Role of genetic polymorphisms within different genes and associated risks of cancer development (Review)

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Abstract. Cancer susceptibility varies widely among individuals due to complex interactions between genetic and environmental factors. Among genetic determinants, polymorphisms within key genes involved in carcinogen metabolism, DNA repair, cell cycle regulation, immune response and epigenetic modification significantly influence cancer risk. The present review comprehensively discusses the role of genetic polymorphisms across diverse gene families, including cytochrome P450 enzymes (notably CYP1A1 and CYP2E1), tumor suppressors (PTEN, TP53), DNA repair genes (XPD) and immune checkpoint regulators (PD-L1), highlighting their contributions to cancer development. Additionally, the interplay between genetic variants and epigenetic mechanisms, such as DNA methylation is discussed, emphasizing their combined effects on gene expression modulation in carcinogenesis. Advances in genotyping technologies and genome-wide association studies have expanded the understanding of these polymorphisms, providing insight into population-specific susceptibilities and pharmacogenomic applications. The integration of genetic and epigenetic profiling holds promise for personalized cancer prevention and therapeutic strategies, tailored to individual genetic makeup and environmental exposures. The present review underscores the importance of continued research into genetic polymorphisms as biomarkers for cancer risk assessment, providing a foundation for targeted interventions and improved public health outcomes.

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1. Introduction

The investigation of the genetic factors influencing cancer susceptibility has been increasing in recent years. The International Human Genome Sequencing Project and the International HapMap Project have both conducted substantial research into the location, amount, type and frequency of genetic variants in the human genome (1-4). Numerous observational studies examining the association among polymorphisms in genetic variations and the risk of cancer development have led to ongoing technology advancements that enable more rapid and more economical genotyping results (5). A recent genome-wide association study identified several novel susceptibility loci for prostate cancer risk, providing new insight into the genetic architecture of this disease across diverse populations (6). A large cohort study involving >113,000 women emphasized the contribution of both common and rare genetic variants to breast cancer susceptibility, demonstrating the complex genetic architecture underlying breast cancer risk (7).

Knowledge of the genetic propensity to cancer has generally improved with the increasing amount of research that has been performed. The lack of replication has been a major critique of

genetic epidemiology. There have been many 'false positive' claims, as evidenced by the failure of numerous research that attempted to reproduce a statistically significant outcome for a genetic condition that had already been published (8,9). Meta- and pooled analyses have been employed to incorporate both statistically meaningful and non-significant data from several studies and grade these results according to their precision. Another significant methodological issue is the scale of these studies of genetic associations (a proportion of sample size) (10-12).

The programmed death-ligand 1 (PD-L1), encoded by the *CD274* gene located on chromosome 9p24.1, plays a critical role in immune regulation by mediating immune checkpoint pathways that allow tumors to evade immune surveillance. PD-L1 expression is detected in various cells, including antigen-presenting cells, lymphocytes and epithelial cells, where its regulated activity helps maintain immune homeostasis during inflammation (13,14). Toll-like receptors (TLRs), expressed in immune cells, have been shown to modulate PD-L1 expression by responding to pathogen-associated molecular patterns, thus influencing the immune microenvironment.

Notably, the aberrant expression of PD-L1 has been implicated in the pathogenesis of several types of cancer. The overexpression of PD-L1 in tumors, such as non-small cell lung cancer is associated with oncogenic mutations, such as those in the epidermal growth factor receptor (EGFR), highlighting the interplay between oncogenic signaling pathways and immune evasion mechanisms. Genetic and epigenetic alterations, including polymorphisms and mutations in PD-L1 regulatory regions or associated signaling genes, such as phosphatase and tensin homolog (*PTEN*) and anaplastic lymphoma kinase (*ALK*), may contribute to a variable PD-L1 expression and consequent differences in tumor immune escape and patient prognosis (15).

Despite the recognized importance of PD-L1, comprehensive studies focusing on genetic polymorphisms within the *CD274* gene and their associations with cancer susceptibility remain limited. Integrating the mechanistic understanding of PD-L1 regulation with genetic variation analyses could provide valuable insight into individual susceptibility and response to immune checkpoint therapies.

TLRs, a subtype of non-catalytic receptor that is widely expressed in APCs and activated by epitope molecular patterns, have a notable impact on PD-L1 expression (16). The driving oncogenic events in carcinogenesis may be the cause of PD-L1 overexpression. For instance, in lung cancer, PD-L1 expression is positively associated with EGFR mutations in the EGFR (17). Through the unregulated stimulation of the protein kinase pathway, PD-L1 overexpression is maintained in enzymatic activity and in PTEN-mutant tumors (18,19). Through constitutive STAT3 activation, the recombinant genes for the protein nucleophosmin (NPM) and ALK enhance the expression of PD-L1 in T-cell lymphoma (20). Lin *et al* (21) explored the genomic and transcriptomic characteristics regulating PD-L1 expression, highlighting the impact of genetic polymorphisms on PD-L1 and its role across various types of cancer.

