Research Progress on *BRCA1/2* Mutations in Sporadic Gastric Cancer: Risk Stratification, Surgical Prognosis, and Individualized Treatment

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Meiqiong Chen[1,†], Yi Dong[2,†], Ru Wang[3], Haihong Cui[4]

[1]Department of Pathology, The 305 Hospital of PLA, 100017 Beijing, China
[2]Department of General Surgery, The 305 Hospital of PLA, 100017 Beijing, China
[3]Department of Clinical Laboratory, The 305 Hospital of PLA, 100017 Beijing, China
[4]Department of Gastroenterology, The 305 Hospital of PLA, 100017 Beijing, China

Gastric cancer is one of the most prevalent malignant tumors worldwide. Sporadic gastric cancer accounts for more than 80% of all gastric cancer cases, and its pronounced heterogeneity underlies the substantial variability in clinical outcomes and the complexity of treatment strategies. The breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) are core regulators of the DNA damage homologous recombination repair (HRR) pathway, and their pathogenic mutations are closely associated with hereditary breast and ovarian cancer syndrome. Recent evidence has shown that *BRCA1/2* mutations also exist in some sporadic gastric cancer patients and may profoundly affect tumor biological behavior, clinical prognosis, and treatment response. This article systematically reviews the latest research progress on *BRCA1/2* mutations in sporadic gastric cancer, focusing on their incidence and molecular characteristics, their impact on patients' postoperative prognosis, and their potential value as novel biomarkers for guiding individualized therapy, thereby providing a theoretical basis for clinical risk stratification and tailored treatment strategies.

Keywords: breast cancer gene 1/2 genes mutations; sporadic gastric cancer; risk stratification; prognosis; individualized treatment

Introduction

Gastric cancer is one of the leading causes of cancer-related deaths worldwide, with its incidence and mortality rates remaining consistently high, posing a significant public health challenge [1]. The vast majority of gastric cancer cases are sporadic, arising without a clear family history of heredity, but multiple factors, including *Helicobacter pylori* infection, high-salt diet, smoking, and exposure to environmental toxins are possibly at play [2,3]. Although surgical resection combined with perioperative chemotherapy or chemoradiotherapy constitutes the standard treatment modality for resectable gastric cancer, considerable prognostic heterogeneity remains among patients with the same TNM stage [4]. The significant prognostic heterogeneity highlights the limitations of relying solely on traditional pathological staging and has driven continuous exploration of the underlying molecular mechanisms, with the aim of identifying novel biomarkers to achieve more precise risk stratification and individualized treatment.

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Correspondence to: Meiqiong Chen, Department of Pathology, The 305 Hospital of PLA, 100017 Beijing, China (e-mail: chenmq202505@163.com).
† *These authors contributed equally.*
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With the advancement of high-throughput sequencing, molecular classification systems for gastric cancer (such as The Cancer Genome Atlas [TCGA] and the Asian Cancer Research Group [ACRG] classifications) have revealed the underlying complex diversity at the genomic, epigenetic, and signaling pathway levels [5]. These classifications have not only deepened our understanding of the gastric cancer pathogenesis, but also informed selection of therapies targeting specific molecular pathways (e.g., human epidermal growth factor receptor 2 [HER2] pathway, vascular endothelial growth factor [VEGF] pathway, mismatch repair [MMR]) [6]. Moreover, abnormalities in the DNA damage repair (DDR) pathway, particularly the homologous recombination repair (HRR) pathway, have emerged as a novel research field and are attracting increasing attention.

The breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) play key roles in suppressing tumor by encoding proteins repairing DNA double-strand breaks and maintaining genomic stability [7]. Pathogenic germline mutations in *BRCA1/2* were initially found to be highly clustered in families with hereditary breast and ovarian cancer syndrome, establishing their classic status as hereditary susceptibility genes [8,9]. However, emerging genomic sequencing study has revealed that in addition to germline mutations, somatic mutations in *BRCA1/2* and the "homologous recombination deficiency (HRD)" phenotype caused by their epigenetic silencing (e.g., methylation) also occur in various sporadic malignancies, such as pancreatic and prostate cancers [10].

The 2014 TCGA molecular classification study was the first to reveal enrichment of somatic *BRCA1/2* mutations in sporadic gastric cancer, especially in the chromosomal instability and microsatellite instability-high (MSI-high) subtypes, thereby catalyzing a new of research [11].

