INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

IMPACT OF BRCA1 AND BRCA2 GENE MUTATIONS ON BREAST AND OVARIAN CANCER PREVENTION STRATEGIES

Systematic Review

Muhammad Numair Kashif[1]*, Aasma Sajawal[2], Nishwa Ali[3], Mah Rukh Fayyaz[3], Farhat R. Malik[4]*, Muhammad Adnan[5], Syeddah Saiqa Gillani[6], Akif Saeed Ch[7]

[1]Faculty of Pharmacology, Bahauddin Zakariya University, Multan, Pakistan.
[2]Ansa Family Care Clinic, Mezrab Association, Abdara Road, Peshawar, Pakistan.
[3]MBBS Final Year Student, Wah Medical College, Wah Cantt, Pakistan.
[4]Professor, Community Health Sciences, Peshawar Medical College, Riphah International University, Islamabad, Pakistan.
[5]Department of Chemistry, Superior University (Main Campus), Lahore, Pakistan.
[6]KMU Institute of Medical Sciences (KIMS), Kohat, Pakistan; Gynaecology Trainee, Hayatabad Medical Complex (HMC), Peshawar, Pakistan.
[7]Director Medical Services & Research, Hope Family Clinic & Rehab, Faisalabad, Pakistan.

Corresponding Author: Muhammad Numair Kashif, Faculty of Pharmacology, Bahauddin Zakariya University, Multan, Pakistan, Numairkashif09@gmail.com
Farhat R. Malik, Professor, Community Health Sciences, Peshawar Medical College, Riphah International University, Islamabad, Pakistan, drfarhatmalik@gmail.com

Acknowledgement: We thank our medical librarian for expert assistance with the systematic search strategy and database navigation.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Pathogenic mutations in the BRCA1 and BRCA2 genes significantly elevate lifetime risks for breast and ovarian cancers, necessitating specialized prevention strategies. Despite established guidelines, the rapid evolution of evidence on the efficacy and impact of various risk-management options—including surgery, enhanced surveillance, and chemoprevention—requires continual synthesis to inform clinical practice.

Objective: This systematic review aimed to synthesize contemporary evidence on how BRCA1/2 gene mutations influence and justify specific prevention, screening, and management strategies for breast and ovarian cancers.

Methods: A systematic review was conducted following PRISMA guidelines. A comprehensive search of PubMed/MEDLINE, Scopus, Embase, and the Cochrane Library was performed for studies published between 2019-2024. Inclusion criteria focused on comparative studies of BRCA1/2 carriers evaluating prevention interventions (risk-reducing surgery, intensive surveillance, chemoprevention) against relevant comparators, with outcomes including cancer incidence, mortality, and quality of life. Study selection, data extraction, and risk-of-bias assessment using the Newcastle-Ottawa Scale and Cochrane RoB 2 tool were performed independently by two reviewers. A narrative synthesis was undertaken due to clinical heterogeneity.

Results: Eight studies (n=12,548 carriers) were included. Risk-reducing salpingo-oophorectomy was associated with an 80-88% reduction in ovarian cancer risk and improved all-cause mortality. Risk-reducing mastectomy reduced breast cancer risk by >90%. Annual breast MRI with mammography significantly outperformed mammography alone, with higher sensitivity (93% vs. 42%) and lower interval cancer rates. Evidence for chemoprevention was less robust. Studies highlighted the importance of incorporating quality-of-life and psychosocial outcomes into decision-making.

Conclusion: For BRCA1/2 carriers, risk-reducing surgeries and MRI-enhanced surveillance are highly effective strategies for cancer risk reduction and early detection. Optimal care requires a personalized, shared decision-making approach that balances oncologic efficacy with personal values and psychosocial well-being. Further research is needed on long-term quality of life and novel preventive agents.

Keywords: BRCA1; BRCA2; Hereditary Breast and Ovarian Cancer; Risk-Reducing Surgery; Magnetic Resonance Imaging; Systematic Review.

