	C>A/T	MV			✔	
15	***TLR4***	9q33.1	Toll Like Receptor 4	rs4986790	A>G	MV	Kashmir	120/100	X	**Qadri et al. [143]**
				rs4986791	C>T	MV			X	
16	***IL-8/ CXCL8***	4q13.3	C-X-C Motif Chemokine Ligand 8	251 T>A	T>A	-			X	
17	***XRCC1***	19q13.31	X-Ray Repair Cross Complementing 1	Arg399Gln		MV	Kashmir	180/200	X	**Nissar et al. [49]**
18	***XP/ ERCC2***	19q13.32	ERCC Excision Repair 2, TFIIH Core Complex Helicase Subunit	rs13181	A>C	MV			X	

Table 8: Thyroid Cancer

S.NO	Gene	Chr	Protein	Variant	Nucleotide Change	Variant type	Studied Region	Case/ Control	Res	References
1	RET	10q11.21	Ret proto-oncogene	rs1799939	G>A	MV	Kashmir	140/180	✔	**Khan et al. [144]**
				rs1800861	T>G	SV	Kashmir	140/180	✔	
				rs1800863	C>G	SV	Kashmir	140/180	✔	