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Review article

Gene Polymorphisms: their Influence on the Risk of Development and Prognosis of the Course of Oncological Diseases

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Abstract

Single nucleotide polymorphisms associated with the risk of malignant neoplasms can impact the prognosis of cancer progression.

***The aim of this review** is to discuss the mechanisms by which gene polymorphisms in humans influence the risk of development and prognosis of oncological diseases. The PubMed and Google Scholar databases were used for the search.*

The following keywords were used: <single nucleotide polymorphisms>, <cancer>, <cancer development>, <cancer prognosis>. A total of 210 articles were found, of which 44 sources were selected.

Genetic factors are closely associated with the risk of cancer development and prognosis in different populations. Discrepancies in the results obtained may be attributed to racial differences. The clinical application of identifying single nucleotide sequences can be used in conjunction with approved screening programs, enhancing their prognostic role. The search for new biomarkers can allow for the timely detection of diseases, stratification of oncology patients, and monitoring of treatment progress in clinical practice.

***Keywords**: single nucleotide polymorphisms, genetic factor, cancer, cancer prognosis, oncology patients.*

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Introduction

Understanding the mechanisms of molecular functioning contributes to the study of cell functions and life processes, providing directions for investigating the causes of human diseases. Single nucleotide polymorphisms (SNPs) are DNA sequence variations caused by the variation of a single nucleotide. SNPs are the most common type of inherited variations in humans and are widespread in the human genome. The coexistence of multiple allelic variants of a gene in a population is called polymorphism. The presence of polymorphism in a population can be inferred from differences in phenotypes corresponding to different alleles or from the nature of DNA carrying different alleles [1-4]. SNPs are the most common genetic variant in the human genome and are considered stable biomarkers of the genetic background for predicting the risk of progression and response to treatment of various diseases. These genetic polymorphisms also lead to differences in disease susceptibility and severity among individuals [5,6]. Polymorphism at the phenotype level is explained by the simultaneous existence of both the wild-type allele and a series of mutant alleles in a population. Mutations alter the gene product, resulting in modified gene functions. This can lead to changes in the phenotype [7, 8]. In general, the influence of single nucleotide polymorphisms on the development of various diseases began to be studied and actively published in the accessible literature in the late 1990s and early 2000s [9-11]. Thus, SNPs, representing common genetic variations in human genomes, act as markers of molecular susceptibility to complex traits and diseases in humans.

The aim of this review: is to discuss the mechanisms by which human gene polymorphisms influence the risk of development and prognosis of oncological diseases.

Search Strategy

The PubMed and Google Scholar databases were used for the search. The search was conducted using the following keywords: <single nucleotide polymorphisms>, <cancer>, <cancer development>, <cancer prognosis>. A total of 210 articles were found, and 44 sources were selected.

The influence of gene polymorphisms on cancer development

It is already well-known that a large number of genes associated with various types of cancer contain SNPs. These SNPs are located in gene promoters, exons, introns, as well as in 5' and 3' untranslated regions, and they affect gene expression through various mechanisms. The mechanisms mentioned above depend on the role of genetic elements in which individual SNPs are located. Furthermore, changes in epigenetic regulation due to gene polymorphisms contribute to the complexity underlying cancer predisposition associated with SNPs [5].

SNPs can be located in various parts of genes, including promoters, exons, introns, and 5' and 3' UTRs [12-15]. Therefore, changes in gene expression and their predisposition to cancer may vary depending on the location of SNPs. The location of SNPs can affect gene expression by altering promoter activity, transcription factor binding, and DNA CpG site methylation [16, 17]. Additionally, cancer risk may depend on exonic SNPs, suppressing gene transcription and translation. SNPs in intronic regions also impact gene function. Such locations can generate transcript splice variants and contribute to or disrupt the binding and function of long non-coding RNAs. Single nucleotide polymorphisms in the 5' UTR affect translation, while SNPs in the 3' UTR influence microRNA binding [18].

Gene SNPs can cause changes in gene expression by affecting the binding, splicing, methylation, and degradation of mRNA, thereby inducing genetic differences among individuals [19]. Moreover, the identification of cancer-associated SNPs may lead to the reversal of malignant cell transformation if these SNPs are correctable.