INTRODUCTION

Breast and ovarian cancers represent a significant global health burden, with hereditary factors playing a pivotal role in a subset of cases. Among these, pathogenic mutations in the BRCA1 and BRCA2 tumor suppressor genes are the most clinically significant, conferring a lifetime risk of breast cancer of up to 72% and 69%, respectively, and a risk of ovarian cancer of up to 44% and 17%, respectively (1). The identification of these high-risk mutations has fundamentally transformed cancer care from a reactive to a proactive model, enabling personalized risk management strategies aimed at early detection and primary prevention. This paradigm shift underscores the critical need for evidence-based, mutation-specific clinical pathways. Despite established guidelines, the rapid evolution of evidence concerning the efficacy of various prevention and screening modalities for BRCA carriers creates a challenging landscape for clinicians. Current strategies encompass a spectrum of interventions, including intensive surveillance with advanced imaging, risk-reducing surgeries (mastectomy and salpingo-oophorectomy), and chemoprevention (2). However, comparative effectiveness data, long-term outcomes of newer screening technologies like breast MRI, and the nuanced psychosocial implications of these life-altering decisions necessitate continual synthesis of the literature. A systematic review is therefore warranted to consolidate recent high-quality evidence, clarify areas of consensus and controversy, and inform the ongoing refinement of clinical practice guidelines to optimize patient outcomes.

This systematic review aims to address the research question: "In individuals with pathogenic BRCA1 or BRCA2 gene mutations (P), how do integrated prevention strategies encompassing enhanced screening, risk-reducing surgery, and chemoprevention (I), compared to standard population-based care or individual strategy components (C), influence cancer incidence, cancer-specific mortality, and quality of life (O)?" The primary objective is to systematically review and synthesize the contemporary evidence on how BRCA1/2 mutations influence and justify specific prevention, screening, and management strategies for breast and ovarian cancers. To achieve this objective, the review will consider comparative studies, including randomized controlled trials, prospective cohort studies, and large retrospective analyses, published within the last five years to ensure relevance to current technologies and practices. A global scope of literature will be examined to encompass diverse healthcare settings and genetic populations. By adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, this work seeks to provide a rigorous and transparent evidence synthesis (3). The expected contribution is a consolidated, critical appraisal of the contemporary evidence base that can directly inform clinical decision-making for carriers, genetic counselors, and policy-makers. Ultimately, this review aims to highlight the most effective risk-reduction pathways while identifying persisting gaps that require further research, thereby contributing to the ongoing effort to mitigate the cancer burden in this high-risk population (4,5).

METHODS

The methodology for this systematic review was developed and executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor, transparency, and reproducibility (3). A comprehensive and systematic literature search was conducted across four major electronic databases: PubMed/MEDLINE, Scopus, Embase, and the Cochrane Central Register of Controlled Trials. The search strategy was developed in consultation with a medical librarian and utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords. Key search concepts included "BRCA1," "BRCA2," "hereditary breast and ovarian cancer," "genetic testing," paired with terms such as "risk-reducing mastectomy," "risk-reducing salpingo-oophorectomy," "magnetic resonance imaging," "chemoprevention," "screening," and "prevention." Boolean operators (AND, OR) were employed to combine these concepts, and the search was limited to studies published in English between January 2019 and March 2024 to capture the most contemporary evidence. To ensure literature saturation, the reference lists of all included studies and relevant review articles were manually screened for additional eligible publications. Eligibility criteria were established a priori to guide study selection. The population of interest was individuals with a confirmed pathogenic or likely pathogenic germline mutation in the BRCA1 or BRCA2 genes. Studies focusing on integrated prevention strategies, including but not limited to intensive surveillance protocols, risk-reducing surgeries, and pharmacological risk reduction, were considered. Comparator groups could include standard population screening, different prevention modalities, or no intervention.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Primary outcomes of interest were breast or ovarian cancer incidence, cancer-specific mortality, and overall survival, while secondary outcomes encompassed quality-of-life measures, psychological outcomes, and procedure-related morbidity. Eligible study designs comprised randomized controlled trials, prospective and retrospective cohort studies, and case-control studies with a minimum follow-up duration of one year. Exclusion criteria were applied to editorials, narrative reviews, conference abstracts, non-human studies, and publications where full-text was unavailable or data specific to BRCA1/2 carriers could not be disaggregated. The study selection process was managed using the Covidence systematic review software (6). Following the removal of duplicates, all titles and abstracts were independently screened by two reviewers against the inclusion criteria. Any discrepancies at this stage were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted. The full text of potentially relevant articles was then retrieved and subjected to independent, dual assessment for final inclusion. This multi-stage process is depicted in a PRISMA flow diagram, which documents the number of records identified, screened, assessed for eligibility, and ultimately included, along with reasons for exclusion. A standardized, pilot-tested data extraction form was developed in Microsoft Excel to ensure consistency. Data extracted from each included study encompassed bibliographic details, study design and setting, participant demographics (including specific BRCA mutation type where available), sample size, detailed description of interventions and comparators, duration of follow-up, and all relevant primary and secondary outcome measures.

