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Short Communication

Promising candidate drug target genes for repurposing in cervical cancer: A bioinformatics-based approach

Nurfi Pratiwi[1,2], Aida J. Ulfah[1], Rachmadina Rachmadina[1], Lalu M. Irham[3,4], Arief R. Afief[5], Wirawan Adikusuma[6,7], Darmawi Darmawi[2,8], Rahmat A. Kemal[9], Ina F. Rangkuti[10] and Maya Savira[8,11*]

[1]Master Program in Biomedical Sciences, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia; [2]Department of Histology, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia; [3]Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia; [4]Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand; [5]Faculty of Pharmacy, Universitas YPIB Majalengka, Majalengka, Indonesia; [6]Department of Pharmacy, Universitas Muhammadiyah Mataram, Mataram, Indonesia; [7]Research Center for Computing, Research Organization for Electronics and Informatics, National Research and Innovation Agency (BRIN), Cibinong Science Center, Cibinong, Indonesia; [8]Graduate School in Biomedical Sciences, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia; [9]Department of Medical Biology, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia; [10]Department of Pathological Anatomy, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia; [11]Department of Microbiology, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia

*Corresponding author: mayasavira@lecturer.unri.ac.id

Abstract

Cervical cancer is the fourth most common cancer among women globally, and studies have shown that genetic variants play a significant role in its development. A variety of germline and somatic mutations are associated with cervical cancer. However, genomic data derived from these mutations have not been extensively utilized for the development of repurposed drugs for cervical cancer. The objective of this study was to identify novel potential drugs that could be repurposed for cervical cancer treatment through a bioinformatics approach. A comprehensive genomic and bioinformatics database integration strategy was employed to identify potential drug target genes for cervical cancer. Using the GWAS and PheWAS databases, a total of 232 genes associated with cervical cancer were identified. These pharmacological target genes were further refined by applying a biological threshold of six functional annotations. The drug target genes were then cross-referenced with cancer treatment candidates using the DrugBank database. Among the identified genes, *LTA*, *TNFRSF1A*, *PRKCZ*, *PDE4B*, and *PARP* were highlighted as promising targets for repurposed drugs. Notably, these five target genes overlapped with 12 drugs that could potentially be repurposed for cervical cancer treatment. Among these, talazoparib, a potent PARP inhibitor, emerged as a particularly promising candidate. Interestingly, talazoparib is currently being investigated for safety and tolerability in other cancers but has not yet been studied in the context of cervical cancer. Further clinical trials are necessary to validate this finding and explore its potential as a repurposed drug for cervical cancer.

Keywords: Cervical cancer, drug target genes, bioinformatic, drug candidate, PARP inhibitor

Introduction

Cervical cancer ranks fourth in terms of incidence and mortality among cancers in women worldwide [1]. As reported by the Global Cancer Observatory (GCO), there were 341,831 deaths

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related to cervical cancer and 614,127 new cases in 2022 [2]. In 37 countries, mainly situated in sub-Saharan Africa, South America, and Southeast Asia, cervical cancer is the primary cause of cancer-related deaths [1]. Based on the Indonesian Ministry of Health report, cervical cancer is the second most common gynecological cancer among women, with an incidence rate of 23.4 cases per 100,000 and a mortality rate of 13.9% [3]. Therefore, cervical cancer is a high-burden disease, especially in developing countries.

Cervical cancer risk is increased by repeated human papillomavirus (HPV) infection and co-infection with sexually transmitted diseases such as HIV, *Chlamydia trachomatis*, and herpes simplex virus type 2 (HSV2) [4]. In some people and certain HPV subtypes, the infection may continue, persist, and lead to more invasive disease progression. Repeated infections can result in the gradual worsening of cervical intraepithelial lesions due to the viral load, which damages the tissue composition at the site of viral integration [4]. This may cause the lesions from cervical intraepithelial neoplasia (CIN) 1 (low grade) to advance to stages 2 and 3 (CIN2; moderate grade and CIN3; high grade) or high-grade squamous intraepithelial lesions (HSIL) before developing into carcinoma in situ (CIS) [5]. This variation in susceptibility is due to the unknown role of genetic variables in host-viral carcinogenesis. HPV is known to cause premature cell division and proliferation, p53 inactivation, and host cell susceptibility to mutagenesis [6].