Recent evidence has indicated that *BRCA1/2* mutations may heighten the risk of developing sporadic gastric cancer, but also influence the pathological characteristics of tumors, the efficacy of surgical resection, and postoperative prognosis. Furthermore, *BRCA1/2* mutations have been reported to possess potential utility in personalized treatment strategies, particularly in the prediction of sensitivity to platinum-based chemotherapy and the therapeutic use of polyadenosine-diphosphate-ribose polymerase [PARP] inhibitors [12]. However, existing findings remain controversial: (i) some cohorts have shown that patients with *BRCA1/2* mutations have longer postoperative survival, while other studies have not observed a significant association; (ii) clinical data on PARP inhibitors playing roles in sporadic gastric cancer were mostly limited to small-sample phase II trials, lacking verification from phase III studies [13]; and (iii) the interaction between *BRCA1/2* mutations and other molecular events (e.g., *TP53* mutations, *HER2* amplification) has not yet been clarified [14].

Therefore, this review focuses on the systematic summary of *BRCA1/2* mutations-related research about sporadic gastric cancer, emphasizing the risk stratification, surgical treatment prognosis, and individualized treatment. By analyzing the consensus and controversies in current research, we seek to delineate the potential role of *BRCA1/2* mutations and propose future research directions for predicting cancer progression and optimizing clinical treatment for sporadic gastric cancer.

BRCA1/2 Mutations and Risk Stratification of Sporadic Gastric Cancer

Characteristics of BRCA1/2 Mutations in Sporadic Gastric Cancer

Risk stratification centers on identifying populations at elevated risk for disease onset and distinguish tumors with significant progression potential. As key genes for DNA damage repair, the biological and clinical significance of *BRCA1/2* mutations in sporadic gastric cancer have been further clarified by multiple studies in recent years.

Findings from large-scale analyses have indicated that *BRCA1/2* mutations, despite their low frequency, confer a disproportionately high risk. A 2025 meta-analysis, which included 14 studies involving 160,551 patients, showed that the risk of gastric cancer in *BRCA1* mutation carriers was significantly higher than that in the general population (pooled risk ratio [RR] = 2.30, 95% CI: 1.33–3.97, $p = 0.003$); the risk was even higher in *BRCA2* mutation carriers (pooled RR = 2.45, 95% CI: 1.82–3.28, $p < 0.001$) [15]. Notably, heterogeneity among study evaluating *BRCA1* mutations was high ($I^2 = 82\%$), whereas heterogeneity for *BRCA2* mutations was low ($I^2 = 25\%$), suggesting that the association between BRCA2 and gastric cancer risk is more stable and broadly generalizable [15]. Also, a meta-analysis of cohort studies, together with a large registry-based case-control study [16,17], reported that *BRCA2* mutation carriers have an approximately 2- to 5-fold increased risk of gastric cancer compared with non-carriers. However, heterogeneity across populations and study designs underscores the need for the large-scale, ethnically diverse validation.

Analyses of specific populations revealed the substantial ethnic variation. For example, the study of 40 gastric cancer patients in Pakistan (with coverage depth $\geq 500\times$) detected one case of *BRCA1* pathogenic mutation (p.Tyr1853Ser) and one case of *BRCA2* pathogenic mutation (p.Trp31Ser). Neither of these two mutations was detected in the Asian population database (gnomAD) nor the TCGA gastric cancer cohort, indicating that the South Asian population may have a unique *BRCA1/2* mutation spectrum [18]. In contrast, a retrospective study of 10 patients found that *BRCA2* 6174delT—a founder mutation prevalent in the Jewish population—accounted for 40% (4/10) of sporadic gastric cancer cases with a *BRCA*-related family history, further confirming the existence of population-specific mutations [19]. These findings underscore the need for reference panels tailored to specific ethnicities and comprehensive sequencing approaches that cover the entire coding region as well as splice site.

It has also been reported that the gene/protein expression in gastric cancer tissues with pathogenic mutations was significantly reduced ($p < 0.05$), which was associated with DNA repair pathways (homologous recombination and Fanconi anemia pathways) [18,19]. These findings substantiate the role of *BRCA1/2* mutations in promoting genome instability in sporadic gastric cancer.

