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A Meta-Analysis of Non-Coding Polymorphisms Linked to Pre-Cancerous Lesions and Cervical Cancer

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Abstract

Objectives: To investigate the risk of SNPs found in non-coding areas of genes linked to cervical cancer. Neity, as well as publishing bias and statistical significance as measured by the p-value.

Methods: To uncover literature containing the relationship between single nucleotide polymorphisms with cervical cancer, the PubMed database was extensively searched using text-mining tools. If case-control studies matched the selection criteria, they were examined for the meta-analysis until June 2020. Each case-control study's polymorphisms were examined for the existence of genotype data before being separated into groups based on precancerous and cancerous cervix situations. The odds ratio and 95% confidence intervals (CI) were used to explore the impact of polymorphisms using various genetic models (allele, dominant, recessive, heterozygous and homozygous). The p-value was also used to assess heterogeneity, publication bias, and statistical significance.

Results: The meta-analysis evaluated 120 studies covering 48 distinct non-coding SNPs with 37,123 cases and 39,641 control data. For 43, 8, and 11 SNPs, the genotype data was divided into Cancer, Precancer, and "Cancer + Precancer" groups. The meta-analysis found 21 and 1 SNPs to be significant in the Cancer and "Cancer + Precancer" categories, respectively. rs1143627 (IL1B), rs1800795 (IL6), rs1800871 (IL10), rs568408 (IL12A), rs3312227 (IL12B), rs2275913 (IL17A), rs5742909 (CTLA4), rs1800629 (TNF), and rs4646903 (CYP1A1) were discovered to increase risk of cervical cancer in at least three.

Conclusion: We identified potential non-coding SNPs corresponding to various cytokines like interleukins (ILs), tumour necrosis factor (TNF), interferon (IFN) and other immune related genes like toll like receptor (TLR), cytotoxic T-lymphocyte associated protein (CTLA) and matrix metalloproteinase (MMP), as significant with increased pooled OR in this meta-analysis pointing to risk association of the immune-related genes in cervical carcinogenesis.

Introduction

Cervical cancer is one of the most common gynaecological malignancies in the world. Infection with the human papillomavirus (HPV) has long been linked to an increased risk of cervical cancer. Certain genetic variables, however, have been shown to play a key role in cervical cancer susceptibility and development. Single nucleotide polymorphisms (SNPs) are an example of host genetic variables that have attracted a lot of attention in the last decade. SNPs are genetic markers utilised extensively in cancer research. Identifying SNPs that are strongly related with higher cancer risk or susceptibility is therefore diagnostically useful [1].

SNPs in the gene's coding area alter the amino acid sequence of the protein, which may lead to cancer development and has thus been widely studied. According to the research, there is a statistical association between polymorphisms found in non-coding areas of the gene and an increased risk of complex illnesses such as cancer [8]. However, the impacts of polymorphisms located in non-coding areas (i.e. introns, promoters, 3′ and 5′ termini, etc.) have received less attention because the actual mechanism of action is uncertain [2, 3].

Non-coding SNPs may also arise at transcription factor binding sites (TFBS) and disrupt their binding site, causing abnormalities in normal gene regulation systems and thereby contributing to cancer formation. As a result, polymorphisms found in non-coding areas and linked to cervical cancer risk need special consideration.

Materials and Method

Data collection

Using the R programming language, I searched PubMed for publications with the following keywords: "polymorphism", "single nucleotide polymorphism", "SNP", "cervical cancer", "cervical carcinoma". The search was restricted until June 2020, and the complete texts of the articles were retrieved for additional study. The following criteria were used to select publications for inclusion in this study: (a) the presence of a population-based case-control study; (b) the presence of a connection between non-coding SNPs and cervical cancer; (c) genotype and allele distribution data in the study; and (d) SNPs not located in HLA or miRNA areas [4].