Cytochrome P450 (CYP450) enzymes, which include those from the CYP1, CYP2 and CYP3 families, as well as additional exogenous and endogenous compounds, metabolize drugs. The key CYP enzymes involved in the metabolic activation of procarcinogens are CYP1A1, CYP1A2, CYP1B1, CYP2E1, CYP3A4 and CYP3A5 (22).

The majority of CYPP450 enzymes that belong to the CYP 1, 2, or 3 groups are polymorphic due to gene deletion, single-nucleotide polymorphisms that occur all alone in combination, or gene duplications, where mutant alleles result in discontinued, reduced, modified, or enhanced enzyme activity. Genetic polymorphisms in CYP enzymes, such as CYP2D6 and CYP2E1 significantly affect enzyme activity and have been linked to altered cancer susceptibility across diverse populations (23,24). Phenotyping experiments were utilized to investigate the potential link between CYP polymorphisms and the risk of developing cancer before genotyping methods were developed. The delivery of CYP enzyme substrate and the analysis of the products in plasma and urine were common procedures used in research. Following the analysis of the associations among CYP polymorphisms and the risk of cancer development over the period of a decade in numerous studies encompassing thousands of patients, the association between CYP polymorphisms and cancer susceptibility is now understood; the mechanisms involved include simultaneous genes that code for phase 1 and phase 2 enzymes (25). Recent studies have shed light on CYP polymorphisms influencing the risk of cancer development and treatment outcomes. Tan *et al* (26) reported on the impact of CYP2D6 genotypes on breast cancer outcomes and pharmacogenomics, emphasizing the clinical relevance of CYP2D6 polymorphisms. Additionally, Jiang *et al* (27) conducted an updated meta-analysis linking CYP2E1 polymorphisms with an increased risk of developing various types of cancer, supporting the role of CYP2E1 genetic variations in cancer susceptibility.

Numerous biological mechanisms, including bone metabolism, inborn resistance, proliferation and differentiation are regulated by the vitamin-D endocrine system (28). Numerous common diseases, such as cancers, diabetes, cardiac disease, autoimmune disorders, rickets, as well as other bone diseases, have been firmly related to vitamin D deficiency by epidemiological and laboratory research (29-32). The biologically highly active naturally occurring metabolite of vitamin D, known as 1,25-dihydroxyvitamin D3 (1,25(OH)2D3, calcitriol), has been found to control the proliferation and differentiation of a range of cell types, including cancer cells (33-35). Research has also demonstrated that angiogenesis, cancer growth and cell death are all regulated in cancer (36-38). Previous research has revealed the existence of intracellular enzyme 25(OH) D3-1-hydroxylase (CYP27B1) activity in a wide range of cell types, including macrophages, keratinocytes, prostate and colon cancer cells (39,40). It has been shown that a number of tissues locally synthesize 1, 25(OH) 2D3. Recent research has uncovered that vitamin D can be activated via an alternative pathway by the steroidogenic enzyme CYP11A1. This pathway complements the classical activation involving CYP27B1 and expands the understanding of vitamin D metabolism beyond traditional mechanisms. The CYP11A1-mediated conversion produces novel secosteroids with potential biological activities relevant to cellular proliferation, differentiation, and immune modulation in cancer and other diseases. This alternative pathway adds complexity

to vitamin D regulation and may have implications for cancer susceptibility and therapy (41,42).

The nucleotide excision repair (NER) system is one of the main mechanisms by which cells defend themselves from genotoxic damage, such as that caused by UV radiation and exposure to chemical carcinogens. Human syndromes, such as trichotillomania, Cockayne syndrome and xeroderma pigmentosum (XP) are caused by NER system anomalies (43,44). An exceptionally high sensitivity to UV light and a comparatively high chance of developing skin cancer are two features of the heritable human condition known as XP. The UV sensitivity of patients with XP led to the initial connection between the illness and DNA repair (45). Based on the ability of distinct cell types to complement UV sensitivity, eight XP-complementation groups were identified (46,47), and the genes encoding the various complementation groups have also been identified (48-50). UV radiation plays a dual role in human homeostasis, with both harmful and beneficial effects that extend beyond simple DNA damage. Beyond its capacity to induce genotoxic lesions repaired by the nucleotide excision repair system, UV radiation also plays a central homeostatic role in neuro-immuno-endocrine regulation. Recent insights highlight how UV exposure modulates systemic physiology by affecting neural, immune and endocrine pathways, thus contributing positively to body regulation and immune surveillance. This dual nature of UV radiation underscores the complexity of its impact on health and carcinogenesis, balancing its carcinogenic potential against vital homeostatic functions (51).

In addition to genetic polymorphisms, epigenetic modifications, such as DNA methylation play a crucial role in regulating gene expression and influencing cancer susceptibility. DNA methylation involves the addition of a methyl group to cytosine residues, typically at CpG dinucleotides, leading to changes in chromatin structure and gene activity without altering the DNA sequence itself. Aberrant DNA methylation patterns can result in gene silencing or activation that contributes to carcinogenesis, affecting tumor suppressor genes, oncogenes and DNA repair genes. The interplay between genetic polymorphisms and epigenetic alterations is increasingly recognized as fundamental to understanding the risk of cancer development, progression and the therapeutic response. Therefore, integrating both genetic and epigenetic perspectives provides more comprehensive insight into cancer susceptibility and personalized medicine approaches.

