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Cervical cancer and XRCC1 gene polymorphisms

Câncer cervical e polimorfismos no gene XRCC1

Cáncer cervical y polimorfismos en el gen XRCC1

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ABSTRACT

Objective: To undertake a literature review on the development of cervical cancer, emphasizing epidemiological data, human papillomavirus (HPV) infection in carcinogenesis, and the role of the XRCC1 gene in DNA repair, in order to provide valuable information for the medical and scientific community. The goal is to provide a valuable resource for clinical practice. **Bibliographic Review:** Cervical cancer ranks as the fourth most common malignancy worldwide. Despite known environmental, behavioral, and genetic risk factors, their management remains inadequate. Persistent infection with oncogenic HPV is a well-established risk factor; however, not all infected individuals develop cervical cancer, suggesting the involvement of additional mechanisms. Among these, polymorphisms in the XRCC1 gene have gained attention. *XRCC1* encodes a scaffold protein essential for DNA repair coordination and cell cycle regulation. Three main *XRCC1* polymorphisms—Arg194Trp, Arg280His, and Arg399Gln—are associated with impaired DNA repair, genomic instability, and increased cervical cancer susceptibility. **Final Considerations:** A deeper understanding of the genetic and cellular mechanisms underlying cervical cancer may facilitate the development of targeted medical interventions for women, contributing to improved quality of life reduced mortality.

Keywords: Cervical cancer, *X-ray repair cross-complementing gene 1 (XRCC1)*, DNA, Cell cycle, Human papillomavirus (HPV).

RESUMO

Objetivo: Realizar uma revisão de literatura sobre o desenvolvimento do câncer cervical, enfatizando os dados epidemiológicos, a infecção pelo papilomavírus humano (HPV) na carcinogênese e o papel do gene XRCC1 no reparo do DNA, a fim de fornecer informações valiosas para a comunidade médica e científica. **Revisão Bibliográfica:** O câncer cervical é a quarta neoplasia maligna mais comum no mundo. Apesar dos fatores de risco ambientais, comportamentais e genéticos conhecidos, seu manejo ainda é inadequado. A infecção persistente por HPV oncogênico é um fator de risco bem estabelecido; no entanto, nem todos os indivíduos infectados desenvolvem câncer cervical, sugerindo a participação de mecanismos adicionais. Dentre esses, os polimorfismos no gene *XRCC1* têm ganhado destaque. O *XRCC1* codifica uma proteína estrutural essencial para a coordenação da reparação do DNA e regulação do ciclo celular. Três

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polimorfismos principais do *XRCC1*—Arg194Trp, Arg280His e Arg399Gln—estão associados à deficiência na reparação do DNA, instabilidade genômica e maior susceptibilidade ao câncer cervical. **Considerações Finais:** Um entendimento mais profundo dos mecanismos genéticos e celulares subjacentes ao câncer cervical pode facilitar o desenvolvimento de intervenções médicas direcionadas para as mulheres, contribuindo para a melhoria da qualidade de vida e redução da mortalidade.

Palavras-chave: Câncer cervical, Gene *de complementação cruzada de reparo por raios-X 1 (XRCC1),* DNA, Ciclo celular, Papilomavírus humano (HPV).

RESUMEN

Objetivo: Realizar una revisión de la literatura sobre el desarrollo del cáncer de cuello uterino, enfatizando los datos epidemiológicos, la infección por el virus del papiloma humano (VPH) en la carcinogénesis y el papel del gen XRCC1 en la reparación del ADN, con el fin de proporcionar información valiosa para la comunidad médica y científica. **Revisión Bibliográfica:** El cáncer cervical es la cuarta neoplasia maligna más común en el mundo. A pesar de los factores de riesgo ambientales, conductuales y genéticos conocidos, su manejo sigue siendo inadecuado. La infección persistente por VPH oncogénico es un factor de riesgo bien establecido; sin embargo, no todos los individuos infectados desarrollan cáncer cervical, lo que sugiere la participación de mecanismos adicionales. Entre estos, los polimorfismos en el gen XRCC1 han ganado atención. XRCC1 codifica una proteína estructural esencial para la coordinación de la reparación del ADN y la regulación del ciclo celular. Tres polimorfismos principales de XRCC1—Arg194Trp, Arg280His y Arg399Gln—se asocian con una reparación del ADN deficiente, inestabilidad genómica y mayor susceptibilidad al cáncer cervical. **Consideraciones Finales:** Una comprensión más profunda de los mecanismos genéticos y celulares subyacentes al cáncer cervical puede facilitar el desarrollo de intervenciones médicas dirigidas a las mujeres, contribuyendo a mejorar la calidad de vida y reducir la mortalidad.