Association Between BRCA1/2 Mutations and Gastric Cancer Risk

Meta-analysis demonstrates a more consistent association between *BRCA2* mutations and gastric cancer risk (pooled relative risk $\approx$ 2–5), whereas estimates for *BRCA1* vary markedly across regions and ethnic groups. The meta-analysis showed that *BRCA2* mutations had a stronger association with gastric cancer risk (RR = 2.45 vs. 2.30 for *BRCA1*) and featured low heterogeneity ($I^2 = 25\%$). Subgroup analysis further suggested that this association remain consistent across different regions. In contrast, the association between *BRCA1* and gastric cancer risk was more significant in the European population (RR = 3.12) but lacked statistical significance in the Asian population (RR = 1.58, $p = 0.12$), suggesting that the risk associated with *BRCA1* may be modulated by genetic background across ethnicities, varying environmental factors, and the prior under-representation of Asian populations in datasets.

Analysis of patients with confirmed gastric cancer revealed a significant increase in the prevalence of *BRCA2* mutations (pooled RR = 4.86, 95% CI: 3.32–7.11, $p < 0.001$, $I^2 = 0\%$), while *BRCA1* mutations only showed a non-significant upward trend (RR = 3.02, $p = 0.101$). These results underscore *BRCA2* as the primary risk gene clinically related to sporadic gastric cancer.

H. pylori infection and *BRCA* mutations may exert a synergistic effect on gastric cancer risk. In a case-control study by Usui *et al*. [20], individuals harboring both risk factors—*H. pylori* infection and pathogenic variants in homologous-recombination genes, including *BRCA2*, demonstrated a substantially higher cumulative risk of gastric cancer than those carrying only a pathogenic variant or only *H. pylori* infection, suggesting the potential cooperative interaction of these factors. However, due to insufficient data and studies, pooling of results was not feasible and such observation remains preliminary.

Additionally, the marked gender disparity is also observed. Globally, the incidence of gastric cancer in men is approximately twice that in women [21], whereas the rate of *BRCA* genetic testing in men remains markedly lower than in women [22]. This has led to an underestimation of the true incidence of *BRCA* mutations in sporadic gastric cancer among men, necessitating the introduction of gender-inclusive genetic testing.

The risk stratification is also modified by family history. Existing data showed that 70% of sporadic gastric cancer patients with *BRCA* mutations had first-degree relatives with *BRCA*-related cancers, while the germline mutation rate was <1% in those without a family history. Subgroup analysis in the meta-analysis indicated that *BRCA2* mutation carriers with a family history of gastric cancer had the highest risk (RR = 5.12), whereas the risk was attenuated in those without a family history (RR = 1.98). This suggests that *BRCA* sequencing may have greater predictive value for individuals with a family history of gastric cancer or *BRCA*-related cancers.

Limitations of Current Research

Although recent meta-analysis significantly enhanced the strength of evidence, limitations still persist. Among the 14 included studies, only two reported *H. pylori* infection status, complicating efforts to quantify the interaction between *BRCA* mutations (genetic) and *H. pylori* infection (environmental). Further, current data from Asian populations account for only 23% of the total sample, limiting the generalization of risk estimates. Larger-scale Asian cohorts, such as those from China and Japan, are needed to clarify the region-specific utility value of *BRCA*. Additionally, low *BRCA* detection rates in men may lead to data bias, resulting in an underestimation of the association between *BRCA* mutations and gastric cancer risk in men.

Future research should focus more on the harmonization of genomic data and validation across ethnically diverse populations, rather than relying solely on extrapolations from hypothetical or incomplete pooled datasets. Moreover, *BRCA* testing methodologies would be essential for cross-study comparability. Also, the integration of multi-omics data, combined with polygenic risk modeling, has the potential to establish a more accurate, personalized risk stratification framework for sporadic gastric cancer.

Summary

Collectively, *BRCA1/2* mutations are rare but influence the risk of sporadic gastric cancer. *BRCA2* mutations were found more associated with cancer susceptibility. These findings lay the foundation for improving screening and detection strategies for high-risk populations. However, validations using large-scale investigations are warranted to facilitate the translation of these findings into clinical settings.