The management of early-stage cervical cancer has undergone a transformation in parallel with the heightened prevalence of the HPV vaccine and cervical cancer screening. In accordance with standard recommendations following a diagnosis of CIN1, patients should be monitored for disease progression [7]. Only persistent lesions should be treated with ablation or excision and this treatment should be continued for at least two years. This will help lower the disease's incidence and mortality [8]. However, there are few options available for individuals with invasive, advanced-stage, or recurrent cervical malignancies. Treatments for CIN2 and CIN3 include cryotherapy, thermoablation, loop electrosurgical excision procedure (LEEP) and cold knife conization (CKC) [9]. When the lesion is fully visible, covers no more than 75% of the ectocervix, and there is no suspicion of cervical cancer, cryotherapy may be an option. However, if the lesion extends into the endocervical canal or beyond the reach of the cryoprobe, the patient should undergo LEEP instead of cryotherapy, while CKC is not recommended in this see-and-treat approach [10,11]. Despite receiving treatment, some patients nevertheless endure unbearable pain and have low survival rates [12]. Additionally, the scientific findings regarding the patterns of interaction between the host and HPV malignancies are not beneficial to patients [11]. Furthermore, research indicates that creating new therapeutic drugs to treat cervical cancer ought to be given top priority [10,11].

Nowadays, genomic-based techniques, including bioinformatic-based approaches, have the potential to be employed for the development of novel treatments. The profusion of genomic data permits the formulation of hypotheses regarding the efficacy of medications employed for one illness indication when applied to other diseases. Furthermore, this avenue enables scientists to construct drugs with greater precision [13,14]. One of the most successful repurposed medications is metformin, which has been recommended for the treatment of diabetes in the United States since 1995. Its cytostatic activity was recently found and applied in the clinical trial for patients with epidermal growth factor receptor (EGFR) mutations in their lung adenocarcinomas and with the addition of metformin, progression-free survival (PFS) increased by 30% and overall survival increased by almost 100% [13].

The aim of this study was to analyze and prioritize the most crucial biological risk genes for cervical cancer, employing a meticulous functional annotation scoring system to establish a robust bioinformatics methodology. In addition, we identified potential drug target genes for cervical cancer therapy by integrating biological risk genes into the analysis.

Methods

Prioritizing genetic variants linked to cervical cancer susceptibility

On May 6, 2023, the Genome-Wide Association Studies (GWAS) Catalogue (https://www.ebi.ac.uk/gwas) [15] and the Phenome-Wide Association Studies Catalogue (https://phewascatalog.org/phewas) [16] were utilized to identify single nucleotide

polymorphisms (SNPs)—variations in a single nucleotide at a specific genomic position—that may influence an individual's susceptibility to diseases or traits associated with cervical cancer. GWAS analyzed hundreds of thousands of genetic variants to identify statistically significant associations with cervical cancer. However, GWAS was limited in scope to specific phenotype domains. To complement this, PheWAS was employed to explore pleiotropic associations, where a single genetic variant influenced multiple health conditions. This approach provides deeper insights into the biological mechanisms underlying cervical cancer and enhances the potential for clinical discoveries, including drug development. By identifying novel SNP-phenotype associations and links between single genetic variants and multiple phenotypes, PheWAS also aids in detecting potential side effects of therapeutic interventions [17,18].

Using GWAS, we identified genetic markers associated with susceptibility to cervical cancer. Concurrently, PheWAS allowed us to examine the influence of phenotypes on genetic traits and disease variants. These combined methods significantly advanced our understanding of the genetic underpinnings of cervical cancer.

For this study, the term "cervical cancer" was used as a keyword to search both databases for relevant traits. The resulting data were downloaded and analyzed to generate a comprehensive list of genetic variations associated with cancer susceptibility, providing a robust foundation for further research.

Prioritization of genes involved in cervical cancer

Following the identification of genetic variants through the use of GWAS and PheWAS methodologies, functional annotation was conducted using the HaploReg v4.1 platform (Broad Institute, Massachusetts, USA). This is a web-based application that integrates information from a range of genetic and epigenetic databases with the aim of providing insight into the role of genetic variants in gene regulation and their potential influence on genetic function [20]. HaploReg application was used to analyze how genetic variants affected regulatory elements near genes involved in immune response or cervical cancer, how they affected the expression of genes that play a role in the mechanism of CC, and how they influence the epigenome. The aim was to obtain a list of genes that were potentially involved in the occurrence of cervical cancer.

Prioritization of biological risk genes for cervical cancer

The use of multiple functional annotations is essential for achieving a comprehensive understanding of gene or protein function. This approach minimizes uncertainty, enhances confidence in the interpretation of research findings, and enables researchers to explore various functional aspects of the same target [21]. To obtain more conclusive results, this study employed six functional annotations: (1) missense mutations; (2) Cis-expression quantitative trait locus (Cis-eQTL); (3) protein-protein interactions (PPI); (4) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways; (5) primary immunodeficiency (PID); and (6) somatic mutations. Each gene was assigned a single point to meet any one of these annotations. Genes satisfying two or more criteria were considered strongly associated with the development of cervical cancer and were prioritized for further investigation.