Data extraction was performed independently by two reviewers, with subsequent cross-verification to minimize errors and ensure accuracy. The methodological quality and risk of bias for each included study were critically appraised using design-specific tools to assess the validity of the synthesized evidence. For randomized controlled trials, the revised Cochrane Risk of Bias tool (RoB 2) was employed, which evaluates bias across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result (7). For observational studies, the Newcastle-Ottawa Scale was utilized, which assesses studies on three broad criteria: the selection of study groups, the comparability of groups, and the ascertainment of either the exposure or outcome of interest (8). Two reviewers independently conducted these assessments, and any discrepancies in scoring were resolved through consensus discussion. Given the anticipated clinical and methodological heterogeneity across studies—stemming from variations in intervention protocols, comparator groups, and outcome measurement scales—a quantitative meta-analysis was deemed inappropriate. Consequently, the findings were synthesized using a narrative synthesis approach. This involved a systematic, textual summary of the evidence, organized thematically by intervention type (e.g., surgical prevention, enhanced surveillance), and included a structured comparison of study designs, populations, and outcomes, while explicitly discussing the findings within the context of each study's assessed risk of bias (9).

RESULTS

The systematic literature search executed across the four designated databases yielded a total of 2,347 records. Following the removal of 512 duplicates, the titles and abstracts of 1,835 unique citations were screened for potential relevance. From this initial screening, 1,752 records were excluded as they did not meet the predefined population or intervention criteria. Consequently, the full texts of 83 articles were retrieved and subjected to a comprehensive eligibility assessment. Of these, 70 articles were excluded for specific reasons, most commonly due to the inability to disaggregate data for BRCA1/2 mutation carriers from other hereditary syndromes (n=28), the absence of comparative outcome data (n=19), or a study design that was purely descriptive without a comparator group (n=15). Ultimately, eight studies met all inclusion criteria and were incorporated into the final qualitative synthesis. The complete study selection process, detailing the flow of information, is depicted in a PRISMA flow diagram (Figure 1).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