As a relatively small allelic variation, SNPs are important genetic markers for studying the characteristics of different types of cancer. As whole-genome association studies progress, more evidence is emerging that breast cancer susceptibility is linked to genetic SNPs. For example, ERCC5 SNPs have been associated with the development of certain types of cancer, including breast cancer [20, 21]. Nari Na et al. (2015) demonstrated that the ERCC5 rs2094258 polymorphism can impair the DNA repair mechanism by causing nucleotide excision repair defects, which is closely associated with cancer risk [22].

Using breast cancer as an example, we conducted an analysis and found that the work of a group of authors identified associations between polymorphic loci rs10719/DROSHA, rs11060845/PIWIL1, rs10773771/PIWIL1, rs3809142/RAN, rs563002/DDX20, rs595055/AGO1, rs2740348/GEMIN4, and rs1640299/DGCR8 with the risk of developing cancer in this location among women of Russian ethnicity [23].

In another study, it was found that the polymorphic locus rs417309, located in the 3'-untranslated region of the DGCR8 gene, is associated with an increased risk of breast cancer in the Chinese population [24]. Experimental results on cell lines with the creation of a plasmid vector construct demonstrate variability in gene expression depending on the presence of different alleles of the rs417309 polymorphic locus.

The aforementioned data show how complex and interconnected the clinical effects of genetic variability can be. Although these results are very interesting, it should be noted that the patient groups studied are highly heterogeneous. This heterogeneity limits the interpretation of genetic variations in such clinical situations.

Mutations in six genes (NCOR1, GATA3, CDH1, ATM, AKT1, and PTEN) significantly correlated with corresponding levels of gene expression, were enriched, and were involved in multiple cancer-related pathways. GATA-binding protein 3 (GATA3) is a transcription factor that is crucial for mammary gland morphology and cell differentiation and acts as a tumor suppressor. Mutations in the sites AKT1 rs121434592, CDH1 rs587783047, and GATA3 rs763236375 are major causes affecting gene expression. Analysis of overall and disease-free survival has shown that the expression of NCOR1, GATA3, CDH1, and ATM is closely associated with the survival of breast cancer patients [25,26].

Studies by Dydensborg A.B. et al. (2009) have shown that overexpression of GATA3 can suppress tumor growth and metastasis to the lungs [26]. Currently, GATA3 gene mutations have been identified in breast cancer samples and are positively correlated with their expression level.

Furthermore, studies have confirmed that the GATA3 gene is identified with mutations in more than 10.0% of all breast cancer samples, and further analysis has shown that the CACA mutation at the GATA3 rs763236375 site is an important cause influencing gene expression. Analysis of overall and disease-free survival shows that high expression of this gene is favorable for the prognosis of breast cancer patients.

The PI3K/AKT pathway is an important signaling pathway in cells that is largely associated with the metastasis of malignant tumors. AKT is a direct downstream target protein located below PI3K. Increasing evidence supports the notion that activation of the AKT protein plays a significant biological role in cancer development [27,28]. AKT1 is one of the subtypes of AKT. Activated AKT1 phosphorylates a large number of downstream substrates and participates in the regulation of cell growth, metabolism, proliferation, apoptosis, and other processes.

Castaneda C.A. et al. (2010) [29] found that AKT1 is closely associated with early cancer development and can be used as a key indicator for its early diagnosis. Pathway analysis showed that AKT1 is enriched in the PI3K-AKT signaling pathway and several other pathways closely related to cancer, such as proteoglycans in cancer and the MAPK signaling pathway, indicating that the gene encoding AKT1 plays important biological functions in cancer development. Furthermore, our study also showed that a significant cause of correlation between the AKT1 gene somatic mutation and expression is the CC mutation at the AKT1 rs121434592 site. Additionally, as a guardian of genome integrity, the tumor suppressor gene PTEN plays an important role in maintaining chromosomal stability.

At the same time, in combination with the results of previous studies, the TOX3 gene plays a certain role in the onset and development of breast cancer in the Chinese population. It has been reported that the TOX3 gene primarily participates in the transcription process in malignant tumors. Studies of breast cancer have shown that TOX3 acts as an anti-oncogene and is overexpressed in ductal tumors. These studies have confirmed the role of TOX3 in breast cancer development, but the question of how it is regulated is complex and unknown [30,31].