Initially, variants were mapped to genes exhibiting missense or nonsense mutations, which represent non-synonymous changes resulting from single base substitutions leading to altered amino acid sequences in proteins. This annotation was integrated with knowledge of the functional effects of these variants on protein expression. Missense and nonsense variations were considered critical due to their potential impact on protein function. According to HaploReg version 4.1, SNPs associated with missense mutations were annotated to their corresponding genes.

Cis-eQTLs, which are genomic regions harboring nucleotides correlated with changes in gene expression, were also analyzed. Variants identified as influencing gene expression in relevant tissues—whole blood and cervix in this study—were prioritized. For instance, if a variant upregulates gene X, thereby increasing disease risk, inhibitors of its protein product may represent potential drug candidates. Cis-eQTL analysis was employed to assess the functional impact of these variants on protein expression in the context of cervical cancer [22,23].

PPI analysis was used to explore the connections between disease pathogenesis and biological protein networks. Genes involved in these networks and linked to cervical cancer

pathophysiology were identified as potential therapeutic targets. By evaluating the contribution of associated protein networks, PPI provided insights into the molecular mechanisms of cervical cancer. Statistically significant results were defined as those with a false discovery rate (FDR) *q*-value below 0.05.

Pathway enrichment analysis was conducted using the KEGG, and genes with FDR *q*-values less than 0.05 were considered significant [24]. Additionally, genes implicated in primary immunodeficiency (PID), an inherited immune disorder associated with cancer, were evaluated. Genes shared between PID and cancer were identified as causal contributors to cervical cancer pathogenesis. This analysis emphasized the importance of exploring PID-related genes as potential targets for therapeutic intervention in cervical cancer [25].

Somatic mutations were also analyzed as contributors to cancer development [26,27]. The STRING database (http://string-db.org/) was used to extend the analysis by identifying and evaluating functional relationships between proteins. STRING integrates information on predicted protein-protein interactions from multiple sources, enabling a broader understanding of cervical cancer risk genes and their biological roles.

Prioritization of cervical cancer drug targets

In the next step of our process, we utilized the mapping between biological CC risk genes and the DrugBank database (https://go.drugbank.com/) to identify potential CC drug candidates. The DrugBank database provides drug and gene target information to the clinical medicine community as a bioinformatics and cheminformatics resource for drug research [28]. A multitude of factors were utilized for querying data sets, encompassing pharmacological activity, human efficacy, clinical trials, and experimental drugs. The question of whether each medication is being studied clinically for CC or other illnesses was then verified. ClinicalTrial.gov (https://clinicaltrials.gov/) was used for this verification. Furthermore, PubMed (https://pubmed.ncbi.nlm.nih.gov/) was used to identify medications undertaking preclinical investigations (in vitro and in vivo). The systematic workflow for utilizing genomic information to identify cervical cancer susceptibility genes and drug targets is depicted in **Figure 1**.