Palabras clave: Cáncer cervical, Gen de *complementación cruzada de reparación por rayos X 1 (XRCC1),* ADN, Ciclo celular, Virus del papiloma humano (VPH).

INTRODUCTION

Cervical cancer, a preventable and treatable disease, still claims the lives of women every year. This malignancy progresses over decades from abnormal cellular changes to invasive cancer. However, in certain cases, including those influenced by risk factors (virus infection, immune system, smoking, diversity of sexual partners, prolonged use of oral contraceptives) this process can be accelerated (WHO,2024a; ACS.ORG, 2025).

A significant contributor to cervical cancer is persistent infection with high-risk human papillomavirus (HPV) types. While most HPV infections are transient and cleared by the immune system, certain oncogenic strains, such as HPV-16 and HPV-18, are responsible for approximately 70% of cases However, not all women exposed to HPV develop cervical cancer, suggesting that additional factors, including genetic predisposition, play a role in disease progression (WHO, 2024a, b).

One of those factors is the *X-ray repair cross-complementing group 1 (XRCC1)* gene, which encodes a crucial protein involved in DNA repair and cell cycle regulation. *XRCC1* plays a fundamental role in maintaining genomic stability by acting as a scaffold in the cell cycle and contributing to single-strand break repair (SSBR), base excision repair (BER), and, indirectly, nucleotide excision repair (NER), thereby ensuring the integrity of the genome during replication (LONDON RE, 2015).

Mutations in the *XRCC1* gene can compromise its function, leading to defective DNA repair mechanisms. As a result, cells with accumulated genetic damage may evade apoptosis and continue proliferating, increasing the risk of malignant transformation (YANG NN, et al., 2017; TAYLOR MR, et al., 2000).

Given the significant burden of cervical cancer, this narrative review explores its epidemiological aspects, the role of persistent HPV infection in carcinogenesis, and the function of the *XRCC1* gene in DNA repair and cell cycle regulation. Additionally, we examine the implications of XRCC1 mutations in the context of cervical cancer development, highlighting its potential as a key player in genomic stability and cancer prevention (WHO, 2024a, b; YANG NN, et al., 2017; LONDON RE, 2015; TAYLOR, MR., et al., 2000).

Thus, the objective of this literature review was to provide information on cervical cancer, the role of human papillomavirus (HPV) infection in carcinogenesis, and the function of the XRCC1 gene and the implications of its polymorphisms, in order to offer insights with the potential to contribute to the medical and scientific community.

BIBLIOGRAPHIC REVIEW

Epidemiology of Cervical Cancer

Cervical cancer is the fourth most common cancer among women, with around 670,000 new cases and 350,000 deaths worldwide in 2024. The highest incidence and mortality rates are found in low- and middle-income regions, particularly in sub-Saharan Africa, Central America, and Southeast Asia (GCO.ORG 2025; WHO, 2024a, b).

There is significant variation in cervical cancer across different countries, with incidence rates ranging from 2 to 84 cases per 100,000 women and mortality rates from 1 to 56 per 100,000 women (WHO, 2024a, b; NIH, 2025a). Younger women are excessively affected, with up to 20% of children losing their mothers to this disease. These differences are primarily due to unequal access to prevention programs, such as HPV vaccination, and differences in healthcare infrastructure and socioeconomic factors (WHO, 2024a, b; GUIDA F, et al., 2022).

HPV is responsible for over 90% of cervical cancer cases, with high-risk types such as 16 and 18 accounting for approximately 70% of these cases. Other high-risk types, including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66, also contribute to the disease. To eradicate cervical cancer, global strategies focus on HPV vaccination, cervical screening, and cancer treatment (NCI, 2025).

WHO aims, by 2030 to vaccinate 90% of girls by age 15, screen 70% of women aged 35-45, and treat 90% of those with positive tests or cervical lesions, including palliative care. Some countries have extended vaccination to boys, reducing HPV prevalence and preventing HPV-related cancers in men (WHO, 2024a, b).

WHO seeks to reduce cervical cancer incidence to fewer than 4 cases per 100,000 women-years globally. Achieving this goal requires early diagnosis through screening and vaccination, integrated into national public health strategies (GUIDA F, 2022; WHO, 2024a).

