REVIEW ARTICLE

# Factors in Genetic Alterations in DNA Repair Pathways and Their Effects on Endometrial Cancer: A Review of the Literature.

M. Uyeda[1], Y. Z.M. Gonçalves[2], G. Maluf[3]

**Keywords**: Endometrial Cancer, Genetic Mutations, DNA Repair Genes, Base Mismatch Repair, Microsatellite Instability

## ABSTRACT

**Background:** Endometrial cancer is the most common gynecological neoplasm, with its origins closely linked to genetic alterations. This study highlights mutations in genes involved in DNA repair, especially the mismatch repair system and the BRCA1/2 genes, as central elements in the development of the disease, its molecular profile, and response to treatments. Understanding these genetic impacts is crucial to improving diagnostic methods and driving the development of personalized therapeutic approaches.

**Objectives:** Review how genetic alterations in DNA repair pathways influence the development and behavior of endometrial cancer.

**Methods:** A review of recent studies examining how mutations in DNA-repair genes—such as MMR defects, BRCA1/2 alterations, and MSI—relate to the molecular profile, prevalence, and therapeutic response of endometrial cancer, with emphasis on implications for immunotherapy.

**Results:** The review shows that 20–30% of endometrial cancers exhibit mismatch repair deficiency, leading to microsatellite instability and a highly immunogenic hypermutated phenotype that responds well to immunotherapy. Germline mutations in MMR are associated with Lynch syndrome, increasing the risk in young women. Alterations in BRCA1/2 also occur, especially in the serous subtype, indicating homologous recombination deficiency and a possible role in tumor progression.

**Conclusion:** Genetic alterations in genes responsible for DNA repair play a key role in the molecular biology of endometrial cancer. They not only determine specific molecular subtypes of the disease but also serve as valuable indicators for diagnosis, prognostic assessment, and patient selection for targeted therapies.

**Main Contribution to Evidence-Based Practice:** Highlights how DNA-repair mutations guide prognosis and support personalized, evidence-based treatment decisions in endometrial cancer.

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Corresponding Author:

M. Uyeda

Universidad Nacional Ecologica _ Bolivia

mari53972@uecologica.edu.bo

Authors' Affiliations:
[1] Universidad Nacional Ecologica -UNE - Bolivia
[2] PUC MINAS - Poços de Caldas Campus – Minas Gerais – Brazil
[3] Universidad Nacional Ecologica -UNE - Bolivia

**What do we already know about this topic?**
Alterations in DNA repair pathways define molecular subtypes of endometrial cancer, influence prognosis, and increase the response to immunotherapy, especially in tumors with MMR deficiency, MSI, or BRCA1/2 mutations, reinforcing the importance of personalized medicine..
What is the main contribution to Evidence-Based Practice from this article?
The article highlights mutations in DNA repair genes as essential biomarkers in endometrial cancer, guiding risk stratification, therapeutic choices, and personalized medicine decisions, especially regarding immunotherapy and DNA damage-based therapies.
**What are this research's implications towards public health policy?**
This article deepens the theoretical understanding of the molecular mechanisms of endometrial cancer, shows that mutations in DNA repair genes guide personalized therapeutic decisions—such as the use of immunotherapy and PARP inhibitors—and highlights, within the scope of health policies, the need to expand access to genetic testing and integrate biomarkers into clinical protocols for more efficient and equitable care.
**Authors' Contributions Statement:**
Uyeda, M.: wrote the introduction and methodology. Gonçalves, Y.Z.M.: wrote the introduction and results.
Maluf, G.: wrote the methodology, results, and conclusion.

## Introduction

Endometrial cancer (EC) is the most prevalent gynecological neoplasm in developed countries, accounting for approximately 7% of all female cancers and the sixth leading cause of death from gynecological neoplasms worldwide. Its etiology is multifactorial (Siegel et al., 2023; Smith & Fornace, 1995). Worldwide, it also ranks sixth as the most common cancer among women, with 417,000 new cases in 2020 (Ferlay et al., 2021; Sung et al., 2021). Traditionally classified based on histopathological criteria, as subtype I (endometrioid, estrogen-dependent) and type II (non-endometrioid, estrogen-independent), EC presents, however, significant biological and clinical heterogeneity, which limits the prognostic value and therapeutic applicability of this traditional approach. In this scenario, the incorporation of molecular characterization has revolutionized the understanding of EC pathogenesis, promoting advances in risk stratification and treatment personalization (Vermij et al., 2022; Galant et al., 2024).