Taken together, the diversity of biological systems, such as immune surveillance (antigen-presenting cells and checkpoint proteins), metabolic detoxification (cytochrome P450 enzymes), cellular signaling (vitamin D pathways), DNA repair (nucleotide excision repair system), and epigenetic regulation (DNA methylation) forms an intricate network maintaining cell homeostasis and genomic integrity. Genetic polymorphisms within the genes governing these systems can significantly alter their functions, leading to variability in how individuals respond to environmental exposures, carcinogens and intrinsic cellular stresses. These variations may influence cancer susceptibility by affecting immune evasion, the activation or detoxification of carcinogens, DNA damage repair efficiency, and the epigenetic regulation of oncogenes and tumor suppressors. Thus, understanding the complex interplay among these elements is essential for elucidating the multifactorial nature of cancer risk and identifying genetic and epigenetic markers for cancer prevention, diagnosis and personalized therapy.

2. Various genes and genetic polymorphisms

The following chapter provides an overview of genes involved in key cellular pathways; it is important to emphasize that the relevance of these genes to the risk of cancer development is principally determined by the specific genetic polymorphisms they harbor. A detailed understanding of the normal function of each gene provides the necessary foundation to appreciate how alterations in the genetic sequence, such as single nucleotide polymorphisms (SNPs), insertions, deletions and copy number variations, can influence an individual's susceptibility to cancer. Throughout this section, gene variants with established or potential links to cancer risk will be highlighted. It should be noted, however, that some gene polymorphisms discussed in the subsequent sections affect human health through mechanisms that may extend beyond cancer alone; these examples are included to underscore both the complexity and the far-reaching consequences of genetic variation in human populations. This integrative approach aims to provide a nuanced perspective, facilitating a comprehensive understanding of the multifactorial risk factors contributing to cancer and related diseases.

Within the broad family of CYP enzymes, several members such as CYP1A1, CYP1A2, CYP1B1, CYP2E1, CYP2D6, CYP3A4 and CYP3A5 participate in the metabolism of carcinogens and drugs. Among these, CYP1A1 and CYP2E1 have emerged as particularly critical, due to their significant roles in activating procarcinogens commonly found in tobacco smoke and other environmental toxins. Genetic polymorphisms in these enzymes influence enzymatic activity and expression levels, thereby modulating individual susceptibility to various cancers. While all CYP enzymes contribute to xenobiotic metabolism, the extent of evidence linking CYP1A1 and CYP2E1 variations to the risk of cancer development is more substantial, warranting focused research attention.

CYP1A1. On human chromosome no. 15, the *CYP1A1* gene is only activated in organs other than the liver, such as the lungs. The enzyme *CYP1A1* converts polycyclic aromatic compounds, which are present in cigarette smoke, into hazardous arene oxide that can result in DNA mutation and cancer (47,48). Since *CYP1A1* is not expressed in the human liver, it is dubious whether human studies on animals have any application (49). There are several polymorphic *CYP1A1* alleles known. A point mutation causes an *Msp*I restriction fragment-length polymorphism in the 3' non-coding region (RFLP). The heme-binding domain of *CYP1A1* contains the exon 7 polymorphism, which increases the inducibility of the enzyme. Recent research suggests that the *Msp*I, as well as exon 7 mutation may increase the risk of developing lung cancer, although Asians are more likely to be affected. In the 3' non-coding region of *CYP1A1*, a second *Msp*I RFLP is only present in individuals of African origin. Its connection to the risk of developing lung cancer remains unclear. According to recent studies, nicotine can boost pulmonary *CYP1A1*

activity (50). This research has important implications for how sensitive humans are to acquiring cancer, even if it is currently only applicable to rats. First, nicotine most definitely contributes to the induction of *CYP1A1* by cigarette smoke. Second, the emergence of smoking cessation aids raises serious concerns about the possibility for nicotine replacement medications to increase *CYP1A1* activity and hence trigger the bio-activation of carcinogens (51). Last but not least, it remains unknown how *CYP1A1* functions in the presence of nicotine and an allele variation.

CYP2D6. *CYP2D6* (debrisoquine hydroxylase) is considered to be involved in the metabolism of 25% of all prescribed medications (52). At least 29 allelic variations of *CYP2D6* have been identified, and this has been linked to significant inter-individual variability in drug metabolism (53).

In ~6% of Caucasians, deletions, abnormal splicing and gene duplication result in the absence of functional *CYP2D6*. It is interesting that *CYP2D6* cannot be induced. It is understood that *CYP2D6* activates metabolism (54).

Smoke from cigarettes contains 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone, which is considered to cause cancer and is a factor in the development of human lung adenomas. Extensive metabolizers may be more susceptible to lung cancer (54).