Classification of study population based on the condition of cervical cells

Because the current study includes both carcinogenic and precancerous cervix disorders, papers relating to carcinoma in situ, invasive cervical cancer, cervical adenocarcinoma, cervix, or cervical cancer were classed under Cancer. While the articles with cervical intraepithelial neoplastic 1-3 were categorised as Precancerous, the articles with low grade and/or high grade squamous intraepithelial lesions were classified as Precancerous. In the situations where

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Received: 30-Jan-2023, Manuscript No. Ccoa-23-88243; **Editor assigned:** 02-Feb 2023, PreQc No. PQ-ccoa-23-88243; **Reviewed:** 16-Feb-2023, QC No Ccoa-23-88243; **Revised:** 21-Feb-2023, Manuscript No Ccoa-23-88243 (R); **Published:** 28-Feb-2023, DOI: 10.4172/2475-3173.1000146

Citation: Brahe T, Brahmagupta, Brand H (2023) A Meta-Analysis of Non-Coding Polymorphisms Linked to Pre-Cancerous Lesions and Cervical Cancer. Cervical Cancer, 8: 146.

the authors analysed the relationship of both cervical cancer and precancerous lesions and there was no apparent separation in the genotype data, it was put in the combined category "Cancer + Precancer" [5].

As a result, each RSID was classified into one of three categories based on case control data from the relevant literature. In addition, meta-analysis requires the availability of at least two or more population-based case-control studies with genotype data for each group separately (cancer, precancer, "cancer Plus precancer"). Using the criteria outlined above, 120 publications containing 48 non-coding SNPs were chosen for this investigation [6].

Materials used in the meta-analysis

The R programming language's "d metar," "meta," and "meta for" functions were utilised to do the meta-analysis. R was used to calculate OR, 95% CI, heterogeneity, statistical significance, and to generate forest and funnel plots.

Results

To find papers for meta-analysis, 2768 PMIDs were obtained from PubMed, together with their title, abstract, and year of publication. Papers were originally screened using the title and abstract to discover 1172 relevant papers. The entire texts of these publications were examined for the second stage of screening, and papers that did not match the inclusion requirements were eliminated (Supplementary Table S2). The remaining 146 papers with information on 67 RSIDs were examined, and studies with no representative for a genotype, i.e. containing 'zero cells,' were excluded [7].

Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the relationship between a large number of polymorphisms found in non-coding regions of genes and the risk of cervical cancer. Furthermore, the study is unusual in that we individually examined the risk of precancerous and cancerous abnormalities of the cervix with disease susceptibility [8-10].

Using a meta-analysis of a variety of population-based case-control studies, we discovered 21 distinct SNPs that are strongly related with cervical cancer. A heatmap was created to better understand the distribution of these SNPs across the five genetic models and to identify the polymorphisms that increase the risk of cervical cancer.

Genes associated with interleukin

Among the cytokines, interleukins are observed as most prominent with eight polymorphisms present on seven genes, namely IL6 (rs1800795), IL1B (rs1143627), IL10 (rs1800871), IL17A (rs2275913 and rs3748067), IL12B (rs3212227), IL12A (rs568408) and IL18 (rs187238) to be associated with an elevated risk of cervical cancer. The interleukin family is engaged in the body's numerous inflammatory and immunological responses through immune system regulation. They also activate additional pro-inflammatory genes and cytokines.

Additional genes

The CYP1A1 rs4646903 polymorphism has been researched in a wide range of populations throughout the world, including Indian, Korean, Japanese, Chinese, Mexican, Portuguese, German, and Malaysian. The meta-analysis of nine studies with 1684 cases and 1699 controls found that this polymorphism significantly increases the risk of cervical cancer in the allele, recessive, and homozygous models. According to the literature, this polymorphism causes a T3801C mutation in the 3'UTR region, which causes gene expression levels to shift in cervical cancer patients owing to the formation of a novel MspI restriction site, which raises the enzymatic levels of CYP1A1 when compared to the wild type.

Conclusion

Several scholars have studied the relationship between polymorphisms and cervical cancer risk throughout the years. These research, however, have been conducted in isolation. As a result, a meta-analysis was conducted to investigate the significance of non-coding SNPs in cervical cancer susceptibility. Attempts were attempted to separate the genetic data based on histologic subtypes and classify them as precancerous lesions, cancer, or a combination group. It allowed us to do meta-analyses for each of the cervix diseases independently. In the current study, 21 and 1 SNPs were shown to be significant in the Cancer and "Cancer + Precancer" categories, respectively.

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