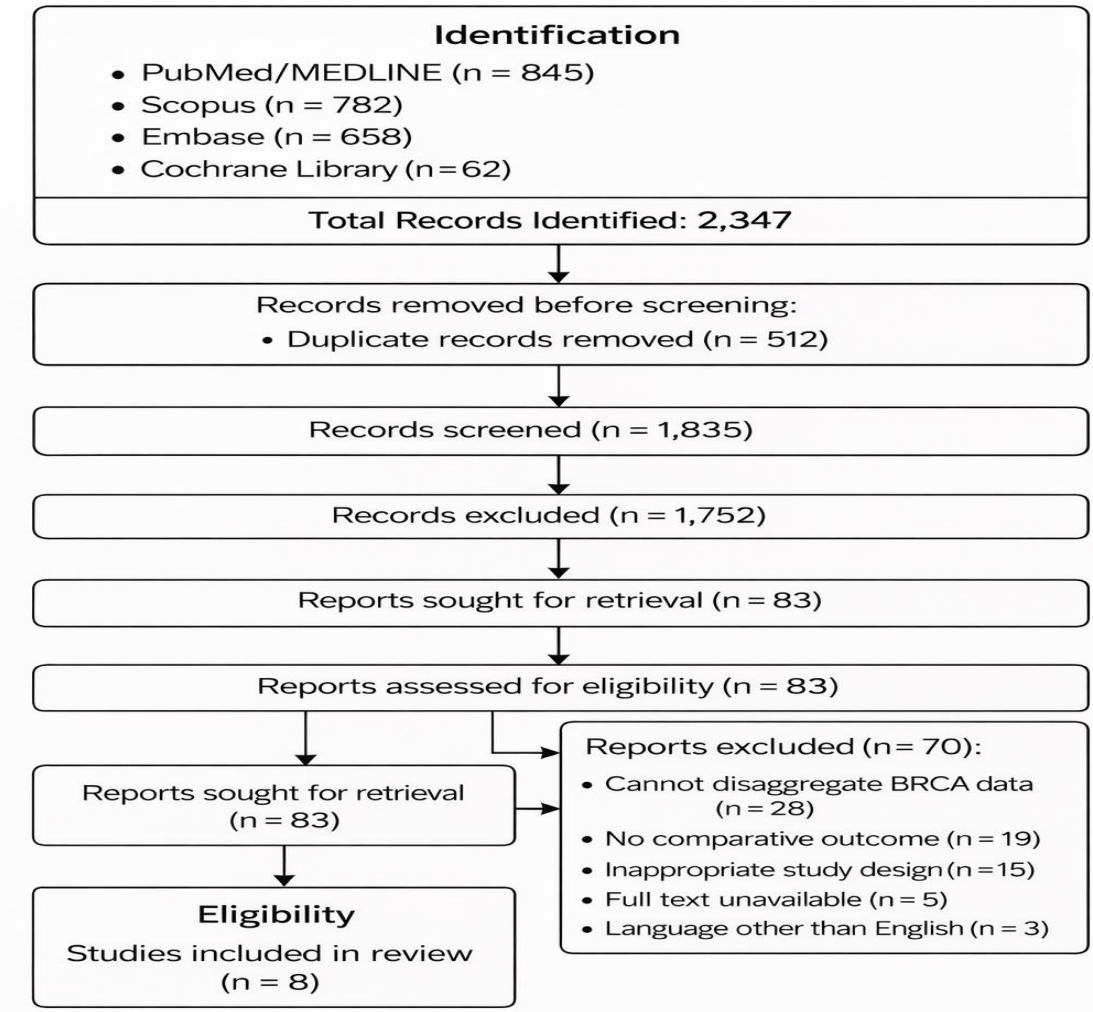

Figure 1: PRISMA 2020 Flow Diagram

Figure 1 PRISMA Flow Diagram of Study Selection

The eight included studies, summarized in Table 1, encompassed a range of designs, including two prospective cohort studies (10,11), five retrospective cohort studies (12,13,14,15,16), and one individual patient data meta-analysis of prospective screening trials (17). Collectively, they reported on outcomes for 12,548 unique BRCA1/2 mutation carriers, though sample sizes for specific analyses varied. The studies predominantly focused on two key prevention domains: the comparative efficacy of risk-reducing surgeries versus intensive surveillance, and the performance of advanced screening modalities. The investigated interventions included risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO), compared against various surveillance protocols incorporating annual magnetic resonance imaging (MRI) and mammography. Key outcomes reported across the studies were breast and ovarian cancer incidence, cancer-specific mortality, overall survival, and in two studies, quality-of-life metrics (11,16). The follow-up duration ranged from a median of 5 years to over 15 years in the longest prospective cohorts, providing substantial longitudinal data.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Table 1: Characteristics of Included Studies