E-Cadherin. The *CDH1* gene, that is found on chromosome 16q22.1, is responsible for producing the 120 kD single transmembrane glycoprotein known as E-cadherin. One intracellular and five external domains are present. It converses with catenins. The development and maintenance of tissue architecture, cell polarity, intracellular signaling and intercellular adhesion depend on this protein. It plays a critical role in the formation of sticky junctions in epithelial cells. The lack of E-cadherin directly affects essential cellular processes including motility. Additionally, it has been demonstrated that its expression decreases typically happen during tissue metastasis. An association has been found between an increased aggressive behavior and the decreased expression of E-cadherin. The frequency of OSCC E-cadherin gene hypermethylation varies between 7 and 46% (55).

PTEN. The tumor-suppressor gene, *PTEN*, is located on chromosome 10q23.3. It is anticipated that essential cellular functions such as survivability, differentiating, proliferating, apoptosis and invasion are affected by the lack of expression Ras/phosphoinositide 3-kinase (PI3K)/Akt, which lack control over the signal transduction that control apoptosis and migration, and also play a crucial role in the survival, proliferation and metastasis of tumor cells. Due to mutations or epigenetic modifications, *PTEN* is frequently lacking in a variety of cancer types. Furthermore, it has been demonstrated that endometrial cancer, gastric cancer, non-small cell lung carcinoma and cervical cancer all exhibit the methylation of the *PTEN* promoter CpG islands (56). The functions, regulation and implications of PTEN polymorphisms in cancer were comprehensively reviewed by Song *et al* (57), detailing the role of PTEN as a key tumor suppressor. Han *et al* (58) further performed a meta-analysis of PTEN mutations, associating genetic alterations with prognosis across multiple cancer types.

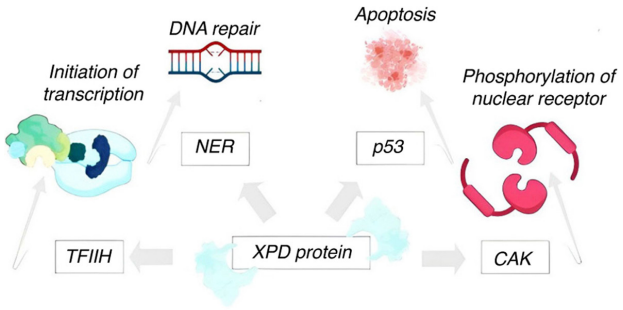

Figure 1. Diagram illustrating the associations between the XPD protein and potential clinical diseases caused by XPD gene mutations.

p53. Cell cycle progression, cellular differentiation, DNA repair and apoptosis are some of the key cell activities that the *TP53* gene, also known as *p53*, is involved in. It is located on chromosome 17p13.1. p53 levels increase in response to endogenous or exogenous stress, which stops the cell cycle and enables DNA repair. Genomic instability results from p53 loss of function, which affects how cells react to stress or damage. With a frequency ranging from 25 to 69%, *p53* is mutated in the majority of human malignancies, including oral tumors (59,60). In addition to this, p53 frequently exhibits a decrease of function brought on by epigenetic rather than genetic processes. Comprehensive analyses of TP53 variations across multiple human cancers were provided by Bouaoun *et al* (61), utilizing database and genomic data to reveal new insight into TP53 mutation patterns. A further mechanistic understanding of mutant p53 roles in cancer pathogenesis was provided by Mantovani *et al* (62), elucidating its function as a cancer cell guardian.

XPD. TFIIH phosphorylates a wide range of substrates, including nuclear hormone receptors such as RAR or ER, transcription activators and RNA polymerase II (63). Additionally, *TFIIH* is present as a nine-subunit complex, a transcriptionally active core *TFIIH*, and a CDK-activating kinase (CAK) complex (Fig. 1). The XPD protein is a component of all three of these complexes (64). The activity of these complexes can be decreased by mutations in the XPD gene, which can cause issues with transcription, the apoptotic response, repair, or, most likely, hormonal function. All of these deficiencies result in syndromes that are associated with immature sexual development, skeletal abnormalities, mental impairment, and, in the case of the majority of patients with XPD mutations, a high propensity for cancer. Only a limited amount of research has been performed into the connection between XPD mutations and DNA repair capacity, as determined by the biological tests mentioned in the literature. The Lys/Lys codon 751 XPD genotype was previously linked to a decreased repair of X-ray-induced DNA damage in a brief study on 31 women at risk of developing breast cancer (65). More chromatid aberrations are present in individuals with the wildtype Lys allele than in those carrying one or more Gln alleles (65).

3. Methods for analyzing genetic polymorphisms

Association studies are most frequently used to determine whether polymorphisms contribute to genetic susceptibility or progression. As a result, the focus is on variables that determine the effectiveness of associations. If a specific allele exhibits a greater frequency in cases compared to controls, that polymorphism is then considered to be linked to the disease (66). Researchers compare individuals with extreme phenotypes when analyzing polymorphisms as contributing factors to the course of disease, rather than diseased individuals with unaffected controls. There are three possibilities if a substantial association is found: Either the polymorphism is at the locus of interest, it is in genetic linkage [namely linkage disequilibrium (LD)] with the locus, or confounding factors are involved.