Human Papillomavirus (HPV)

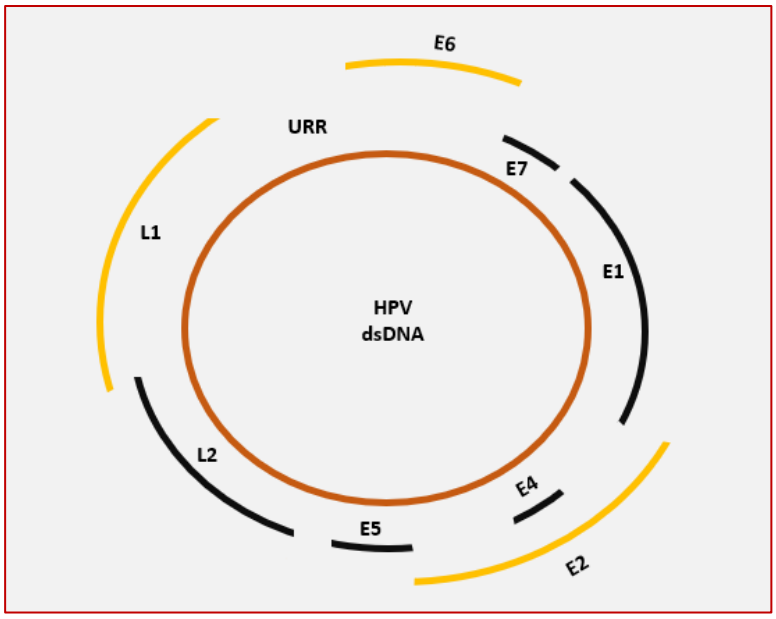
Human Papillomavirus (HPV) is a non-enveloped virus with a small size, approximately 60 nm in diameter. Its icosahedral capsid is composed of 60 asymmetric units, made up of seven proteins (T=7), resulting in a total of 420 capsid proteins. These capsids exhibit skewed symmetry, which leads to their classification as either right-handed (dextrorotatory) or left-handed (levorotatory) (E VZ.ORG, 2024).

The viral genome consists of circular double-stranded DNA, although only one strand is transcribed. This results in the production of two classes of proteins. The early non-structural regulatory proteins (E1-E7) are responsible for controlling viral replication and transcription, while the late structural proteins (L1 and L2) form the viral capsid. Both classes of proteins are expressed through an alternative splicing mechanism, which enables the encoding of multiple proteins from a limited number of messenger Ribonucleic Acid (mRNA) molecules. Additionally, HPV possesses Untranslated Regions (UTRs) that regulate viral gene expression, with the 5' UTR influencing transcription and the 3' UTR playing a key role in mRNA stability (NELSON CW and MIRABELLO L, 2023).

HPV replication occurs in two distinct stages—plasmid and vegetative—corresponding to the differentiation state of the host epithelial cells. Plasmid replication occurs in the basal cells of the squamous epithelium, where viral DNA replicates in sync with the host cell chromosome, ensuring at least one copy of the viral genome per cell. First, viral proteins bind to host cell receptors, mediating endocytosis via vesicles. Afterward, the viral DNA is transported to the nucleus, where it undergoes uncoating. This is followed by the transcription and translation of early proteins (E1-E7). At this point**,** viral DNA replication occurs in the nucleus, primarily requiring the activity of the E1 and E2 proteins. Vegetative replication takes place in differentiated epithelial cells, the keratinocytes, which no longer undergo cellular DNA synthesis. In this phase, viral DNA synthesis increases significantly, leading to the active production of virions. The transcription of the late region (L1 and L2) of the viral genome enables capsid protein synthesis. Finally, viral capsids assemble in the nucleus, and infectious particles are released (E VZ.ORG, 2024).

The oncogenic potential of HPV arises from its interaction with the host genome. While low-risk HPVs retain their genetic material intact within the host cell, high-risk HPVs, through non-specific recombination, integrate their genome into the host's chromosome. This integration inactivates the virus but can enhance the host cell's replicative capacity, disrupting cell cycle regulation and driving cancer progression (NELSON CW and MIRABELLO L, 2023; E VZ.ORG, 2024) **(Figure 1)**.

Figure 1 - Genomic Organization of the Human Papillomavirus (HPV) double strand DNA (dsDNA).



Note: Image constructed using PowerPoint software. **Legend:** Schematic representation of the HPV double-stranded DNA genome. The early proteins (E1, E2, E4, E5, E6, and E7) are involved in viral replication, transcription regulation, and oncogenic transformation, with E6 and E7 playing key roles in disrupting tumor suppressor pathways. The late proteins (L1 and L2) form the viral capsid, essential for virion assembly and infection. The upstream regulatory region (URR) reasonable for viral gene expression. **Source:** Alcântara AMAC, et al., 2025. **Based on:** E VZ.ORG (2024); Nelson CW and Mirabello L (2023); NCI (2025).