BRCA1/2 Mutations and Prognosis of Surgical Treatment for Sporadic Gastric Cancer

BRCA1/2 Mutations and Surgical Outcomes

Radical surgical resection serves as the core treatment for resectable sporadic gastric cancer, while surgical efficacy and postoperative prognosis are significantly influenced by the *BRCA1/2* mutations. The previous surgical cohort study of sporadic gastric cancer has shown that loss of *BRCA1* expression, reflecting impaired *BRCA* function, was associated with poorer prognosis and might indicate more aggressive tumor biology [23].

A study on gastric cancer patients receiving radical resection demonstrated that the loss of *BRCA1* expression (21.4%, 24/112) was significantly associated with the diffuse-type Lauren classification (31.7% vs. 8.2% in intestinal type, $p = 0.001$), advanced clinical stage (45.5% of patients with stage IV disease had loss of *BRCA1* expression, which was significantly higher than the 12.9% in stage I/II, $p = 0.006$), and high tumor grade (54.5% of grade IV tumors had loss of BRCA1 expression, higher than the 10.7% in grade I/II, $p = 0.047$) [23]. These data showed that gastric cancers with such loss of BRCA1 expression often exhibit extensive tumor invasion and strong metastatic potential. Even when radical resection is surgically achievable (e.g., the R0 resection rate of 88.3% achieved in the study), the intrinsic malignant characteristics of the tumor may increase the complexity of surgical procedures, necessitating more extensive lymph node dissection and management of more complex anatomical invasion, thereby elevating the risk of postoperative recurrence and metastasis. These intrinsic malignant characteristics likely reflect the functional consequence of BRCA1-mediated repair failure, leading to chromosomal instability, high-grade histology, and invasive growth. Such genomic instability may further account for the observed survival disparity and differential responses to DNA-damaging adjuvant therapies discussed below.

BRCA1/2 Status and Postoperative Survival in Surgical Patients

When discussing the prognostic role of BRCA1/2, it is critical to distinguish among germline mutations (inherited variants), somatic mutations (tumor-acquired events), and loss of protein expression (often due to epigenetic silencing). Each of these may carry distinct biological and clinical implications, since germline mutations indicate systemic homologous recombination defects while somatic mutations and protein loss primarily reflect tumor-specific DNA repair deficiencies.

Relevant studies have confirmed that BRCA1/2 status is a key influencing factor for postoperative survival in surgical patients, although data remain limited. In a small case series consisting of only four surgical patients [19], the median overall survival of three patients with *BRCA2* mutations was significantly longer than that of one patient with *BRCA1* mutation. Additionally, two patients with *BRCA2* mutation receiving platinum-based adjuvant chemotherapy after surgery experienced no recurrence, suggesting the potential therapeutic advantage conferred by chemosensitivity associated with HRD. Importantly, such anecdotal evidence should be hypothesis-generating, serving only as a preliminary signal for future validation, due to the limited sample size, insufficient statistical power, and the lack of follow-up. Moreover, interpretation of such results should consider the molecular context; otherwise, it is impossible to determine whether the improved survival stems from the mutation itself or the resulting DNA repair deficiency.

Furthermore, data from Zhang *et al*. [23] showed that the loss of BRCA1 expression was significantly associated with severe disease progression and poorer survival outcomes in gastric cancer patients. Patients with BRCA1 deficiency had significantly shorter survival than those with positive BRCA1 expression (2-year survival rate, 32.4% vs. 62.8%, $p = 0.015$), suggesting that BRCA1 deficiency can serve as a prognostic biomarker.

Although *BRCA2* mutations are often associated with better postoperative outcomes and BRCA1 loss with poorer survival, these associations should be interpreted cautiously. The heterogeneity in mutation type, detection method, and sample size across studies limits the robustness of conclusions. Integration of functional HRD metrics and prospective validation in multicenter cohorts is needed to clarify whether BRCA status independently predicts prognosis or merely reflects underlying genomic instability.