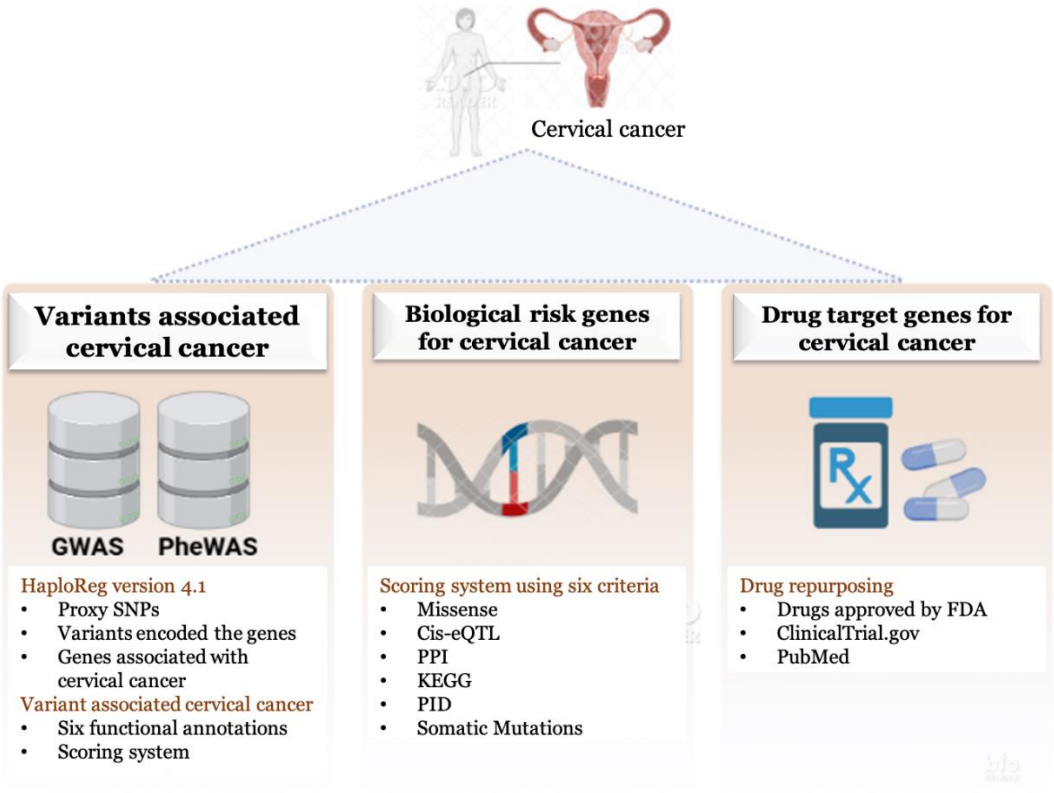

Figure 1. Flow study of utilizing genomic information to be repurposed for cervical cancer.

Results

Identification of genetic variations linked to cervical cancer susceptibility

A total of 232 variations were identified as being linked to cervical cancer susceptibility through the GWAS and PheWAS analysis. The SNPs were then expanded using the proxy SNPs that had the best r^2 value (>0.8) according to HaploReg version 4.1. After combining the genomic variants of the SNPs, we found 77 genes linked to cervical cancer (**Underlying data**). We then used functional annotation criteria to rank these genes.

Identification of genes related to cervical cancer

The variants were mapped to the corresponding genes using the six functional annotations described earlier. In order to achieve non-identical changes in single base changes of various types of amino acids in the final protein, missense mutation was used in this process. This stage detected missense mutations in a total of 14 genes. With the knowledge that protein expression may be impacted by the functional principles governing protein variation, particular annotations were subsequently used.

The present study identified 18 genes with cis-eQTL, eight genes with PPI, six genes with KEGG, two genes with PID, and 60 genes with somatic mutations (**Figure 2**). It should be noted that somatic mutations had the highest number of genes identified among functional annotations. This suggested that the identified genes were associated with somatic mutations in cervical cancer. The correlation between somatic mutations and the clinicopathological characteristics of cervical cancer at all stages has been documented in a substantial number of research [29].

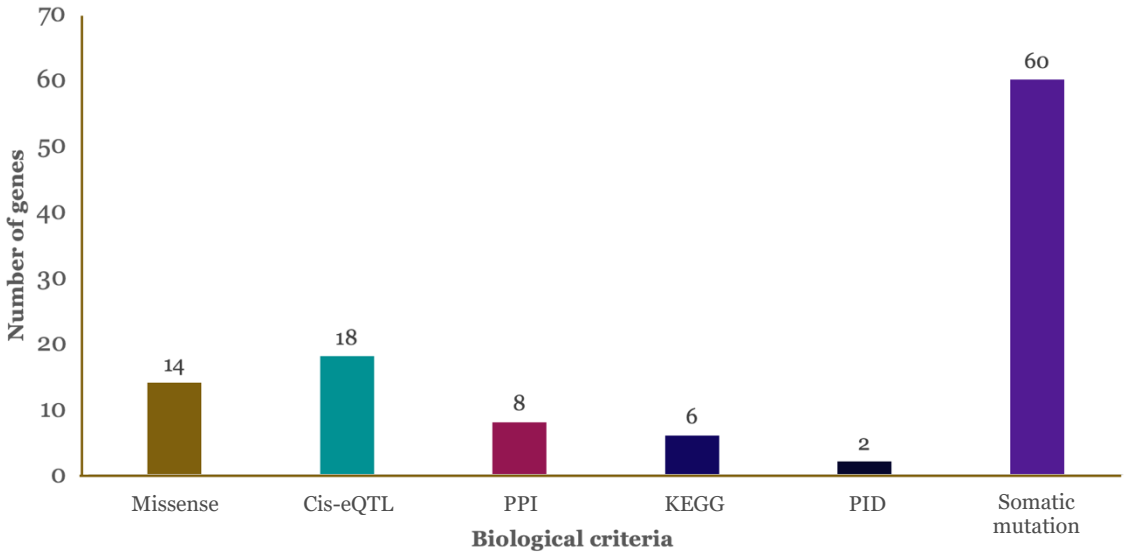

Figure 2. Summary of distribution of functional annotations to identify the genes related to cervical cancer. Our result identified missense mutations in a total of 14 genes, 18 genes with cis-expression Quantitative Trait Loci (cis-eQTL), eight genes with protein-protein interaction (PPI), six genes with Kyoto Encyclopedia of genes and genomes (KEGG), two genes with primary immunodeficiency (PID), and 60 genes with somatic mutations.