When alleles from two different genetic loci co-occur more frequently than would be predicted according to their respective allelic frequencies, a population is considered to exhibit LD. Possible sources of LD include early mutation, founder effects and selection. Population admixture, which occurs when groups that have been separated for a long time unite to form a hybrid population, is another possible source of LD (67). The resulting LD can be prolonged beyond distances typically observed in populations with greater stability, depending on the sort of mixing. The most precise estimates of LD in an outbred population indicate that LD is unlikely to span distances >1-2 centimorgans (cM), or ~1-2 million base pairs, whereas LD may occur across 10-fold that distance in an inbred group, such as the Hutterites (68).

Confounding variables need to be taken into account, particularly when polymorphisms reported in one study are absent in another ethnic group. One perplexing aspect is population stratification. This could be brought on by unequal ethnic admixture, such as the presence of Caucasians in the gene pool of an African-American community. Fortunately, this issue can be resolved by taking great precautions during the analysis or research plan phases. Association studies based on families are specifically created to take into account the genetic background that may add confounding variables, and they include genotyping of affected people, their parents, and/or their unaffected siblings (69). These types of investigations frequently employ the transmissions disparity test (TDT), as well as the haplo-type relative risk test statistics (HRR). The TDT compares how frequently each allele is transferred from a heterozygous parent to a child who has the disease. Similar to the TDT, the HRR analyses genetic transmission (haplotype) as compared to allele transmission (70).

The decision of which phenotype to explore is crucial in genetic polymorphism investigations. In fact, the presence of numerous phenotypes in the case sample has hampered much research that analyzing genetic polymorphisms. For instance, research on asthma has used patient samples from patients with mild, severe, adult-onset, intrinsic and extrinsic asthma (71). Studying a more precisely defined intermediate phenotype can significantly enhance studies that aim to ascertain whether there is a link between a polymorphism and disease. Total IgE and bronchial hyper responsiveness are examples of intermediate phenotypes in the case of asthma. Another factor to take into account is the possibility that the genes involved in illness progression may not be the same genes responsible for disease susceptibility. It may be helpful to restrict the sample to those with a particular stage or severity of disease. In a previous study, to evaluate potential genes for the disease, the researchers focused on patients with severe early-onset chronic obstructive pulmonary disease (71).

The evaluation of DNA polymorphisms close to or within putative genes is the only application of association studies. Linkage analysis employing families or affected siblings is necessary to carry out a genome screen to look for candidate genes. Although linkage analysis is rigorous and uncovers genes that significantly affect disease susceptibility, it has very limited power and will miss genes that merely increase the risk of mild to moderate disease. For instance, hundreds to thousands of families would need to be typed if a disease susceptibility allele increased disease risk by 2-fold relative to the wild-type allele, which may not be a realistic sample size (72). Although linkage analysis detects connections over considerably larger genomic regions (thousands of base pairs), association studies have a stronger power (millions of base pairs). Including current technology, a genome scan with association studies would need tens of thousands of markers. The majority of lung diseases need some type of environmental trigger before they may become visible. Given that genetic susceptibility only accounts for a small part of illness variation, failure to consider environmental factors can drastically degrade gene-finding research for the majority of complex disorders. Furthermore, genome screening or association studies carried out on populations that were neither chosen nor stratified according to their environmental exposure could only be able to find genes whose environmental exposure is common in that group. For instance, investigating a randomly chosen sample of asthmatics from the Midwest region of the USA would be able to discover genes crucial for regulating the response to house dust mites, although possibly not with absolute certainty (73).

Gene-environment interactions can take on many different shapes, such as distinct exposure risk implications based on the genotype of an individual or diverse gene risk implications based on the exposure of an individual. Biological and statistical interactions are the two main interactions. The coefficient of the product term of the genetic and environmental risk variables represents a statistical risk factor interaction, and the interaction is quantified as a divergence from a multiplicative model (gene and environment). This approach is arbitrary, relies on models, and may overlook biological synergy or interaction. The biologic interaction paradigm states that when two factors cause a disease to start, they interact. Occasionally, this co-participation could stand out as a divergence from an additive model (74).

4. SNPs in the human population

SNPs are single nucleotide variations in the genomic DNA that occur at different positions in different individuals in a community (75). Genome-wide datasets are more frequently used in the drug development process, as well as to identify molecular pathways and networks underlying complex disorders (Table I) (76-79). In particular, functional pathway analysis of genomic data provides the possibility of greater

Table I. Methods of selecting SNPs.