Interaction Between Adjuvant Therapy and BRCA1/2 Mutations

Adjuvant therapy could modulate the impact of *BRCA1/2* mutations on surgical outcomes. In the study by Halpern *et al*. [19], two patients harboring the *BRCA2* mutation who received adjuvant chemotherapy with the capecitabine plus oxaliplatin (XELOX) regimen after surgery encountered no recurrence or metastasis, but in another case, a patient with *BRCA2* mutation who did not receive adjuvant therapy experienced recurrence of metastatic lesions 29 months after surgery. Although anecdotal, this suggested that *BRCA2* mutations could enhance the chemotherapy sensitivity. Thus, *BRCA* profiling may serve as a predictive biomarker for postoperative treatment strategies. However, current evidence remains insufficient to support the inclusion of *BRCA* testing in clinical guidelines. As of 2025, the National Comprehensive Cancer Network (NCCN) does not endorse its routine use as a prognostic or predictive biomarker in gastric cancer management.

Summary and Future Direction

In summary, among sporadic gastric cancer patients who undergo surgery, *BRCA2* mutations (especially in early-stage disease and with biallelic deletion) are associated with better postoperative survival and response to platinum-based adjuvant therapy, while loss of BRCA1 expression is linked to aggressive pathological features and poor survival [19,23]. However, current evidence is based on small sample sizes in retrospective and exploratory studies. To clarify the prognostic significance of *BRCA1/2* mutations in surgical gastric cancer, consistent methods for assessing *BRCA* and scoring HRD are required to be established. Moreover, large trials are also needed for verifying the role of *BRCA1/2* in predicting postoperative survival and adjuvant therapy benefit. In addition, the mechanisms by which BRCA1/2 influences tumor evolution and modulates therapeutic response require further investigation.

BRCA1/2 Mutations in Individualized Treatment of Sporadic Gastric Cancer

Biological Basis for Therapeutic Vulnerability

BRCA1/2 mutations induce HRD, rendering tumor cells more susceptible to DNA-damaging agents, underpinning the rationale for individualized treatment of sporadic gastric cancer. Recent years have witnessed the gradual incorporation of *BRCA1/2* mutations and HRD phenotype into patient stratification criteria, owing to their potential value in platinum-based chemotherapy, PARP inhibitors (PARPi), and immunotherapy.

Evidence of Sensitivity to Platinum-Based Chemotherapy

Several small-sample retrospective and tissue sequencing studies have observed that gastric cancer patients with *BRCA1/2* mutations or high HRD scores, who received platinum-based chemotherapy, demonstrated higher objective response rates and longer progression-free survival. Multicenter retrospective analyses from South Korea, Europe, and the United States have consistently found that patients with pathogenic *BRCA* mutations (p-*BRCA*) or loss of heterozygosity had significantly higher initial response rates to platinum-based regimens than those with wild-type *BRCA* or monoallelic mutations [24]. These tumors most belong to the chromosomal instability subtype, indicating

the mechanistic convergence between genomic instability and drug sensitivity. These observations support the notion that BRCA/HRD status could serve as a predictive biomarker for identifying patients most likely to benefit from chemotherapy.

Exploration of PARPi

Following the successful application of PARPi in *BRCA*-mutated breast and ovarian cancers, researchers have begun exploring their feasibility in gastric cancer. Multiple reviews and early clinical trial summaries have shown that a small number of gastric cancer patients with *BRCA2* mutations or more broadly HRR gene mutations achieve partial response or stable disease when treated with olaparib, niraparib, or talazoparib. Some studies have explored combinations of PARPi with platinum agents or immune checkpoint inhibitors to evaluate potential synergistic effects [25,26]. While PARPi have demonstrated early evidence of objective responses in BRCA- or HRD-positive gastric cancer, a survival benefit has yet to be established in phase III trials. The optimal predictive biomarkers, combination regimens, and treatment sequencing therefore remain to be defined [25]. Nevertheless, the low prevalence of pathogenic *BRCA1/2* mutations in unselected gastric cancer, along with the lack of disease-specific companion diagnostics and heterogeneity in HRD testing, currently hinders broad clinical implementation.

Immunotherapy Combination Strategies

Recent fundamental and translational study has shown that *BRCA*-mutated or HRD-positive gastric cancers often exhibit higher tumor mutation burden, neoantigen production, and upregulated programmed death ligand-1 (PD-L1) expression—features associated with increased response probability to immune checkpoint inhibitors [27]. Based on this theory, researchers have used BRCA/HRR status as a stratifying factor in early-phase clinical trials and basket studies across multiple tumor types to explore the feasibility of combining PARPi with programmed death 1 (PD-1)/PD-L1 inhibitors. Nevertheless, relevant studies are still in their infancy stage, and more prospective data are required to support their efficacy and safety.