Cervical cancer and HPV

Cervical cancer arises from the cells of the cervix, which connects the uterus to the vagina. The process begins with dysplastic cells—atypical cells in the cervical epithelium—that, if left untreated, can transform into neoplastic cells, leading to their invasion into deeper cervical layers and surrounding tissues (NCI, 2023).

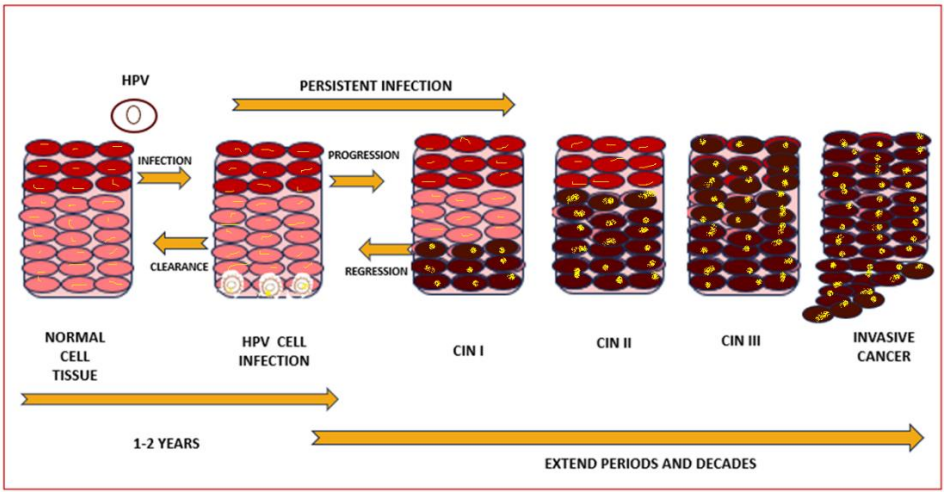
The cervix is cylindrical and divided into two regions: the ectocervix, lined by thin, flat Squamous Epithelial Cells (SEC); and the endocervix, composed of Columnar Glandular Cells (CGC) responsible for

mucus secretion. Cervical cancer is classified based on its cellular origin, primarily as squamous cell carcinoma or adenocarcinoma. Squamous cell carcinoma, the most common type of cervical cancer, arises from the squamous epithelial cells (SEC); adenocarcinoma originating from the glandular columnar cells (CGC), is a less common variant. Aden squamous carcinoma combines features of both types. In rare cases, malignancies can also develop from other cervical cellular components (NCI, 2025; US NLM, 2021).

The connection between the CGC and SEC of the cervix is referred to as the squamocolumnar junction (SCJ). Depending on the woman's life stage and hormonal status, the SCJ can occur in both the exocervix and endocervix. In addition to the SCJ, the transformation zone (TZ) is a critical cervical area. TZ area is where squamous metaplasia (CGC being replaced by SEC) occurs, between the original SCJ and the SCJ after metaplasia (US NLM, 2021).

Although metaplasia is a physiological and benign process, HPV infection in these areas increases the risk of oncogenic alterations, including Cervical Intraepithelial Neoplasia (CIN I, II and II) and cancer. CIN I involves cellular changes in the lower third of the epithelium, CIN II affects up to two-thirds, CIN III encompasses the full epithelial thickness, and cervical cancer progresses beyond CIN III, invading the basal membrane or underlying connective tissue (NCI, 2025) **(Figure 2).**

Figure 2 - Progression of HPV Infection to Carcinogenesis.



Note: Image constructed using PowerPoint software. **Legend:** Cancer progression follows a timeline: initial HPV infection - CIN I development within one to two years - invasive cancer extended within decades. Initially, normal epithelial cells become infected by HPV, leading to a transient infection that may be cleared by the immune system. Next, CIN I affects the lower one-third of the epithelial layer. After, CIN II extends to the lower two-thirds of the epithelium. Then, CIN III involves the full thickness of the epithelium (three-thirds) but has not yet breached the basement membrane, meaning it remains a precancerous condition. Finally, the malignant transformation, where cancerous cells spread beyond the epithelial layer into surrounding tissues. **Source:** Alcântara AMACA et al., 2025**. Based on**: NIH (2023); NCI (2025); US NLM (2021).

Nevertheless, it is crucial to underscore that, while infection with high-risk-HPV is documented risk factor in tumorigenesis, many HPV carriers do not develop cervical cancer, thereby suggesting the presence of additional risk factors, including genetic variants, which represent the most prevalent primary determinant. One significant genetic variant that has been extensively investigated as correlated with different types of cancer, and specifically with cervical cancer is polymorphisms in the XRCC1 gene (YANG NN, et al.,2017; ZHAO DY, et al., 2014).