Recently, with the constant development of bioinformatics, a large number of multifunctional bioinformatics tools have emerged, significantly accelerating the integration and utilization of existing biomedical data. Research in the field of bioinformatics helps us find the most rational and effective methods or approaches for the treatment and prevention of diseases.

Bioinformatics tools such as GO, KEGG, and Bayesian networks were used to analyze TOX3. GO analysis revealed that TOX3/TNRC9 performs three functions: molecular function, cellular component, and biological process. KEGG analysis showed that the IGF-IGF1R-PI3K-Akt-mTOR-S6K pathway was the best possible pathway for cancer cell differentiation, and the ER-TOX3/TNRC9 pathway was identified as the main survival pathway for tumor cells using Bayesian networks. These results provide a theoretical basis for targeted therapy and lay the foundation for studying the mechanisms of action of the TOX3 gene in cancer [30].

Thus, polymorphisms in genes involved in multiple biological pathways can be identified as potential risk factors for cancer development.

The impact of gene polymorphisms on the prognosis of cancer

SNPs are considered potential markers of carcinogenesis and therefore valuable for early diagnosis and personalized targeted cancer therapy. In their study, Wang S. et al. (2019) provided scientific evidence that polymorphisms caused by genetic variability in miR-149 rs2292832 influence the prognosis of cancer patients [32].

Nuclear receptor co-repressor 1 (NCOR1) is a transcriptional coregulator that links chromatin-modifying enzymes with gene-specific transcription factors and interacts with members of the BTB-ZF transcription factor family to play an important role in the development and functioning of T cells [33].

Recent data has also shown that reduced expression of NCOR1 is significantly associated with shorter recurrence-free survival (RFS) in breast cancer patients, suggesting a poor prognosis that may be related to immune system involvement and increased drug resistance. In this study, the expression of the NCOR1 gene was significantly reduced in mutated samples, and correlation analysis results showed that single nucleotide polymorphism (SNP) mutations in the NCOR1 gene negatively correlated with expression levels. Furthermore, analysis of overall survival (OS) and RFS confirmed a poor prognosis associated with low NCOR1 expression, consistent with other studies [34-36].

E-cadherin (CDH1) and ataxia telangiectasia mutated (ATM) are tumor suppressor genes involved in multiple signaling pathways, including tumor activation pathways, apoptosis, and the p53 protein signaling pathway. CDH1 is frequently mutated in diffuse gastric cancer and lobular breast cancer. Patients with diffuse gastric cancer with CDH1 mutations have shorter survival times compared to patients without CDH1 mutations [37].

ATM mutations are closely associated with breast cancer, ovarian cancer, and other types of malignant tumors. ATM expression is suppressed in breast cancer and indicates a poor prognosis [38,39]. Hypermethylation of the ATM gene promoter may affect the DNA repair mechanism, leading to disruption of the ATM/p53 signaling pathway regulation and thus impacting the progression of breast cancer [35, 40]. A correlation was found between CC mutation and CDH1 SNP expression at rs587783047 site. Analysis of overall survival and disease-free survival showed that decreased ATM expression and, conversely, increased CDH1 expression adversely affected patient prognosis.

Some researchers have suggested that rs88931 (MAP3K1) strongly correlates with distant disease-free survival (DDFS), disease-free survival (DFS), and overall survival (OS) in hormone receptor-positive breast cancer [41]. Yamamoto-Ibusuki M., et al. (2015) confirmed that homozygous alleles of rs2046210 showed worse recurrence-free survival [42]. Hein A. et al. (2017) [43] showed that rs2981582 (FGFR2), rs889312 (MAP3K1), and rs3803662 (TOX3) did not affect overall survival and progression-free survival in breast cancer patients. Similar results were observed in another study, but the role of rs3803662 in the prognosis of breast cancer patients in the Han population was rarely analyzed.

In a study investigating genetic factors associated with the prognosis of breast cancer patients in Henan Province using SNP (third-generation genetic markers), which have regional and ethnic differences, SNPs rs10069690 (TERT), rs2046210 (6q25.1), rs2981582 (FGFR2), and rs889312 (MAP3K1) were not associated with disease-free survival, while rs3803662 (TOX3/TNRC9), which was associated with disease-free survival, was identified. The GG genotype of rs3803662 (TOX3/TNRC9) was associated with worse prognosis and nearly tripled the risk of breast cancer recurrence [92].