Other DNA Damage Repair Targets and Biomarkers

In addition to *BRCA1/2*, abnormalities in other HRR genes such as partner and localizer of breast cancer 2 (*PALB2*), ataxia-telangiectasia mutated (*ATM*), and *RAD51* have also been reported to be associated with a "BRCA-like" phenotype [28]. In genomics research landscape, multigene panels, HRD scores, and genomic scar indicators have been gradually adopted in recent years to enable a comprehensive assessment of DDR deficiency and guide targeted drug selection [29]. Such a trend is expected to expand the potential beneficiary population and improve prediction accuracy.

Functional Divergence Between BRCA1 and BRCA2: Mechanistic Interpretation

Although BRCA1 and BRCA2 cooperate within the HRR pathway, accumulating mechanistic evidence reveals that they play non-redundant roles in DNA damage response and cell fate determination, which may explain their distinct clinical associations observed in gastric cancer [7,9,10].

Functionally, BRCA1 acts primarily as a DNA end-resection gatekeeper and checkpoint regulator. It participates in damage sensing, recruitment of the MRE11-RAD50-NBS1 (MRN) complex, and activation of ataxia telangiectasia mutated Rad3-related kinase (ATR)/checkpoint kinase 1 (CHK1)-mediated S and G2/M arrest [7]. Loss of BRCA1 therefore shifts double-strand break (DSB) repair toward error-prone non-homologous end joining (NHEJ), leading to chromosomal instability, aneuploidy, and aggressive tumor histology [8,14]. This mechanism is consistent with the diffuse, high-grade, and invasion-prone phenotypes reported in BRCA1-deficient gastric cancer [23].

BRCA2, in contrast, functions downstream as the RAD51 loader, stabilizing replication forks and directly promoting strand invasion during HRR [7,30]. BRCA2 deficiency gives rise to a more distinct HRD phenotype marked by extensive genomic scarring, yet with reduced mitotic catastrophe relative to BRCA1 loss [10,24]. Consequently, *BRCA2*-mutated tumors retain better sensitivity to DNA-damaging agents such as platinum and PARP inhibitors [24,26], resulting in the more stable risk association and favorable treatment response observed in clinical studies.

Additionally, BRCA1 interacts extensively with p53, ATM, and G2/M checkpoint proteins, linking DNA repair failure to transcriptional reprogramming and epithelial-mesenchymal transition (EMT) [9,14]. These non-canonical functions of BRCA1 further contribute to tumor aggressiveness and chemoresistance, which are independent of HRD.

Taken together, these functional differences suggest that the loss of BRCA1 drives genomic chaos and poor differentiation, whereas BRCA2 loss primarily produces therapeutic vulnerability associated with HRD. This conceptual framework may reconcile the observation that BRCA1 deficiency predicts poor prognosis, while *BRCA2* mutations are linked to improved response to DNA-damaging regimens in sporadic gastric cancer.

Summary and Future Trends

Overall, despite the relatively low frequency of *BRCA1/2* mutations in sporadic gastric cancer, their strong associations with drug sensitivity and clinical outcomes underscore their potential utility as biomarkers. *BRCA2*-mutated tumors exhibit enhanced responsiveness to chemotherapy and PARPi, while BRCA1-deficient tumors show complex phenotypes. The HRD-based biomarkers also offer broader prediction of therapeutic benefit. These results highlight the

need for HRD assessment, prospective clinical validation, and combination strategies for maximizing therapeutic potential.

Despite encouraging evidence from small-scale studies, no phase III trial has yet validated the clinical benefit of PARPi in sporadic gastric cancer. While the underlying biological rationale is well-established, with HRR deficiency conferring DNA repair vulnerabilities, achieving consistent therapeutic benefit necessitates larger, biomarker-driven cohorts. The future research should prioritize phase II/III trials, robust HRD quantification, and patient stratification informed by multi-omics approaches.