XRCC1 Gene

The *XRCC1* gene encodes a protein of the same name, XRCC1. This gene is located on chromosome 19q13.31 in the human genome, spanning approximately 31,775 base pairs and comprising 17 exons, which contribute to the synthesis of its associated protein (GC.ORG, 2024a).

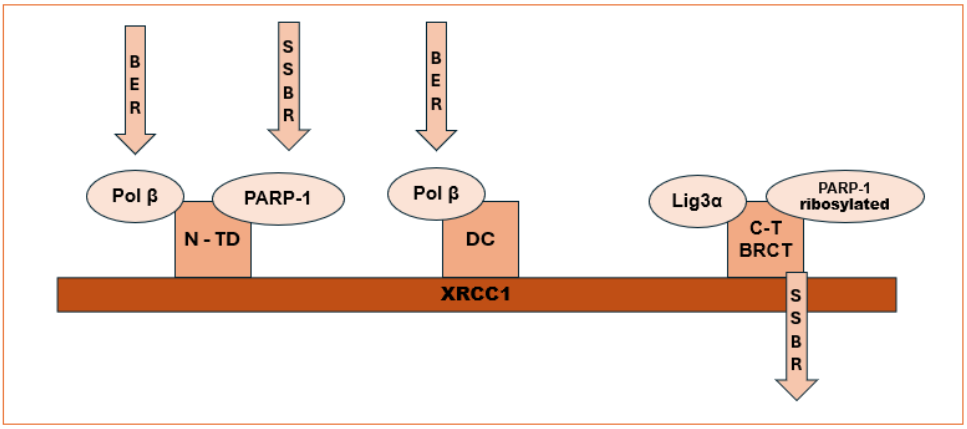
Structurally, the XRCC1 protein consists of three globular domains: the N-terminal Domain (N-TD), the Central Domain (CD), and the C-terminal (BRCT) Domain. Additionally, it contains two Extended Interdomain Linkers (EIL-1 and EIL-2) (LONDON RE, 2017; TAYLOR MR, et al., 2000).

N-TD: Crucial for recognizing and binding to DNA damage sites. This domain interacts with enzymes such as poly (ADP-ribose) polymerase 1 (PARP1), involved in single-strand break repair (SSBR). Additionally, the N-terminal domain (X1NTD) binds to DNA polymerase β (pol β), which plays a key role in base excision repair (BER) (CALDECOTT KW, et al., 1996; DAVIS M, et al., 2022).

C-D This domain encompasses a critical region required for the interaction with DNA (Pol β) during BER pathway. Furthermore, the central domain (X1BRCTa) harbors a poly (ADP-ribose) (PAR)-binding motif – enzymes that catalyze the transfer of ADP-ribose moieties to target proteins, playing a role in diverse cellular functions, including chromatin structure modulation, transcriptional regulation, DNA replication, recombination, and repair processes. The PAR-binding motif within XRCC1 facilitates its recruitment to polymeric ADP-ribose chains break sites (LONDON RE, 2015; GC. ORG, 2024a, b).

C-T BRCT is a highly involved in protein-protein interactions during the DNA damage response. In XRCC1, the C-T BRCT domain interacts with DNA ligase IIIα, enabling the final step of DNA strand ligation during repair processes, and with DNA Ligase3α (Lig3α), it is involved in excision repair (TAYLOR MR, et al., 2000) (**Figure 3**).

Figure 3 - Representation of XRCC1 protein Interactions.



Note: Image constructed using PowerPoint software. **Legend:** XRCC1 and its domains: N-TD, interacting with Pol β in BER and with PARP-1 in the SSBR pathway. DC, interacting with Pol β in BER, allowing Pol β to add nucleotides also in single-strand break (SSB) repair. CT-BRCT, XRCC1 interacts with Lig3α (which ligates DNA strands); interacts with ribosylated PARP-1, facilitating the recruitment of other proteins, and enables XRCC1 to repair SSBs in its region antagonistic to PARP-1 binding, while simultaneously maintaining its interaction. **Source:** Alcântara AMAC et al., 2025. **Based on:** Davis M, et al. (2022); London RE (2017); Taylor MR, et al. (2000).

The two Extended Interdomain linkers (EIL-1 and EIL-2) also contain functionally regions. EIL-1 contains a Nuclear Localization Sequence (NLS), which functions as a signal directing proteins from the cytoplasm to the nucleus. After reaching its target organelle, the NLS remains intact and can be found at various points within the protein sequence. Additionally, the NLS includes a Rev1-Interacting Region (RIR), which engages is involved in recruiting Translesion Polymerases (TPs) (CALDECOTTKW, 2023). These polymerases help resolve replication fork stalling caused by DNA damage, allowing DNA synthesis to continue. This process provides the cell with additional time to repair the damage before resuming normal replication (OHASHI Y, et al., 2009; DUROCHER D, et al., 1990).