With approximately 7,840 new cases per year, the disease has grown by 20% from 2023 to 2024 (Mauro & Carvalho, 2023). This increase is driven by population aging, rising obesity, and lifestyle changes. Advances in genetics reveal that mutations in DNA repair genes, such as MLH1, MSH2, MSH6, PMS2, and POLE, play a key role in genomic instability and directly affect tumor behavior, treatment response, and prognosis. These mutations are especially relevant in Lynch syndrome cases and in ultramutated tumors, particularly those with ultramuted (POLE) gene mutations, which are generally linked to better clinical outcomes (Yokoyama et al., 2018). Table 1 presents a diagram of the main DNA repair systems and genes involved in EC.

Table 1. Diagram of the Main DNA Repair Systems and Genes Involved

| DNA Repair System | Main Function | Genes Involved | Relation to Endometrial Cancer |
|---|---|---|---|
| Mismatch Repair (MMR) | Corrects base-pairing errors during DNA replication | MLH1, MSH2, MSH6, PMS2 | Mutations or epigenetic silencing (e.g., *MLH1* methylation) lead to microsatellite instability (MSI), common in type I endometrial tumors. |
| Homologous Recombination (HR) | Accurately repairs double-strand DNA breaks using a homologous template | BRCA1, BRCA2 | HR defects increase genomic instability; *BRCA1/2* mutations are associated with aggressive subtypes of endometrial cancer. |
| Base Excision Repair (BER) | Repairs oxidative lesions and small base modifications | POLE, POLD1 | *POLE* mutations cause an ultramutated phenotype, often linked to better prognosis in some endometrial cancer cases. |
| Nucleotide Excision Repair (NER) | Removes bulky adducts and DNA helix distortions | Genes such as *XPA*, *ERCC1* | Less frequently implicated in endometrial cancer, but may contribute in tumors exposed to genotoxic agents. |

Source: The author.

In Brazil, the regional distribution of cases reflects inequalities in access to healthcare. The Southeast and South regions account for approximately 70% of diagnoses. This is partly due to the greater availability of medical services, genetic testing, and hospital infrastructure. In these areas, identification of specific molecular profiles is more common. This enables the application of personalized therapies and precision medicine strategies. In the North and Northeast regions, the recorded incidence is lower. However, limited access to early diagnosis and genetic testing can lead to underreporting and delayed treatment, which compromises clinical outcomes. The presence of mutations in DNA repair genes in these populations may be underestimated. This hinders the adoption of more effective therapeutic approaches. This perspective also reflects the global scenario. Evidence shows the number of EC cases increases as human development levels (HDI) rise. Three-quarters of cases occurred in countries with high or very high HDI, such as North America and Europe. These regions also report the highest incidence. These statistics reinforce the possibility of underreporting bias in countries with lower HDIs due to limited reporting and early diagnosis capacity (Ferlay et al., 2021; Sung et al., 2021; Wild, Weiderpass, & Stewart, 2020). Projections for the coming years indicate a significant increase in the incidence of EC throughout the country, in line with the global trend of increasing cancer cases. By 2030, Brazil is expected to contribute a significant portion of the more than 25 million new cases predicted worldwide (Siegel et al., 2023).

The Cancer Genome Atlas (TCGA) consortium redefined the EC classification by grouping it into four distinct molecular subgroups: POLE, hypermutated (MSI-H/dMMR), copy-number high (p53-aberrant), and copy-number low (NSMP). This new taxonomy demonstrated

prognostic and predictive superiority compared to the traditional histological classification, allowing greater precision in therapeutic selection, especially in the decision-making process regarding adjuvant chemotherapy and surveillance of intermediate-risk patients, as demonstrated in the molecular analysis of the PORTEC-3 trial (Vermij et al., 2022; Galant et al., 2024). Among the subgroups, MSI-H/dMMR tumors stand out for their high mutational burden, unique immunological profile, and remarkable response to immunotherapy (Oaknin et al., 2022), which in turn proved to be a highly relevant advance, bringing new therapeutic possibilities in the fight against EC. Unlike its predecessors, such as the use of platinum-based chemotherapy (characterized by unfavorable prognoses (Coleman et al., 2023), immunotherapy controls and sometimes eliminates different tumor types, and has a considerably more tolerable toxicity profile (Kennedy & Salama, 2020). The MMR system is essential for maintaining genomic stability. It is mediated by proteins encoded by the MLH1, MSH2, MSH6, and PMS2 genes, which detect and correct mismatches during DNA replication. Deficiency in this system, whether due to somatic or germline alterations, leads to the accumulation of mutations and the phenomenon of MSI, found in approximately 20 to 30% of endometrioid carcinomas and in over 90% of cases related to Lynch Syndrome (LS), a hereditary cancer predisposition condition with an autosomal dominant inheritance pattern (Peltomäki et al., 2023; Riedinger et al., 2024; Mendiola et al., 2023). Among the genes involved, germline mutations in MSH6 confer a cumulative risk of up to 71% for EC by age 70 (Chow et al., 2023).

