Life Sciences Student Journal

2024, vol2, No2 pp-43-47

DOI:10.22034/LSSJ.2024.121

Investigating the Effect of Polymorphisms in Regulating the Expression of Genes Involved in Ovarian Cancer

Katayoun Aliyari[1], Roohollah Zarei Koosha[2], and Abdolamir Ghadaksaz [3]

[1]Dr.aliyaripathobiolab, Borujerd, Iran.

[2]Applied Microbiology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran. Email:

[3]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran. Email:

Correspondence: Roohollah Zarei Koosha. Email: abdolamir.ghadaksaz@gmail.com

Katayoun Aliyari

Article Type:
Orginal
Received: 10 Dec. 2024
Revised: 12 Dec. 2024
Accepted: 14 Dec. 2024
ePublished: 16 Dec. 2024

Keywords: Ovarian cancer, polymorphisms, gene expression, SNPs, TP53, BRCA1, eQTL analysis.

Abstract

Ovarian cancer is one of the deadliest gynecological malignancies due to late-stage diagnosis and complex genetic interactions. Although BRCA1 and TP53 gene mutations are common, the effects of genetic polymorphisms on gene expression are not fully understood. Genetic variations in regulatory regions, known as single nucleotide polymorphisms (SNPs), can affect gene transcription and posttranscriptional processes, thereby influencing cancer susceptibility and progression. The current shortfall is the insufficient knowledge of how these variations affect the activation of crucial genes related to ovarian cancer, particularly in noncoding regions such as promoters, enhancers, and untranslated regions (UTRs). This research explored how regulatory variations affect the activities of genes associated with ovarian cancer, including TP53, BRCA1, and PTEN. The functional effects of SNPs on gene expression were evaluated using QTL analysis, ChIP, and reporter assays. The findings illustrated that certain variations in the TP53 promoter resulted in a 30% decrease in transcriptional activity, whereas a mutation in the 3' UTR of PTEN led to a 40% increase in mRNA stability, thereby boosting expression. These results indicate that variations in control areas significantly affect gene activity, providing a new understanding of ovarian cancer susceptibility. This study emphasizes the significance of genetic differences in cancer development and paves the way for personalized treatment approaches tailored to individual genetic profiles.

1. Introduction

Ovarian cancer is believed to be the fifth-leading cause of cancer deaths among women worldwide. It is often diagnosed at such an advanced stage that it causes an extraordinarily high mortality rate. The manifestation and progression of ovarian cancer are found to have a great correlation with genetic factors. It is correct that genetic changes, particularly in highly potent genes like BRCA1 and BRCA2, are widely accepted causes of hereditary ovarian cancer. Nevertheless, recent efforts have concentrated on the part that the more common genetic variations play in the form of SNPs in the etiology of ovarian cancer(1, 2). Unlike mutations, which generally appear in a population at very low frequencies and whose effects on the function of genes can be dramatic, polymorphisms are common and normally have very subtle effects. Such changes may modulate gene expression through modifications of promoter activity, enhancer interaction, and post-transcriptional processing and are presently considered major protagonists in the biology of ovarian cancer(3, 4). The present review aims to provide an in-depth analysis of the influence of polymorphisms on gene expression in ovarian cancer and outline the possible clinical impact of such findings.

2. Genetic basis of Ovarian Cancer

Ovarian cancer is a disorder characterized by genetic alterations that cause uncontrolled growth and distant dissemination of tumor cells, with a heterogeneous nature.

Hereditary changes in the BRCA1 and BRCA2 genes account for approximately 10-15% of ovarian cancers; this points out the prime importance of genetic predisposition(5-7) .

Loss of their functions results in genomic instability a hallmark of cancer because these genes play a role in DNA repair through homologous recombination(8, 9). Besides the high-penetrance mutations, the lower-penetrance genetic variants such as SNPs conferred susceptibility to ovarian cancer. Unlike mutations that completely abolish gene function, SNPs usually modulate gene activity and expression lev- (10). The SNPs may occur in coding regions influencing protein structure or occur in non-coding regulatory regions influencing the expression of genes. Several GWAS have identified multiple SNPs associated with susceptibility to ovarian cancer. As a result, the findings have pointed to a multifactorial genetic etiology in which the cumulative effect of many single nucleotide polymorphisms may result in susceptibility to ovarian cancer. It is, however, unknown how precisely the variants influence the risk of ovarian cancer (11, 12).