Conclusions

Current evidence supports a model in which *BRCA* mutations create HRD-driven therapeutic vulnerability in selected subsets of sporadic gastric cancer. Their clinical applicability, however, depends on robust functional HRD assessment and prospective validation. In clinical practice, *BRCA* mutations or HRD testing should be used primarily for trial stratification and exploratory decision-making, rather than as a universal determinant of routine management.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

MQC and YD designed the research study. RW and HHC performed the research. MQC, YD, RW and HHC analyzed the data. MQC drafted the manuscript. All authors have been involved in revising the manuscript critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Hartgrink HH, Jansen EPM, van Grieken NCT, van de Velde CJH. Gastric cancer. Lancet (London, England). 2009; 374: 477–490. https://doi.org/10.1016/S0140-6736(09)60617-6.

[2] Polk DB, Peek RM, Jr. Helicobacter pylori: gastric cancer and beyond. Nature Reviews. Cancer. 2010; 10: 403–414. https://doi.org/10.1038/nrc2857.

[3] Ansari S, Gantuya B, Tuan VP, Yamaoka Y. Diffuse Gastric Cancer: A Summary of Analogous Contributing Factors for Its Molecular Pathogenicity. International Journal of Molecular Sciences. 2018; 19: 2424. https://doi.org/10.3390/ijms19082424.

[4] Soon YY, Leong CN, Tey JCS, Tham IWK, Lu JJ. Postoperative chemo-radiotherapy versus chemotherapy for resected gastric cancer: a systematic review and meta-analysis. Journal of Medical Imaging and Radiation Oncology. 2014; 58: 483–496. https://doi.org/10.1111/1754-9485.12190.

[5] Lin X, Zhao Y, Song WM, Zhang B. Molecular classification and prediction in gastric cancer. Computational and Structural Biotechnology Journal. 2015; 13: 448–458. https://doi.org/10.1016/j.csbj.2015.08.001.

[6] Röcken C. Molecular classification of gastric cancer. Expert Review of Molecular Diagnostics. 2017; 17: 293–301. https://doi.org/10.1080/14737159.2017.1286985.

[7] Prakash R, Zhang Y, Feng W, Jasin M. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harbor Perspectives in Biology. 2015; 7: a016600. https://doi.org/10.1101/cshperspect.a016600.

[8] Varol U, Kucukzeybek Y, Alacacioglu A, Somali I, Altun Z, Aktas S, *et al*. BRCA genes: BRCA 1 and BRCA 2. Journal of B.U.ON.: Official Journal of the Balkan Union of Oncology. 2018; 23: 862–866.

[9] Rosen EM, Fan S, Pestell RG, Goldberg ID. BRCA1 gene in breast cancer. Journal of Cellular Physiology. 2003; 196: 19–41. https://doi.org/10.1002/jcp.10257.

[10] Shao C, Wan J, Lam FC, Tang H, Marley AR, Song Y, *et al*. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environmental and Molecular Mutagenesis. 2022; 63: 308–316. https://doi.org/10.1002/em.22505.

[11] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014; 513: 202–209. https://doi.org/10.1038/nature13480.

[12] Darabi S, Braxton DR, Xiu J, Carneiro BA, Swensen J, Antonarakis ES, *et al*. *BRCA1/2* Reversion Mutations in Patients Treated with Poly ADP-Ribose Polymerase (PARP) Inhibitors or Platinum Agents. Medicina (Kaunas, Lithuania). 2022; 58: 1818. https://doi.org/10.3390/medicina58121818.

[13] Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet (London, England). 2010; 376: 235–244. https://doi.org/10.1016/S0140-6736(10)60892-6.

[14] Kim J, Jeong K, Jun H, Kim K, Bae JM, Song MG, *et al*. Mutations of TP53 and genes related to homologous recombination repair in breast cancer with germline BRCA1/2 mutations. Human Genomics. 2023; 17: 2. https://doi.org/10.1186/s40246-022-00447-3.

[15] de Moraes FCA, Matheus GTFU, Souza MEC, Burbano RMR. Gastric cancer risk and BRCA1/2 mutations: a systematic review and meta-analysis. Personalized Medicine. 2025; 22: 245–256. https://doi.org/10.1080/17410541.2025.2531737.

[16] Momozawa Y, Sasai R, Usui Y, Shiraishi K, Iwasaki Y, Taniyama Y, *et al*. Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. JAMA Oncology. 2022; 8: 871–878. https://doi.org/10.1001/jamaoncol.2022.0476.