Accurately identifying the etiology of MMR deficiency is critical, as it may involve Hereditary Breast and Ovarian Cancer Syndrome (HBOC), epigenetic silencing (MLH1-PM), double somatic events (DS-MMRd), or as yet undefined mechanisms (Kempers et al., 2011). Even in the presence of MLH1 hypermethylation, HBOC cannot be excluded without further investigation, since cases with mutations in MSH2 or MSH6 may also exhibit this profile (Helderman et al., 2024). Depending on the diagnostic method used, such as immunohistochemistry, there is a risk of missing functional deficiency in cases with sub clonal expression of MMR proteins, a phenomenon associated with epithelial-mesenchymal transition and increased tumor aggressiveness (Riedinger et al., 2024). Riedinger et al. (2024) demonstrated that up to 17% of cases present discordance between immunohistochemistry (IHC) and next-generation sequencing (NGS), compromising patient eligibility for immunotherapy or genetic screening.

From a therapeutic perspective, MSI-H/dMMR tumors exhibit high mutational burden (TMB), neoantigen production, and intense lymphocytic infiltration, making them ideal targets for immunotherapies with immune checkpoint inhibitors. The KEYNOTE-158 and GARNET clinical trials (Marabelle et al., 2020; Oaknin et al., 2021) demonstrated objective response rates of up to 45% and prolonged survival in patients with advanced MSI-H/dMMR cancer refractory to conventional chemotherapy, consolidating the international recommendation for universal MSI/MMR testing (Galant et al., 2024).
However, dMMR tumors are not biologically homogeneous. Studies have shown that the mechanism of deficiency influences the pattern of immune activation: mut-MMRd tumors promote robust CD8+ T lymphocyte infiltration, while epi-MMRd tumors are

associated with CD16+ NK cell activation, reflecting distinct transcriptomic signatures (Chow et al., 2023). These functional differences may explain variations in response to immunotherapy and suggest that MSI-H/dMMR status alone may not be a sufficient biomarker for therapeutic prediction.

Furthermore, other molecular pathways also interact with the DNA repair system in EC, indicating that EC harbors a network of complex molecular alterations. Mutations in ARID1A, PIK3CA, PTEN, SMARCA4, BRCA1/2, and POLE are frequently found and act synergistically with DNA repair defects, favoring genomic instability, immune escape, and tumor progression (Chow et al., 2023; Kempers et al., 2011). Activation of LINE-1 retrotransposons, often associated with TP53 mutations, has also been implicated in double-strand breaks and the perpetuation of genetic damage (McKerrow et al., 2022). Notably, rare pathogenic variants in genes such as POLD1, SPARC, and FBN1 have been detected in suspected LS cases, suggesting new targets for investigation (Oaknin et al., 2021).

Clonal and molecular evolution over time is also relevant. Comparative studies between primary and recurrent EC samples have revealed secondary alterations in MLH1 and molecular subtype changes in up to 20% of relapsed cases, with direct implications for the immune response and subsequent therapeutic decisions (O'Malley et al., 2022).

Despite the advances achieved, critical gaps remain in understanding the functional and clinical heterogeneity of DNA repair gene mutations in EC. Identifying these mutations is crucial not only for early diagnosis and molecular classification of EC, but also for choosing personalized therapeutic approaches. With the advancement of precision medicine, genetic testing and next-generation sequencing are being incorporated into clinical practice, allowing patients to be stratified according to their molecular profiles and offering more effective treatments. Therefore, understanding the role of mutations in DNA repair genes is essential to expanding knowledge about tumor biology and improving clinical outcomes for patients.

## Methodology

This is a literature review aimed at gathering, analyzing, and discussing relevant studies on the impact of genetic mutations in DNA repair genes on EC. To this end, a twelve-year literature search was conducted from January 2013 to June 2025, covering a period of twelve years in recognized scientific databases such as PubMed, Scopus, SciELO, Web of Science, and Google Scholar. The latter was used to locate gray literature and complementary articles not indexed in other platforms. The search strategy involved the use of controlled descriptors and keywords combined with Boolean operators, such as: "Endometrial cancer" OR "Uterine cancer" AND "DNA repair genes" OR "MMR" OR "BRCA1" OR "BRCA2" OR "POLE" OR "MSH2" OR "MLH1" AND "mutation" OR "genetic alteration." Filters were applied to restrict the results to publications in Portuguese, English, and Spanish, as well as original articles, systematic reviews, and meta-analyses with full-text access. The inclusion criteria included studies published within the defined period that addressed genetic mutations in DNA repair genes in the context of EC, with relevant clinical, molecular, or epidemiological data. Articles that dealt exclusively with other types of cancer, studies focused solely on therapeutic approaches

without genetic analysis, duplicate studies or studies with insufficient data, and conference abstracts without full publications were excluded.