Biological risk gene identification for the development of cervical cancer

Our study's findings showed that when the biological score criterion increased, the number of biological genes that could be identified decreased. As a result, there were fewer pharmacological targets available for observation.

Based on six functional annotations, scores were added to the 77 genes linked to cervical cancer that had previously been found. A gene was assigned a single score if it met one of the six biological requirements. In this investigation, we were able to identify 48 genes with a total score of 1, 8 genes with a total score of 2, 9 genes with a total score of 3, 3 genes with a total score of 4 and 1 gene with a total score of 5. The distribution of scores for each criterion is presented in **Figure 3**.

We used 21 genes associated with a higher risk of cervical cancer (**Table 1**), each of which had at least two functional annotations based on biological criteria. We then extended these 21 genes using a STRING database to identify additional therapeutic target genes. Consequently, we were able to extract 71 drug-target genes from the expansion of the 21 cervical cancer risk genes.

Table 1. Six functional annotations applied to prioritize the cervical cancer risk genes

Gene name	Missense	Cis-eQTL[a]	PPI[b]	KEGG[c]	PID[d]	Somatic mutation	Total score
HLA-DPB1	1	1	1	1	0	1	5
BAG6	1	1	1	0	0	1	4
ELF1	1	1	1	0	0	1	4
HLA-B	1	1	0	1	0	1	4
CDC42	0	0	1	0	1	1	3
HLA-G	0	0	1	1	0	1	3
CCHCR1	1	1	0	0	0	1	3
GSDMB	1	1	0	0	0	1	3
HLA-DQA1	0	1	0	1	0	1	3
HLA-DQA2	0	1	1	1	0	0	3
MICB	1	1	1	0	0	0	3
PRRC2A	1	1	0	0	0	1	3
ZPBP2	1	1	0	0	0	1	3
MECOM	0	0	0	0	1	1	2
PARP2	1	0	0	0	0	1	2
PDE4B	0	0	1	0	0	1	2
ATXN7L1	0	1	0	0	0	1	2
FCRL4	0	1	0	0	0	1	2
LTA	0	1	0	1	0	0	2
MICA	1	1	0	0	0	0	2
ZKSCAN3	0	1	0	0	0	1	2

ATXN7L1: Ataxin 7 Like 1; *BAG6*: BAG Cochaperone 6; *CCHCR1*: coiled-coil alpha-helical rod protein 1; *CDC42*: cell division cycle 42; *ELF1*: E74 like ETS transcription factor 1; *FCRL4*: Fc receptor-like protein 4; *GSDMB*: Gasdermin B; *HLA-B*: major histocompatibility complex, class I, B; *HLA-DPB1*: major histocompatibility complex, class II, DP beta 1; *HLA-DQA1*: major histocompatibility complex, class II, DQ alpha 1; *HLA-DQA2*: major histocompatibility complex, class II, DQ alpha 2; *HLA-G*: major histocompatibility complex, class I, G; *LTA*: lymphotoxin alpha; *MECOM*: MDS1 and EVI1 complex locus; *MICA*: MHC class I polypeptide-related sequence A; *MICB*: MHC class I polypeptide-related sequence B; *PARP2*: poly(ADP-ribose) polymerase 2; *PDE4B*: phosphodiesterase 4B; *PRRC2A*: proline rich coiled-coil 2A; *ZKSCAN3*: zinc finger with KRAB and SCAN domains 3; *ZPBP2*: zona pellucida binding protein 2
[a]Cis-eQTL: cis-Expression Quantitative Trait Loci
[b]PPI: protein-protein interaction
[c]KEGG: Kyoto Encyclopedia of genes and genomes
[d]PID: primary immunodeficiency