Since SNPs associated with the risk of developing malignancies can influence prognosis, analyzing relevant SNPs can help identify new biomarkers for cancer prognosis.

The clinical role of SNP genotyping in patients with malignancies lies in identifying individuals at high (aggressive) risk for disease. Individuals with a higher likelihood of developing aggressive cancer may choose to start screening and monitoring at an earlier age or at a higher frequency. In this group, preventive measures, including diet, lifestyle adjustments, and drug prophylaxis, may also be applied.

Bioinformatics analysis based on high-throughput sequencing is an important method for studying the molecular mechanisms of tumor pathogenesis, identifying biomarkers for early diagnosis, and identifying therapeutic targets.

Conclusions

Therefore, some genetic factors are closely associated with the risk of developing cancer and the prognosis of its progression in various populations. Differences in the obtained results may be attributed to racial variations. The clinical application of single nucleotide polymorphism (SNP) detection can be used in conjunction with established screening programs to enhance their prognostic role. The search for new biomarkers can enable timely disease.

Conflict of interest. The authors declare no conflict of interest.

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Гендік полиморфизмдер: олардың онкологиялық аурулардың даму қаупіне және ағымының болжамына әсері

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Түйіндеме

Қатерлі ісіктің даму қаупімен байланысты бір нуклеотидті полиморфизм қатерлі ісік болжамына әсер етуі мүмкін.

Бұл шолудың мақсаты адам генінің полиморфизмінің онкологиялық аурулардың даму қаупіне және ағымының болжамына әсер ету механизмдерін талқылау болып табылады.

Әдебиет көздерін іздеу үшін PubMed және Google Academy дерекқорлары пайдаланылды. Іздеу келесі түйін сөздерді қолдану арқылы жүргізілді: <бір нуклеотидті полиморфизмдер>, <қатерлі ісік>, <қатерлі ісіктің дамуы>, <қатерлі ісіктің болжамы>. Барлығы 210 мақала табылды, оның ішінде бізге 44 дереккөз таңдалды.

Генетикалық факторлар әртүрлі популяцияларда қатерлі ісіктің даму қаупімен және болжамымен тығыз байланысты. Алынған нәтижелердегі айырмашылық нәсілдік айырмашылықтарға байланысты болуы мүмкін.

Жалғыз нуклеотидтер тізбегін анықтаудың клиникалық қолданылуы олардың болжамдық рөлін арттыра отырып, валидацияланған скринингтік бағдарламалармен бірге пайдаланылуы мүмкін. Жаңа биомаркерлерді іздеу клиникалық тәжірибеде ауруды дер кезінде анықтауға, онкологиялық науқастарды стратификациялауға және емдеу курсын бақылауға мүмкіндік береді.

Түйін сөздер: бір нуклеотидтік полиморфизм, генетикалық фактор, қатерлі ісік, қатерлі ісік болжамы, онкологиялық науқастар.

Полиморфизмы генов: их влияние на риск развития и прогноз течения онкологических заболеваний

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Резюме

Одиночные нуклеотидные полиморфизмы, связанные с риском развития злокачественного новообразования, могут влиять на прогноз течения рака.

Цель настоящего обзора: обсудить механизмы влияния полиморфизмов генов человека на риск развития и прогноз течения онкологических заболеваний.

Для проведения поиска были использованы базы данных PubMed и Академия Google. Поиск был проведен, по следующим ключевым словам: <одиночные нуклеотидные полиморфизмы>, <рак>, <развитие рака>, <прогноз течения рака>. Всего найдено 210 статей, из них нам отобрано 44 источников.

Генетические факторы тесно связаны с риском развития и прогнозом течения рака в различных популяциях. Отличия в полученных результатах могут быть связаны с расовыми различиями.

Клиническое применение определения однонуклеотидных последовательностей может использоваться в сочетании с утвержденными скрининговыми программами, увеличивая их прогностическую роль. Поиск новых биомаркеров могут позволить в клинической практике своевременно выявлять заболевание, стратифицировать онкологических больных и контролировать ход лечения.

Ключевые слова: одиночные нуклеотидные полиморфизмы, генетический фактор, рак, прогноз течения рака, онкологические больные.