Located just before XRCC1's C-terminal BRCTb domain, EIL-2 features a Per-Phosphorylated Motif (P-FM), which is recognized by kinases that add phosphate groups to the sequence. This phosphorylation regulates various cellular functions, including signal transduction, enzyme activity, and protein interactions.

Moreover, EIL-2 interacts with Fork-Head-Associated (FHA) domains of binding partners, playing a critical role in DNA remodeling, the regulation of DNA ligation, and the repair of double-strand breaks (LONDON RE, 2015).Here is a structured table categorizing the three domains of the XRCC1 protein, the enzymes they interact with, and the repair pathways involved (**Table 1**).

Table 1 - XRCC1 protein Domains and Functions.

Domain	Interacting Enzymes	Repair Pathways	References
N-Terminal Domain (N-TD)	Poly (ADP-ribose) polymerase 1 (PARP1), DNA polymerase β (Pol β)	Single-Strand Break Repair (SSBR), Base Excision Repair (BER)	CALDECOTT KW (1996)
Central Domain (CD)	Poly (ADP-ribose) (PAR)-binding motif, DNA polymerase β (Pol β)	Base Excision Repair (BER), Chromatin Structure Modulation, DNA Replication, Recombination, and Repair	MOK MCY, et al. (2019)
C-Terminal BRCT (C-T BRCT)	DNA ligase IIIα (Lig3α)	DNA Strand Ligation in Repair Pathways, Nucleotide Excision Repair (NER)	LONDON RE (2015)
Extended Interdomain Linkers (EIL-1 and EIL-2)			
Interdomain Linker	**Functional Regions**	**Functions**	**References**
EIL-1	Nuclear Localization Sequence (NLS), Rev1-Interacting Region (RIR)	Directs proteins from the cytoplasm to the nucleus; recruits Translesion Polymerases (TPs) for replication fork rescue	OHASHI Y, et al. (2009)
EIL-2	Per-Phosphorylated Motif (P-FM), Fork-Head-Associated (FHA) domain interactions	Regulates cellular functions via phosphorylation; facilitates DNA remodeling and double-strand break repair (DSBR)	DUROCHER D, et al. (1999)

Source: Alcântara AMAC, et al., 2025.

XRCC1 structure operates synergistically to detect, signal, and rectify DNA damage or facilitate cellular tolerance, ensuring the maintenance of genomic stability and the overall viability of the organism. This intricate network highlights the critical importance of DNA repair pathways in safeguarding cellular integrity against the constant threat of genetic damage (VASIL'EVA IA, et al., 2020).

DNA Repair Pathways and XRCC1 in Genomic Stability

To mitigate the detrimental effects of DNA damage, cells have evolved a repertoire of sophisticated defense mechanisms. Damage is often detected at specific cell cycle checkpoints, which provide time for repair and prevent the progression of cells harboring significant DNA lesions. DNA repair operates through six primary mechanisms: Base Excision Repair (BER), Nucleotide Excision Repair (NER), Single-Strand Break Repair (SSBR), Direct Reverse Repair (DRR), Double-Strand Break Repair (DSBR), and Mismatch Repair (MMR) (GC. ORG, 2024a; TAMANG S, 2023). Below is a summary outlining six major DNA repair mechanisms (**Table 2**).

Table 2 - Six Primary DNA Repair Pathways - Mechanisms and Associated Damage.

Repair Pathway	Mechanism	Damage	References
Direct Reversal Repair (DRR)	Fixes DNA damage without the need for excision or replacement.	UV-induced lesions and alkylated bases.	SMITH J, et al. (2024)
Base Excision Repair (BER)	Recognizes, removes, and replaces damaged bases, through the action of DNA glycosylases.	Uracil-containing DNA.	LEE A, et al. (2023)
Nucleotide Excision Repair (NER)	Removes a fragment of nucleotides containing the damaged lesion and synthesizes a new DNA strand. Consists of two pathways: Global Genome NER (GG-NER) and Transcription-Coupled NER (TC-NER).	Bulky adducts and cross-linking lesions caused by UV radiation or chemical exposure.	JONHSON P, et al. (2024)
Mismatch Repair (MMR)	Involves recognition of mismatches, degradation of the error-containing strand, and synthesis of the correct DNA sequence.	Base mismatches and insertion-deletion loops that occur during replication.	BROWN R, at al. (2023)
Single-Strand Break Repair (SSBR)	Accomplished through various pathways, including BER, NER, and MMR.	Due to oxidative damage, abasic sites, or DNA topoisomerase enzyme activity errors. Exposure to radiation, chemicals, or errors during DNA replication.	DAVIS M, et al. (2022)
Double-Strand Break Repair (DSBR)	DNA can be repaired through two pathways: homologous recombination (HR), which is most active during the S, G2, and M phases of the cell cycle; and non-homologous end joining (NHEJ).	Unsealed broken ends of DNA.	WILSON G, et al. (2023)

Source: Alcântara AMAC, et al., 2025.