The initial search yielded 312 articles. After reading the titles and abstracts, 87 studies were selected for full-text reading. Of these, 42 met the inclusion criteria and were considered in the final analysis, comprising the body of evidence used to discuss the impact of mutations in DNA repair genes on the development and prognosis of endometrial cancer.

Clinical Implications and Applications in Medical Practice

Understanding the genetic mechanisms involved in SCC has direct implications for clinical practice, especially for early diagnosis, risk stratification, and the selection of personalized therapies. The following are practical recommendations based on literature findings

- Genetic Screening and Screening
  - Universal MSI/MMR testing is recommended for all cases of EC, according to international guidelines, to identify patients with potential benefit from immunotherapy (Galant et al., 2024; Oaknin et al., 2022). Women diagnosed with EC before age 50 or with a family history of colorectal cancer should be evaluated for MSI/MMR and referred for genetic counseling (Peltomäki et al., 2023; Chow et al., 2023).
- Molecular Diagnosis

The IHC remains a useful initial tool for assessing MMR protein expression, but should be complemented by NGS in cases with clinical suspicion or discordance between methods (Riedinger et al., 2024; Galant et al., 2024). Differentiating between germline and epigenetic deficiencies (such as MLH1 hypermethylation) is essential for defining therapeutic approaches and family screening strategies (Yokoyama et al., 2018; Helderman et al., 2024).

- Risk Stratification

The molecular classification proposed by the TCGA allows for more accurate patient stratification, overcoming limitations of traditional histological classification (Vermij et al., 2022). Tumors of the POLE-mut and MSI-H/dMMR subtypes have a better prognosis and can be managed with less aggressive therapy (Galant et al., 2024; Oaknin et al., 2022).

- Personalized Treatment

Patients with MSI-H/dMMR tumors should be considered for immunotherapy with immune checkpoint inhibitors, such as pembrolizumab or dostarlimab, especially in chemotherapy-refractory cases (Marabelle et al., 2020; Oaknin et al., 2021; O'Malley et al., 2022). BRCA1/2 mutations, although less frequent, may indicate benefit with PARP inhibitors, especially in aggressive serous tumors (Chow et al., 2023).

- Genetic and Family Counseling

The identification of germline mutations in DNA repair genes should be followed by genetic counseling, with risk assessment for family members and implementation of prevention strategies (Peltomäki et al., 2023; Kempers et al., 2011). In cases of confirmed LS, periodic screening for colorectal, ovarian cancer, and other associated tumors is recommended (Chow et al., 2023).

Results

The scientific literature has established a strong correlation between mutations in DNA repair genes and the development of specific EC subtypes. The impact of these mutations goes beyond mere predisposition, shaping the

tumor's molecular profile, aggressiveness, prognosis, and, crucially, response to targeted therapies. Alterations in genes such as MLH1, MSH2, MSH6, PMS2, BRCA1, and BRCA2 are key events that compromise genomic integrity, driving endometrial carcinogenesis.

One of the best-characterized mechanisms is a deficiency in the MMR system, which corrects base pairing errors during DNA replication. Loss of MMR gene function leads to MSI, a molecular marker present in approximately 20% to 30% of endometrioid EC cases. This instability results in a hypermutated phenotype, characterized by a high mutational burden. This accumulation of mutations produces numerous neoantigens, which are abnormal proteins recognized as foreign by the immune system. This high immunogenicity makes the tumor more "visible" to T cells, which explains the effectiveness of immunomodulatory therapies such as immune checkpoint inhibitors.

The cause of MMR deficiency in EC can be sporadic or hereditary. Most sporadic cases are driven by hypermethylation of the MLH1 gene promoter, an epigenetic event that silences gene expression. In contrast, germline mutations in MMR genes are the hallmark of LS, an inherited condition that confers a significantly higher risk for EC. In these cases, the cancer tends to manifest in younger women, often before menopause, and may be the first clinical sign of the syndrome even before the emergence of other associated cancers, such as colorectal cancer.