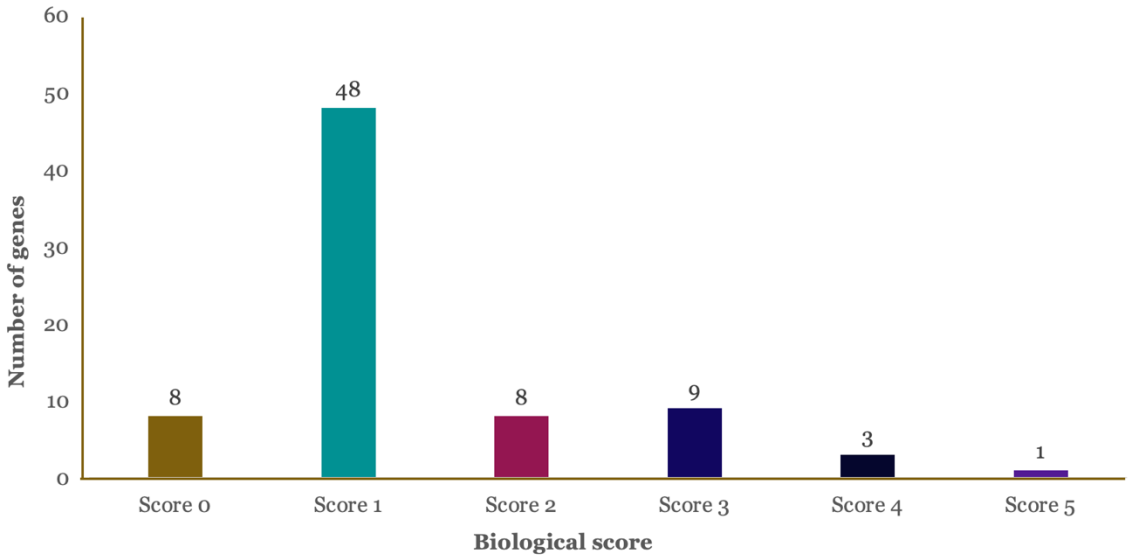

Figure 3. Histogram distribution of gene scores. Out of the total genes, there are 21 genes with total biological scores ≥2 and are identified as “cervical cancer risk genes”.

Potential drugs that could be repurposed for the treatment of cervical cancer identification

Using the DrugBank database, a comparison was made between the drug-targeted genes and the cervical cancer therapeutic candidates. Unfortunately, not every gene we discovered as a drug target has a pharmacological application. Thus, the genes may not be recognized as drug targets (unsuitable for drugs).

Only five biological risk genes for cervical cancer were found to be linked to genes that were targeted by drugs, according to the Drugbank database. These five drug-targeted genes were found to overlap with 12 potential drugs for cervical cancer that had been genetically predicted to be administered as drugs (**Table 2**). As promising proposed cervical cancer targets, we highlighted two genes: protein kinase C zeta (*PRKCZ*) gene and poly(ADP-ribosyl)transferase-like 2 protein (*PARP2*) gene.

Table 2. List of biological risk genes for cervical cancer which found to be linked to genes that were targeted by drugs according to the Drugbank database

Biological risk gene	Drug
Lymphotoxin alpha (*LTA*)	Etanercept
Tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*)	Tasonermin
Protein kinase C zeta (*PRKC*)	Tamoxifen
Phosphodiesterase 4B (*PDE4B*)	Theophylline
PDE4B	Dyphylline
PDE4B	Enprofylline
PDE4B	Papaverine
PDE4B	Amrinone
Poly(ADP-ribose) polymerase 2 (*PARP2*)	Olaparib
PARP2	Talazoparib
PARP2	Niraparib
PARP2	Rucaparib

There are currently four drugs in clinical trials that target potential genes for cervical cancer. These include tamoxifen, rucaparib, niraparib, and olaparib, whose drug targets are *PRKCZ* and *PARP2* (**Figure 4**). In this study, we found that talazoparib was the novel candidate drug for the repurposing of cervical cancer among others. Talazoparib has one drug target gene, *PARP2*. It has a score of 2 for functional annotation of cervical cancer risk genes (**Figure 5**).

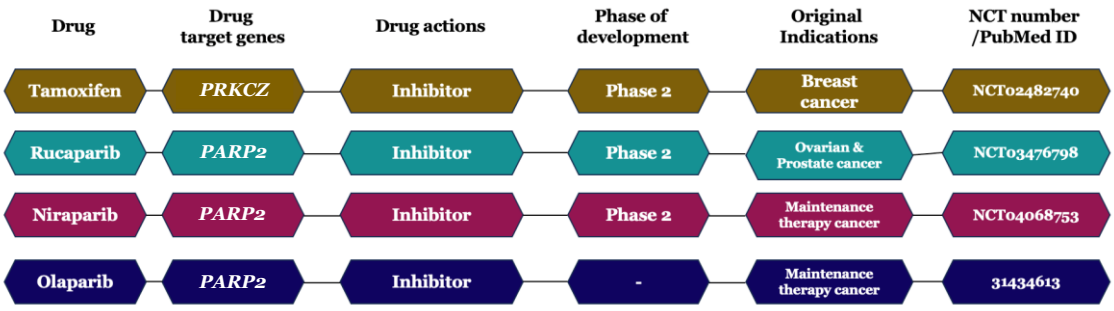

Figure 4. Summary of ongoing cervical cancer pharmacologic therapies development.

Figure 5. Summary of genomics-based approach identifies a drug repurposing candidate for cervical cancer. The diagram shows the target gene, drug action and the total of biological score.