Among the six repair pathways presented in the table, XRCC1 protein plays a crucial role about three: Single-Strand Break Repair (SSBR), Base Excision Repair (BER), and Nucleotide Excision Repair (NER). These pathways rely on XRCC1 for efficient DNA damage recognition, coordination of repair proteins, and maintenance of genomic stability (GC. ORG, 2024b).

Single-Strand Break Repair (SSBR) addresses DNA damage involving the breakage of only one strand, which, if left unrepaired, can lead to mutations and cellular dysfunction. These breaks arise from radiation exposure, chemical agents, or replication errors. XRCC1 facilitates SSBR by assembling repair protein complexes, interacting with polynucleotide kinase, DNA polymerase β, and DNA ligase III.

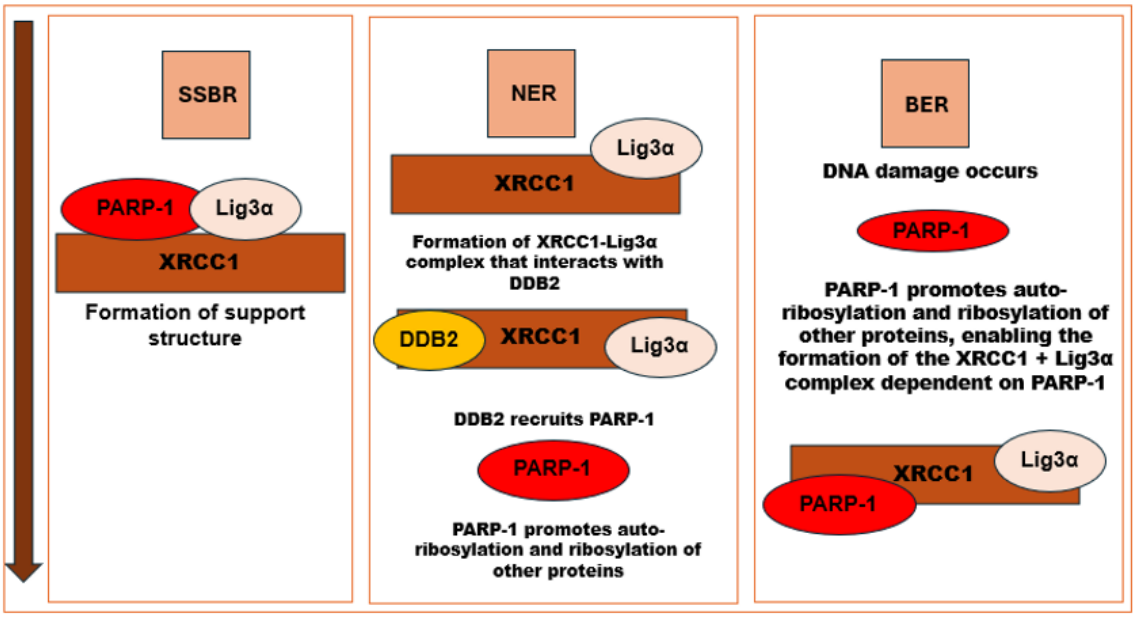
These proteins form multiprotein complexes in human cells, repair breaks induced by reactive oxygen species and ionize radiation. Notably, XRCC1 enhances the kinase and phosphatase activities of polynucleotide kinase at damaged sites, accelerating the repair process (WHITEHOUSE CJ, et al., 2001).

Base Excision Repair (BER) operates throughout the cell cycle, correcting DNA damage caused by oxidative stress, alkylation, and environmental insults. The process begins with DNA glycosylases that remove altered bases, generating AP sites, which are then cleaved by AP endonuclease. XRCC1 plays a crucial role in BER by stabilizing repair complexes and facilitating strand re-ligation. It interacts with DNA polymerase β, DNA ligase III, and PARP1, regulating the latter's ADP-ribosyl transferase activity. XRCC1 specifically binds auto-poly-ADP-ribosylated PARP1, moderating its function to allow sufficient time for DNA repair. Additionally, XRCC1 is engaged in DNA processing during meiotic recombination in germ cells (HANSSEN-BAUER A, et al., 2012).