In addition to the MMR genes, mutations in the BRCA1 and BRCA2 genes, classically associated with breast and ovarian cancer, have also been investigated in the context of EC. Although their prevalence is lower, these mutations lead to a deficiency in the homologous recombination pathway, a process for repairing double-strand breaks in DNA. The resulting deficiency in homologous recombination contributes to genomic instability, and studies suggest that this defective pathway may be particularly associated with the serous subtype of EC. This subtype is known for its greater aggressiveness and poorer prognosis, highlighting the importance of investigating these mutations for more accurate risk stratification.

Molecular analysis of these hypermutated tumors, often associated with MMR deficiency, reveals a tumor microenvironment with greater immune cell infiltration, reinforcing the potential of immunotherapy-based therapies for these patients. Thus, a detailed understanding of mutations in DNA repair genes not only sheds light on the pathogenesis of the disease but also provides crucial biomarkers for selecting patients who will benefit from personalized therapies, optimizing clinical outcomes, and prognosis. Table 2 shows a simplified view of mutations in DNA repair genes in EC, with types, tumor subtypes, and therapeutic implications.

Table 2. Mutations in DNA Repair Genes in Endometrial Cancer: Types, Tumor Subtypes, and Therapeutic Implications

| Gene Involved | Type of Mutation | Associated EC Subtype | Therapeutic Implications |
|---|---|---|---|
| MLH1 | Epigenetic (hypermethylation); Germline | Endometrioid; MSI-H/dMMR | Immunotherapy (Oaknin et al., 2022); genetic screening (Yokoyama et al., 2018) |
| MSH2 | Germline | MSI-H/dMMR; LS | Immunotherapy; genetic counseling (Peltomäki et al., 2023) |
| MSH6 | Germline | MSI-H/dMMR; LS | Immunotherapy; elevated cumulative risk (Chow et al., 2023) |
| PMS2 | Germline | MSI-H/dMMR | Immunotherapy; genetic testing (Peltomäki et al., 2023) |
| POLE | Somatic | Ultramutated | Favorable prognosis; reduced therapeutic aggressiveness (Galant et al., 2024) |
| BRCA1/BRCA2 | Germline; Somatic | Serous subtype (aggressive) | Potential use of PARP inhibitors (Chow et al., 2023) |
| TP53 | Somatic | Copy-number high (p53-aberrant) | Poor prognosis; possible therapeutic resistance (McKerrow et al., 2022) |
| ARID1A, PTEN, PIK3CA, SMARCA4 | Somatic | Variable; interactions with MMR and BRCA | Potential synergy with immunotherapy and targeted therapies (Chow et al., 2023; Kempers et al., 2011) |

Source: The author.

## Conclusion

The molecular biology of disease is a fundamental pillar of modern diagnosis and treatment. The understanding that dysfunction of the MMR system, and to a lesser extent, of genes such as BRCA1, leads to genomic instability has transformed clinical approaches. The presence of MSI, a result of MMR deficiency, is not only a molecular marker but a signature that defines a subgroup of tumors with distinct characteristics. The high mutational load and consequent production of neoantigens in these tumors make them particularly sensitive to immunotherapy with immune checkpoint inhibitors.

In this context, the incorporation of immunotherapy and molecular classification into treatment has opened new perspectives for patients with advanced or recurrent EC with dMMR/MSI-H status, offering more effective options after failure of standard therapy and bringing back a medicine that strategically utilizes all available scientific and technological resources.

Thus, molecular analysis has become indispensable, enabling the precise identification of patients who will benefit from personalized and more effective treatments. Differentiation between sporadic cases (due to MLH1 promoter methylation) and hereditary cases (associated with LS) also has a crucial impact, guiding genetic counseling and family screening

## Abbreviations

**BER-** Base Excision Repair, **DS-MMRd-** Double Somatic Events, **EC-** Endometrial Cancer, **HBOC-** Hereditary Breast and Ovarian Cancer Syndrome, **HDI-** Human Development Levels, **HR-** Homologous Recombination, **IHC-** Immunohistochemistry, **LS-** Lynch Syndrome, **MLH1-PM-** Epigenetic Silencing, **MMR-** Mismatch Repair, **MSI-** Microsatellite Instability, **MSI-H/dMMR-** Hypermutated, **NER-** Nucleotide Excision Repair, **NGS-** Next-Generation Sequencing, **NSMP-** Copy-Number Low, **POLE-** DNA Polymerase Epsilon, **p53-aberrant-** Copy-Number High, **TCGA-** The Cancer Genome Atlas, **TMB-** High Mutational Burden

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