Methods	Advantages	Limitations	(Refs.)
Pathway gene method	It is simple to study a subset of SNP based on a description of the pathways relating to the drug's pharmacokinetics and mechanism of action. Clinically, general vulnerability is observed in complex genetic disorders.	The pathway gene approach will result in fewer false-positive findings than the genome wide approach because of the disadvantage of multiple testing.	(76,77)
Candidate gene method	Functional SNPs are those whose genetic variant affects how a protein functions. This technique has resulted in the identification of a sizable number of pertinent SNPs in pharmacogenetics.	As the majority of complex traits are not considered to be monogenetic, selecting SNPs using this strategy will frequently result in a limited explanation of variation in medication response.	(78,79)
Genome-wide method	This strategy may identify unexpected SNPs linked to drug response. New associations between SNPs and medication response have been found in genome-wide association investigations, and complicated features can be studied, while taking into account polygenetic variation.	In identifying a related SNP, the discrepancy between type I errors (false positive findings) and eventually type II faults (false negative results) may create some issues.	(78,79)

SNP, single nucleotide polymorphism.

capability for discovery and organic links to biological phenomena. SNPs are the consequence of single base-pair variations (substitutions or deletions) caused by point mutations in chromosome sequences, and account for a large portion of the genetic variation found in the human genome. Finding SNPs in a genome can be achieved in a variety of laboratories and via computational mechanisms; however, they all involve comparing the same DNA segment from various individuals or haplotypes.

SNPs can be located using expressive sequence tags, which are created by single-run sequencing of cDNAs obtained from various individuals and the assembly of overlapping sequences for the same region. This allows for the discovery of novel SNPs. Depending on whether they are located in regions of the genome that regulate genes, non-coding SNPs can be categorized. A number of complex disorders may be caused by quantitative discrepancies in gene products rather than qualitative differences. Based on whether they alter the amino acid sequences of the protein that the altered gene encodes, coding SNPs can be categorized. By their impact on protein structure, modifications that change protein sequences can be categorized (80).

Genome-wide association studies have emerged as a crucial method for identifying genes that predispose to complicated disorders. With the aid of population-based information like as allele frequency, LD and recombination rates, researchers may perform genome-wide association analysis on millions of SNP markers. Some of the discrepancies in association results between populations for particular traits of interest can be explained by HapMap data, such as population-specific common variants and LD blocks (81).

5. VNTR polymorphisms in the human population

CYP2E1 is a key enzyme found in the microsomal ethanol oxidation system. It belongs to the CYP superfamily and is primarily located in the membranes of the endoplasmic reticulum. CYP2E1 plays a crucial role in the metabolism of various hydrophobic toxic compounds (82-84). Additionally, it contributes to the conversion of certain pro-carcinogens and drugs into highly reactive metabolites.

The activation of N-nitrosamines, which are present in tobacco smoke, foodstuffs, and certain industrial and endogenous carcinogens, is facilitated by CYP2E1. Furthermore, this enzyme can generate highly reactive compounds, such as superoxide anion radical (O^{2-}), singlet oxygen (O_2), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH\cdot$) by reducing molecular oxygen. These reactive species are capable of causing DNA damage and promoting carcinogenesis (85-87). The human *CYP2E1* gene is situated on chromosome 10q26.3 and consists of 9 exons and 8 introns. The expression of the *CYP2E1* gene can be regulated at multiple levels, including transcription, translation, mRNA stability and protein degradation. As with other CYP genes, CYP2E1 exhibits various polymorphic sites in its 5'-flanking region, introns, and transcribed gene regions. One notable polymorphism is a variable number tandem repeat (VNTR) sequence located ~2.0 kilo base pairs upstream of the transcription start site (88-90).

The activity of the CYP2E1 enzyme exhibits significant variability among different ethnic groups, influenced by both environmental and genetic factors, such as polymorphisms. Polymorphic CYP genes can lead to differences in the ability to metabolize, detoxify, or activate various substances. Several

studies have indicated that certain polymorphic genes, in conjunction with alcohol consumption, play a role in the development of specific types of cancer. Although alcohol itself is not a carcinogen, it can function as a co-carcinogen by amplifying the effects of other chemicals that are activated by enzymes, such as CYP2E1. Research has demonstrated that CYP2E1 is highly expressed in the liver and pancreas following ethanol ingestion. The production of acetaldehyde during ethanol oxidation may directly cause cell damage through the generation of reactive oxygen species (91-95).

Furthermore, it is widely known that certain tumors have a hereditary component, and environmental factors associated with specific habits can increase the risk of tumor occurrence.

6. Using a different approach to identify human gene polymorphisms

The function of biotransformation enzymes with reference to occupational health exposure is to provide effective purification of endogenous or exogenous substances by particular biochemical pathways. These turn harmful molecules into inactive compounds, which are then eliminated in urine, preventing the buildup of metabolites and injury to the human body (96). Although the scanning of specific gene polymorphisms by molecular biology laboratories is the optimal approach to determine each the susceptibility of each study participant, the willingness of study participants to provide the biosample is essential to move forward with the genetic analysis. There are some issues, such as the unwillingness of study participants to consent to venipuncture or, more generally, to the collection of biopsies, either as they are simply unaccustomed to the procedure as they consider it to be an invasive and painful technique, or because they are afraid of the possible outcomes of the analysis (97). However, the evaluation of gene polymorphisms does not provide any diagnostic information regarding the propensity of an individual to develop a specific disease. In comparison to collecting urine samples, collecting blood samples may be more difficult. The lack of language proficiency, the difficulties in communicating, and the study participants varied cultures, customs, dietary preferences, and religious beliefs could all play a role in this. To combat this critical issue and obtain ethnic-specific genotype information without using laboratory analysis, a publicly available online library (http://grch37.ensembl.org/Homo sapiens/Variation) appears to contain a tentative catalogue of the majority of genotype and allele frequencies of several ethnic groups. It is possible to collect the genetic profiles of many ethnic groups using this resource, which aids in the prediction and identification of population-specific susceptibilities *in silico* study. This model was created to assess the risk level of the homozygous variation and heterozygous genotype in relation to the world population in four macro-groups that includes Africans, Eastern Asians, South Asians and Europeans. The principal component analysis statistical technique serves as the foundation of the model (98). It is intended to identify the crucial vulnerabilities in the polymorphisms of genes linked to three main functional biochemical processes, including detoxification, oxidative stress and DNA repair, following exposure to the harmful compounds. The SNPs were selected based on their exposure to harmful and cancer-causing chemicals that are frequently present in manufacturing plants and shipyards (99).