Discussion

Cervical cancer remains a significant public health challenge, particularly in developing countries. Despite well-established screening and immunization programs, the incidence and mortality

rates remain unacceptably high. Cervical cancer, predominantly caused by persistent infection with human papillomavirus (HPV), is largely preventable. However, patients with metastatic, persistent, or recurrent disease that is not amenable to curative therapies have a poor prognosis. Currently, the primary treatment option for these patients is cisplatin combined with bevacizumab [30]. These therapies are associated with side effects and low patient compliance due to adverse drug reactions. This study was conducted to propose novel drug repurposing strategies to offer more effective therapeutic alternatives, especially given the limited availability of novel clinical treatments for cervical cancer.

In this study, we prioritized cervical cancer-associated genes to explore their potential for drug repurposing in cervical cancer treatment. Our hypothesis was that prioritizing genetic variations in cervical cancer using six functional annotations would enhance the understanding of risk genes involved in cervical cancer pathogenesis. Since there are several benefits of drug repurposing, this study holds a significant interest. The pharmacological activity, pharmacokinetic properties, metabolic pathways, and toxicity profiles of the drug candidates under consideration for repurposing can also be assessed [31].

Six functional annotations were utilized to prioritize genes associated with cervical cancer: Missense, Cis-eQTL, PPI, KEGG, PID, and Somatic mutation. Each gene was assigned an additional score of 1 for possessing any of these functional annotations. Through this prioritization, *HLA-DPB1* emerged as the only gene with five distinct functional annotations, strongly suggesting its significant association with an elevated risk of cervical cancer. As such, *HLA-DPB1* can be considered a predictive biomarker for cervical cancer. Nevertheless, while a high annotation score indicates relevance to cervical cancer, not all prioritized genes exhibit a clear pharmacological action [31,32]. To address this, further validation via DrugBank was conducted to determine whether these genes serve as drug targets. This verification process identified 12 potential repurposed drugs that overlap with five key target genes: *LTA*, *TNFRSF1A*, *PRKCZ*, *PDE4B*, and *PARP2*.

HPV infection in the cervix is characterized by persistent inflammation, which triggers extensive immune responses, including phagocytosis, cellular immunity, and the release of a multitude of inflammatory cytokines. Recent studies indicate that cervical lesions express tumor necrosis factor-alpha (TNF-α) [33,34]. Another significant member of the tumor necrosis factor (TNF) ligand family, *LTA*, also plays a key role in immunological and inflammatory reactions. Both *LTA* and *TNF-α* genes are located within the major histocompatibility complex on chromosome 6p21.3, situated between the HLA class I and II regions. Due to the presence of biologically significant SNPs, both *TNF-α* and *LTA* are critical in cancer development. These genes influence all stages of cancer progression, with the potential to either promote or suppress tumorigenesis [35,36]. Previous studies have highlighted that the function of *LTA* can vary depending on the patient's condition. Often classified as an immune-related gene (IRG), *LTA* is most recognized for its association with the regulation of cervical and endometrial cancer [36]. It has also been identified as a tumor marker useful for assessing breast cancer prognosis [37]. Interestingly, a study on stomach cancer found a correlation between *LTA* genetic variations and the incidence of gastric cancer [38]. However, the available evidence is currently insufficient to provide a comprehensive understanding of this gene's role in cancer. Further studies are warranted to elucidate its precise mechanisms and implications in various cancer types [36].

Tumor necrosis factor receptor 1 (*TNFR1*), also known as tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*), is a ubiquitous membrane receptor that interacts with TNF-α to mediate inflammation, tissue apoptosis, and/or necrosis, depending on the specific cell type involved, including in cases of HPV infection. A prior study demonstrated that *TNFR1* expression is upregulated in inflammatory stromal cells but downregulated in the cervical epithelium, which is the primary site of HPV-induced premalignant lesions [39]. This suggests that *TNFR1* could serve as a valuable biomarker for monitoring the progression of cervical precancerous lesions [39]. Tasonermin, a recombinant TNF-α therapy (DrugBank ID: DB11626), exerts its effects on the microvascular walls of tumors or cancerous lesions in a manner similar to endogenous TNF-α. However, the use of tasonermin is associated with several adverse effects, including hypotension, elevated liver enzyme levels, and hematologic abnormalities, such as anemia and variations in leukocyte and platelet counts. These side effects are dose- and duration-

dependent. Given these safety concerns, tasonermin is not recommended as an alternative therapy for cervical cancer.