Nucleotide Excision Repair (NER), specifically the transcription-coupled sub pathway (TC-NER), removes bulky DNA lesions such as pyrimidine dimers from transcribed gene strands. XRCC1, in complex with Lig3α, recruits PARP1 and DNA-binding protein 2 (DDB2), offering an alternative PAR-dependent mechanism for repair complex assembly (MOSER J, et al., 2007; GC.ORG, 2024b).

Disruptions in the XRCC1 gene can impair its protein's function, compromising these repair pathways, promoting genomic instability, and increasing susceptibility to DNA damage-related diseases (YANG NN et al., 2017) (**Figure 4**).

Figure 4 - Representation of XRCC1 Repair Pathways and Its Interactions with DNA Repair Proteins.



Note: Image constructed using PowerPoint software. **Legend:** Three DNA repair pathways in which the XRCC1 gene is involved and its interactions. In SSBR pathway, XRCC1 interacts with PARP-1 and Lig3α, forming a carrier structure that supports other proteins in DNA repair. In NER, XRCC1 interacts with Lig3α, forming the XRCC1-Lig3α complex, which in turn interacts with DDB2. DDB2 recruits PARP-1, which undergoes auto-ribosylation and ribosylation of other proteins, facilitating signaling and the recruitment of additional DNA repair proteins. In BER, upon DNA damage, PARP-1 promotes ribosylation, favoring the formation of the PARP-1-dependent XRCC1-Lig3α complex. Finally, the XRCC1-Lig3α-PARP-1 complex promotes the repair of damaged DNA.
Source: Alcântara AMAC, et al., 2025. **Based on:** Moser J, et al. (2007); GC.ORG, 2024b; Davis M, et al. (2022); Jonhson P, et al. (2024); Lee A, et al. (2023).

XRCC1 MUTATIONS AND DNA REPAIR

While more than 300 *XRCC1* Single nucleotide polymorphisms SNPs have been described, three functional SNPs - rs25487 (Arg399Gln), rs1799782 (Arg194Trp) and rs25489 (Arg280His)- have been

extensively studied Associated with lung, breast, and colorectal cancers, particularly cervical cancer (ZHAO DY, et al., 2014).

The rs25487 (Arg399Gln) polymorphism, located in exon 10, results in a substitution of arginine (Arg) with glutamine (Gln) in the BRCT1 domain of XRCC1, impairing protein-protein interactions and reducing DNA repair efficiency (CHAUHAN A, et al., 2018**).** The rs1799782 (Arg194Trp) polymorphism, located in exon 6, alters the N-terminal domain of XRCC1, affecting interactions within the DNA repair complex, altering base excision repair (BER) capacity. While some studies suggest a protective effect against specific cancers, others report increased susceptibility, highlighting its complex role in DNA repair fidelity (ZHAO DY, et al., 2014).

The rs25489 (Arg280His) polymorphism, located in exon 9, causes a substitution of arginine (Arg) with histidine (His) in the XRCC1 C-Domain, influencing its interaction with repair proteins. Evidence of its functional consequences emphasizes the genetic variability in DNA repair mechanisms and their potential implications for cancer development (YANG NN, 2017).

Once XRCC1 serves by coordinating the assembly and recruiting repair factors at the cell cycle checkpoints through SSBR, BER and NER pathways, polymorphisms in this gene (XRCC1) can lead to repair errors, resulting in genomic instability (MA C and GURKAN-CAVUSOGLU E, 2024).

Taken together, the polymorphisms in the mentioned genes interfere with the structure and function of their encoded proteins, compromising their interactions during DNA repair and cell cycle progression. This disruption can significantly impact the efficiency of repair mechanisms, ultimately contributing to genomic instability and cancer susceptibility (CHAUHAN A, et al., 2018; YANG NN, 2017; MA C, GURKAN-CAVUSOGLU E, 2024).

FINAL CONSIDERATIONS

Cancer results from a complex interaction of a range of factors, including genetic and cellular mechanisms. In cervical cancer, HPV infection is a significant risk factor. However, since not all HPV-infected women develop cancer, other factors, such as genetic variations, may play a crucial role. One example is polymorphisms in the XRCC1 gene, involved in DNA repair and cell cycle regulation. Alterations in this gene can impair protection against genetic damage, contributing to cancer susceptibility and disease development. The integrity of the XRCC1 gene is crucial for maintaining proper DNA repair mechanisms and ensuring cell cycle regulation. This review provides a comprehensive analysis of cervical cancer epidemiological factors, the relationship between HPV infection and cervical cancer, the role of the XRCC1 gene in DNA repair, as well as contributes to a valuable resource for clinical practice.

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