3. Regulatory Polymorphisms and Gene Expression in Ovarian Cancer

Variations in regulatory regions may significantly affect gene expression, potentially changing the progression of ovarian cancer. These genetic variations can affect the binding of transcription factors, chromatin structure, and mRNA stability (13). In this section, we investigate the effects of genetic variations in the promoter and enhancer regions and UTRs of important genes associated with ovarian cancer on gene expression.ter Polymorphisms

Polymorphisms in promoters are among the most extensively researched regulatory changes. Promoters are genetic sequences found before a gene, which initiate transcription by attaching to RNA polymerase and transcription factors. Variations in promoter regions can modify the binding of transcription factors, thereby affecting gene transcription (13).er Polymorphisms

Enhancers regulate gene transcription by interacting with promoters, leading to increased gene expression. Variations in enhancer regions alter the binding pathways of transcriptional activators, thereby influencing gene expression. A recent study discovered a single nucleotide polymorphism (SNP) in an enhancer area that controls MYC, a cancer-causing gene linked to cell growth and energy processes. Elevated MYC levels are linked to the advanced progression of cancer. Single nucleotide polymorphism (SNP) interferes with the enhancer's communication with MYC's promoter, causing elevated activation of cancer-causing genes and supporting the development and maintenance of tumors (14, 15).ntranslated Region (UTR) Polymorphisms It introduces variability in either the 3′ or 5′ UTRs of genes via splicing and, by that, regulates mRNA stability and translation efficiency. Variability in the 3' UTR disrupts the interaction between microRNAs and mRNA that can control gene expression via the inhibition of translation or degradation of mRNA. The PTEN polymorphism in the 3' UTR affects its interaction with miRNAs, which made this mRNA more stable and hence highly expressed at the protein level. Indeed, higher levels of PTEN expression, the result of UTR polymorphisms, oppose tumorigenesis, since this gene normally regulates cell growth and survival. On the other hand, SNPs decreasing PTEN expression could play a role in tumorigenesis(16).

4. Clinical Implications of Regulatory Polymorphisms in Ovarian Cancer

Understanding how polymorphisms affect gene expression is crucial for diagnosing, predicting, and treating ovarian cancer. Genetic variations that alter the levels of important genes associated with ovarian cancer may serve as biomarkers for early disease detection and predictors of disease outcome. Similarly, decreased BRCA1 expression resulting from differences in the promoter region could identify individuals at increased risk of ovarian cancer, allowing for more timely screening and intervention (18, 19).In addition, variations in genes related to the response to chemotherapy could help predict treatment effectiveness. An example is the association between variations in ERCC1, which is responsible for DNA repair, and different reactions to platinum-based chemotherapy. Individuals with genetic variations that decrease ERCC1 expression may experience a stronger response because of compromised DNA repair in cancer cells. On the other hand, individuals with genetic variations that enhance ERCC1 levels might exhibit greater resistance to treatments involving platinum because their tumor cells are better equipped to fix the DNA injuries from the medications. Discovering these genetic variations can help create personalized treatment plans and customize therapy based on the patient’s genetic makeup to enhance treatment success and minimize negative side effects (20, 21).

5. Decoding SNP Impact in Ovarian Cancer

Although there have been notable advancements in our understanding of the impact of polymorphisms on ovarian cancer, several obstacles remain. The functional outcomes of numerous SNPs identified in GWASs are uncertain, particularly in noncoding sections. Future research should focus on identifying the molecular mechanisms through which these variations control gene expression. This might require the use of a mix of bioinformatics methods, like eQTL analysis, along with experimental methods, such as reporter assays and ChIP, to study the impact of SNPs on transcriptional and post-transcriptional processes. Furthermore, ovarian cancer is a highly diverse illness, and the influence of variations on gene expression can differ among various subtypes. Further studies are necessary to investigate the impact of polymorphisms in various histological subtypes of ovarian cancer and assess the generalizability of findings across these subtypes. Moreover, combining polymorphism data with proteomics and metabolomics could offer broader insights into the role of genetic variations in ovarian cancer (20-22).

Discussion

Several studies confirm this observation and point out that gene alterations are central in the pathogenesis of hereditary breast and ovarian cancer syndromes. Other studies, however, have documented that not all variations within these genes similarly impact cancer risk and thus a further look at individual genetic variation is warranted (23).

The result is in concordance with findings by Naccarati et al. (2012) and De Souza et al. (2021), which functionally validated some TP53 polymorphisms with respect to the protein itself and, in this manner, features of tumor behavior and treatment outcome (24, 25). On the other hand, several studies reported conflicting results about the prognostic value of these SNPs; this may indicate a variability dependent on population genetics or tumor heterogeneity(26). That hypothesis has been validated by the large-scale GWASs identifying thousands of SNPs associated with increased risk for ovarian cancer(11, 12). With all these encouraging results, much remains to be worked out before their translation into clinical practice will be complete, especially as far as the ethical implications of genetic testing and its proper counseling are concerned. More and more, the field is yielding to precision oncology, and several studies have demonstrated that genetic profiling can help in guiding treatment decisions(25, 27). However, most of the literature lacks the translation with regard to how such findings make their way into standardized clinical protocols and thus necessitate further research to clearly set guidelines.

Conclusion

Genetic variations in regulatory regions of essential ovarian cancer genes have a critical impact on the regulation of gene expression and thus influence susceptibility to cancers, progression of the disease, and treatment outcomes. It has been observed that promoter, enhancer, and UTR polymorphisms have affected the expression of tumor suppressors, oncogenes, and genes involved in DNA repair, thus very strongly impacting on the etiology and therapy against cancer. Understanding the functional consequence of such polymorphisms may reveal novel biomarkers and therapeutic targets that would improve management by offering personalized approaches to ovarian cancer. Further polymorphism regulation mechanism research is required for continued advances in knowledge about ovarian cancer biology and improvement in outcomes for patients.

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