7. Benefits of including polymorphisms in studies on health-related effects

Incorporating polymorphisms opens up a wide range of intriguing options for investigating the health effects of exposure to toxins and toxicants in the environment. It is possible to identify various risk ranges in subgroups of individuals who were exposed by stratifying a health result or biomarker in accordance with the relevant genotype (or phenotype) (100), as illustrated in Fig. 2. An implication that corresponds to the average risk for both fast and slow acetylators is shown by research evaluating the probability of bladder cancer linked to exposure to aromatic amines (100). This estimate does not imply that aromatic amines are as significant etiological factors for sub-populations or as powerful carcinogens as a stratified study might. For routine exposures, to food ingredients or carbon emission, for example, whose relation to a disease consequence is normally small, effect dilution may be especially crucial. Second, proof of impact change by genotype provides insight into the fundamental biologic mechanism of cytotoxicity or carcinogenicity when substrates or targets of possible genetic variants are identified as likely causal agents (101). Lipopolysaccharide (LPS), a constituent of particulates in rural regions and sometimes known as an endotoxin, may have a negative impact on lung function metrics. Kelada *et al* (101) demonstrated that the response to LPS varied by TLR4 genotype. The TLR4, which is encoded by TLR4, binds LPS and begins a signaling pathway that causes lung inflammation. According to their findings, although individuals with the mutated TLR4 genotype may be more susceptible to an inflammatory process, they may not be as susceptible to an inflammation of the lungs brought on by LPS. These results may contribute to answering the difficult question of whether particulates matter component(s) is/are accountable for the multitude of documented health consequences, particularly in rural areas where LPS levels are substantial. The development of drugs or dietary interventions that postpone the start or progression of disease may be made possible by the increased understanding of pathologic pathways gained via combined epidemiological and toxicological investigations. Oltipraz [OPZ; 5-(2-pyrazinyl)-4-methyl-1, 2-dithiole-3-thione] is an example of a medication that activates phase II XMEs, specifically the GSTs (102). Aflatoxin B1 can cause liver cancer in rats, according to early research. Research has also revealed that administering OPZ to patients significantly improved the clearance of a phase II substance known as aflatoxin-mercapturic acids (103). Research suggests that OPZ may function by competitively inhibiting CYP1A2, preventing the activation of aflatoxin. Ultimately, hypothesis-based epidemiological research and the knowledge of aflatoxin biotransformation routes from investigations on human tissue grown *in vitro* and animal models has helped to establish a chemoprevention method for aflatoxin-induced hepatocellular carcinoma. Studies on the consequences of exposure to controlled environmental pollutants that take genetic sensitivities into consideration will increase our understanding of the range of human genetic variation in response to these pollutants. Genes

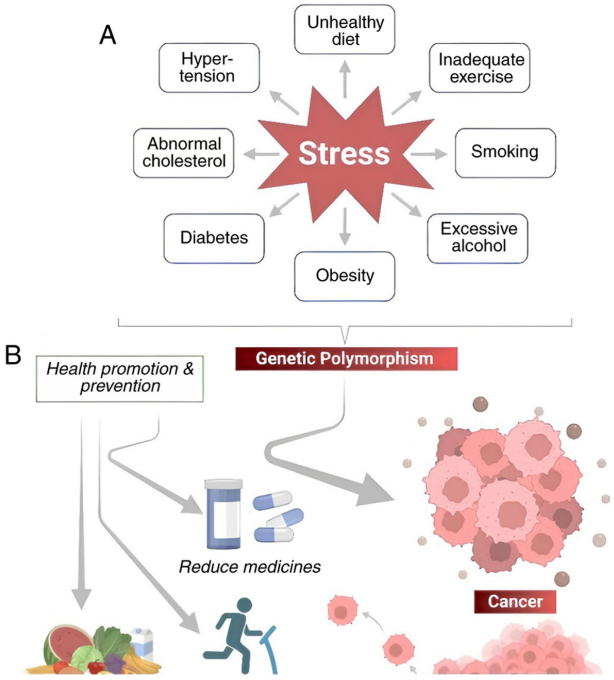

Figure 2. Schematic depiction of (A) various risk factors associated with genetic polymorphism-induced cancer, and (B) various health promotion approaches for the management of genetic polymorphism-induced cancer.

that may be associated with susceptibility should be included in studies designed to examine the effects of these substances. By replacing the standard default assumptions (i.e., uncertainty factor of 10) with more accurate estimates of human variability, the risk assessment may be improved. As a result, acceptable exposure levels may be redefined, improving overall public health protection and industry regulation. Although this benefit has been promoted for some time, there is still no concrete illustration of how it may be achieved, particularly in light of the myriad social, legal, or ethical issues that surround use of genetic data (104). Preventive efforts on those who are genetically sensitive to disease has started in the environmental health field, with a focus on the intrinsically complicated ethical, legal and social issues (105).