Within the serine/threonine protein kinase C (PKC) family, *PRKCZ* represents an atypical subclass encoding proteins involved in regulating cellular transformation and carcinogenesis. *PRKCZ* contributes to cancer development by activating various signal transduction pathways, including the p70 ribosomal S6 kinase signaling cascade, the ERK/MAPK pathway, the NF-κB transcription factor, and cell polarity regulation. Loss of cell polarity, resulting in tissue disarray, is a key factor that may facilitate cancer progression. *PRKCZ* acts as a downstream mediator in the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway, which has been shown to drive cell migratory responses. This gene is also activated in epidermal growth factor (EGF)-induced chemotaxis, a process that has been explored in the context of lung and breast cancer. However, studies investigating *PRKCZ* in cervical cancer remain limited, underscoring the need for further research to determine its potential role in this malignancy [40].

Among the potential therapeutic targets for cervical cancer is the *PDE4B* gene, which encodes phosphodiesterases (PDEs) that specialize in the breakdown of cyclic nucleotides, such as cAMP and cGMP. By degrading these critical intracellular second messengers, PDEs modulate various cellular signaling pathways. Several studies have explored the role of *PDE4B* in various cancers, including hematologic, colon, and lung malignancies [41-44]. Furthermore, *PDE4B's* involvement has been investigated in endometrial, skin, prostate, liver, kidney, oral cavity, breast, and central nervous system cancers. In particular, *PDE4B* is implicated in the regulation of cell proliferation through cAMP signaling in malignant melanoma, and it has been associated with anti-apoptotic and metastatic effects in kidney and endometrial cancers. Two additional studies have highlighted that inhibition of *PDE4B* can exert growth-inhibitory effects in oral cancer cells and induce selective cytotoxicity in A549 lung cancer cells. While a study has also shown that *PDE4A* downregulation is linked to breast cancer, it is important to consider that different PDE4 subtypes may have distinct roles in hormonally driven malignancies. This distinction represents an intriguing avenue for further research [45].

Currently, four medications targeting potential cervical cancer genes are being investigated in clinical trials: rucaparib, niraparib, talazoparib, and olaparib. These drugs target *PARP2*, a member of the PARP superfamily of nuclear enzymes, which plays a crucial role in repairing single-stranded DNA breaks. Inhibition of PARP enzymes is expected to result in increased DNA damage accumulation, leading to enhanced cytotoxicity. This is particularly relevant in the context of ionizing radiation, which can damage both single- and double-stranded DNA. Beyond their use in radiation therapy, PARP inhibitors may also serve as radiosensitizers, improving the therapeutic ratio by shifting the tumor control probability curve to the left while minimizing side effects [46-49].

Among these inhibitors, talazoparib (also known as MDV3800 or BMN 673) stands out as a highly effective PARP inhibitor. It is distinguished by its best-in-class ability to trap PARP-DNA complexes in vitro and its reduced concentration requirements to elicit antitumor responses. A preclinical study found that talazoparib monotherapy exhibited strong anticancer activity and could sensitize various tumor types, including BRCA1-mutant MX-1 breast cancer xenografts, to radiation and chemotherapy [46]. Talazoparib was FDA-approved under the brand name Talzenna on October 16, 2018, for the treatment of germline BRCA-mutated, HER2-negative, locally advanced, or metastatic breast cancer [47-48]. Currently, a phase I clinical trial is ongoing to assess the safety, tolerability, and maximally tolerated dose of talazoparib in combination with radiation therapy for women with recurrent gynecologic cancers, including ovarian, primary peritoneal, fallopian tube, endometrial, vaginal, or cervical cancers (ClinicalTrials.gov ID: NCT03968406) [49]. Our bioinformatics analysis also indicates that talazoparib represents a promising drug repositioning target for cervical cancer.

This study has some limitations that need to be discussed. The utilization of GWAS and PheWAS data frequently depends on particular populations, which may restrict the scope for generalizing the findings. Variations in genetic background, environmental factors and lifestyle can affect the outcomes of the studies, potentially leading to biased or incomplete conclusions. Furthermore, numerous traits and diseases are influenced by multiple genetic variants, each

exerting a minor effect. This polygenic nature may complicate the identification of specific targets for drug repurposing.

Conclusion

This study identified potential biological cervical cancer risk genes and translated them into therapeutic implementation through pharmaceutical repurposing for cervical cancer caused by genetic variations. The significant genes identified were *PRKCZ* and *PARP2*, which are promising proposed target genes for cervical cancer. The *PRKCZ* and *PARP2* genes are targeted by five drugs that are now undergoing clinical studies: tamoxifen, rucaparib, niraparib, olaparib and talazoparib. Our bioinformatics research has confirmed that talazoparib is a highly potential drug repositioning target for cervical cancer.

Ethics approval

Not required.

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Competing interests

The authors of this work have all declared that they have no conflicts of interest.

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Underlying data

A detailed list of 77 genes linked to cervical cancer based on analysis is available here: DOI: https://dx.doi.org/10.6084/m9.figshare.27906420.

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