[17] Lee YC, Lee YL, Li CY. *BRCA* Genes and Related Cancers: A Meta-Analysis from Epidemiological Cohort Studies. Medicina (Kaunas, Lithuania). 2021; 57: 905. https://doi.org/10.3390/medicina57090905.

[18] Li F, Abdel-Maksoud MA, Ullah T, Ul Haq M, Khan A, Olatunji AO, *et al*. Detection of genomic variants in BRCA1 and BRCA2 across gastric cancer patients using next generation sequencing. American Journal of Translational Research. 2024; 16: 7898–7910. https://doi.org/10.62347/MRIE2131.

[19] Halpern N, Grinshpun A, Boursi B, Golan T, Margalit O, Aderka D, *et al*. Clinical Characteristics and Prognosis of Gastric Cancer Patients with *BRCA 1/2* Germline Mutations: Report of Ten Cases and a Literature Review. OncoTargets and Therapy. 2020; 13: 11637–11644. https://doi.org/10.2147/OTT.S276814.

[20] Usui Y, Taniyama Y, Endo M, Koyanagi YN, Kasugai Y, Oze I, *et al*. *Helicobacter pylori*, Homologous-Recombination Genes, and Gastric Cancer. The New England Journal of Medicine. 2023; 388: 1181–1190. https://doi.org/10.1056/NEJMoa2211807.

[21] Lou L, Wang L, Zhang Y, Chen G, Lin L, Jin X, *et al*. Sex difference in incidence of gastric cancer: an international comparative study based on the Global Burden of Disease Study 2017. BMJ Open. 2020; 10: e033323. https://doi.org/10.1136/bmjopen-2019-033323.

[22] Cheng HH, Shevach JW, Castro E, Couch FJ, Domchek SM, Eeles RA, *et al*. BRCA1, BRCA2, and Associated Cancer Risks and Management for Male Patients: A Review. JAMA Oncology. 2024; 10: 1272–1281. https://doi.org/10.1001/jamaoncol.2024.2185.

[23] Zhang ZZ, Liu YJC, Yin XL, Zhan P, Gu Y, Ni XZ. Loss of BRCA1 expression leads to worse survival in patients with gastric carcinoma. World Journal of Gastroenterology. 2013; 19: 1968–1974. https://doi.org/10.3748/wjg.v19.i12.1968.

[24] Oh JH, Sung CO, Kim HD, Chun SM, Kim J. BRCA-mutated gastric adenocarcinomas are associated with chromosomal instability and responsiveness to platinum-based chemotherapy. Journal of Pathology and Translational Medicine. 2023; 57: 323–331. https://doi.org/10.4132/jptm.2023.10.22.

[25] Petrelli A, Rizzolio S, Pietrantonio F, Bellomo SE, Benelli M, De Cecco L, *et al*. BRCA2 Germline Mutations Identify Gastric Cancers Responsive to PARP Inhibitors. Cancer Research. 2023; 83: 1699–1710. https://doi.org/10.1158/0008-5472.CAN-22-2620.

[26] Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science (New York, N.Y.). 2017; 355: 1152–1158. https://doi.org/10.1126/science.aam7344.

[27] Fan Y, Ying H, Wu X, Chen H, Hu Y, Zhang H, *et al*. The mutational pattern of homologous recombination (HR)-associated genes and its relevance to the immunotherapeutic response in gastric cancer. Cancer Biology & Medicine. 2020; 17: 1002–1013. https://doi.org/10.20892/j.issn.2095-3941.2020.0089.

[28] Wu A, Hu T, Lai C, Zeng Q, Luo L, Shu X, *et al*. Screening of gastric cancer diagnostic biomarkers in the homologous recombination signaling pathway and assessment of their clinical and radiomic correlations. Cancer Medicine. 2024; 13: e70153. https://doi.org/10.1002/cam4.70153.

[29] Dodson AE, Shenker S, Sullivan P, Nayak SU, Middleton C, McGuire M, *et al*. Pan-Cancer Analysis of Homologous Recombination Deficiency in Cell Lines. Cancer Research Communications. 2024; 4: 3084–3098. https://doi.org/10.1158/2767-9764.CRC-24-0316.

[30] Le HP, Heyer WD, Liu J. Guardians of the Genome: BRCA2 and Its Partners. Genes. 2021; 12: 1229. https://doi.org/10.3390/genes12081229.