8. Synopsis

Polymorphisms and DNA methylation both play critical roles in the development of cancer. Polymorphisms are DNA sequence variations that occur when a single nucleotide in the DNA sequence is altered. These variations can lead to changes in the function of the gene or the expression of the gene product, which can result in cancerous changes to cells. Epigenetic changes, such as DNA methylation are biochemical processes wherein enzymes add a methyl group to the DNA strand at 5th position of the cytosine to be precise. These methylation sites can control gene expression by either silencing a gene or increasing its activity depending upon the number of methylation sites present. DNA methylation can also alter splicing patterns, downregulate or 'turn off' gene expression, which can lead to cancerous changes in cells. Overall, both polymorphisms and DNA methylation function as key regulators of gene expression and can therefore exert significant effects on the development of cancer (106). However, they do differ in their mechanisms of action.

The role of genetic polymorphisms within different genes in the development and risk of cancer development is a complex and multifactorial process. While genetic polymorphisms can contribute to the susceptibility of an individual to cancer, they are not the sole determinant. Environmental factors, lifestyle choices and other non-genetic factors also play a crucial role. Numerous studies have identified specific genetic polymorphisms that are associated with an increased risk of developing cancer. For example, variations in the *BRCA1* and *BRCA2* genes have been linked to an increased risk of developing breast and ovarian cancer, while variations in the *TP53* gene have been linked to an increased risk of developing several types of cancer, including breast, ovarian and colorectal cancer (107,108). However, it is important to note that the presence of a genetic polymorphism does not necessarily mean that an individual will develop cancer. A number of individuals with these genetic variations never develop cancer, and numerous individuals without these genetic variations do develop cancer.

Emerging evidence demonstrates that tumors possess the capacity not only to modulate their local microenvironment, but also to dysregulate systemic body homeostasis through neuroendocrine pathways. This tumor-driven autoregulation interferes with normal physiological processes, such as metabolism, immune function and stress response, effectively hijacking the neuroendocrine system of the body to support cancer progression and evade host defenses. Understanding this intricate interplay reveals cancer as a systemic disease with extensive body-wide impacts, highlighting potential therapeutic targets to restore homeostatic balance and counter tumor-driven systemic disruption (109).

The study of genetic polymorphisms and cancer risk is an active area of research, and new discoveries are continuously being made. As the understanding of the genetic basis of cancer increases, it is likely that the identification of novel genetic variations that are associated with an increased risk of cancer development will be achieved, and the development of novel strategies for the prevention and treatment of cancer may be possible.

9. Limitations and future challenges

While the present review comprehensively covers the role of genetic polymorphisms across various genes associated with susceptibility to cancer, several limitations should be acknowledged. First, the heterogeneity of study designs, sample sizes and populations in the original research contributes to variability and potential inconsistency in reported associations. A number of genetic association studies face challenges, such as population stratification, limited replication and publication bias, which affect the strength and generalizability of conclusions. Second, the complex interplay between genetic polymorphisms, epigenetic modifications and environmental factors remains incompletely understood, limiting the ability to fully elucidate causal mechanisms. Third, the functional characterization of numerous polymorphisms is still lacking, impeding translation to clinical applications. Finally, rapidly evolving genomic technologies and the emergence of multi-omics approaches necessitate continuous updates to maintain a current and holistic perspective

on genetic risks in cancer. Future studies incorporating large, well-characterized cohorts with integrated genomic, epigenetic, and environmental data are essential to overcome these limitations and advance personalized cancer prevention and therapy.

10 Conclusion

In conclusion, DNA methylation and genetic polymorphisms both have a major impact on the occurrence and risk of developing cancer. Genetic polymorphisms are differences in DNA sequence that may have an impact on gene expression and function, possibly causing malignant cell alterations. Contrarily, DNA methylation is an epigenetic change that can influence gene expression by activating or silencing genes, having an effect on the onset of cancer. New findings are continuously being made as a result of ongoing research into genetic variants and the risk of developing cancer. Additional genetic variants linked to the risk of developing cancer will probably be discovered as the knowledge of the genetic basis of cancer increases. This knowledge could potentially lead to the development of personalized strategies for cancer prevention and treatment based on the unique genetic makeup of an individual.

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RM and NK conducted a significant portion of the literature search and drafted the manuscript. GS contributed to editing specific sections of the manuscript. SPS edited and proofread the manuscript. AKJ contributed to the initial conception and scope of the review, provided critical review and feedback on the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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