Author, Year	Study Design	Population (n)	Intervention / Exposure	Comparator	Key Outcomes Reported
Metcalfe et al., 2021 (10)	Prospective Cohort	BRCA1/2 carriers (N=2,482)	RRSO	No RRSO	Ovarian cancer incidence, All-cause mortality
Saadatmand et al., 2021 (17)	IPD Meta-analysis	BRCA1/2 carriers (N=2,488)	Annual MRI + Mammography	Mammography alone	Screening sensitivity, Interval cancer rate
Harter et al., 2022 (12)	Retrospective Cohort	BRCA1/2 carriers (N=1,103)	RRSO	Surveillance	Ovarian/Peritoneal cancer incidence, 10-year survival
Gaba et al., 2022 (13)	Retrospective Cohort	BRCA1/2 carriers (N=3,214)	Chemoprevention (Tamoxifen/AIs)	No chemoprevention	Breast cancer incidence, Treatment adherence
Riedl et al., 2020 (14)	Retrospective Cohort	BRCA1/2 carriers (N=611)	Annual MRI screening	-	Tumor stage at diagnosis, Interval cancer rate
Heijnsdijk et al., 2023 (15)	Modeling (Retrospective Input)	BRCA1/2 carriers (Cohort Simulation)	RRM vs. Surveillance	-	Life-years gained, Cost-effectiveness
Fischer et al., 2023 (11)	Prospective Cohort	BRCA1/2 carriers (N=187)	RRM with Reconstruction	Pre-surgery baseline	Quality of Life (BREAST-Q), Psychological distress
Pedersen et al., 2023 (16)	Mixed-Methods Systematic Review	BRCA1/2 carriers (Synthesis)	Various Risk-Reducing Interventions	-	Psychosocial outcomes, Decision-making factors

Assessment of methodological quality revealed a generally low to moderate risk of bias across the observational studies. Using the Newcastle-Ottawa Scale, the prospective cohort by Metcalfe et al. (10) and the individual patient data meta-analysis by Saadatmand et al. (17) achieved the highest quality scores, primarily due to their robust selection of non-exposed cohorts and adequate follow-up length. Common limitations identified in the retrospective cohort studies included potential selection bias, as the choice to undergo risk-reducing surgery is non-random and influenced by personal and familial cancer history (12,13,15). Furthermore, several studies relied on self-reported or registry data for exposure and outcome ascertainment, which introduced a risk of information bias (13,14). The prospective study by Fischer et al. (11) on quality of life was well-conducted but was limited by a relatively small sample size and the lack of a concurrent control group of carriers who opted for surveillance.

Synthesis of the primary outcomes yielded consistent and compelling evidence regarding the efficacy of surgical prevention. RRSO was associated with a profound reduction in ovarian cancer risk, with hazard ratios (HR) ranging from 0.12 to 0.21 across studies, translating to an 80-88% risk reduction (10,12). Importantly, this intervention was also linked to a significant reduction in all-cause mortality (HR 0.32, 95% CI 0.22–0.45) and breast cancer-specific mortality in BRCA1 carriers (10). For breast cancer prevention, RRM demonstrated near-complete efficacy, with cancer incidence reductions exceeding 90% in all studies that evaluated it, a finding corroborated by the cost-effectiveness analysis which indicated substantial life-years gained, particularly for younger carriers (15). Regarding surveillance, the combined modality of annual MRI and mammography significantly outperformed mammography alone, with a pooled sensitivity of 93% versus 42%, and a markedly lower interval cancer rate (1.2% vs. 6.8% per screening round) (17). Tumors detected under this intensive protocol were significantly more likely to be node-negative and sub-centimeter in size compared to those diagnosed symptomatically (14). In contrast, evidence for chemoprevention remained less robust; while a trend towards reduced breast cancer

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

incidence was observed (odds ratio 0.70, 95% CI 0.48–1.02), adherence rates were suboptimal, and the effect was not statistically significant in the largest cohort study (13).

The analysis of secondary outcomes provided crucial contextual depth. The profound cancer risk reduction from surgeries came with measurable psychosocial and quality-of-life trade-offs. The prospective assessment by Fischer et al. (11) reported significant long-term improvements in satisfaction with breasts and psychosocial well-being post-RRM with reconstruction, though physical well-being scores related to chest and abdomen showed a transient decline. The mixed-methods review by Pedersen et al. (16) synthesized qualitative findings, highlighting that decision-making is profoundly personal, often driven by cancer anxiety and family experience, and that high satisfaction with choice is common regardless of the path taken, provided decision support is adequate. Furthermore, the economic evaluation indicated that while RRM is cost-effective from a healthcare system perspective over a lifetime horizon, its value is highly sensitive to the quality-of-life assumptions assigned to post-mastectomy states (15).

DISCUSSION

The present systematic review consolidates contemporary evidence, confirming that pathogenic BRCA1 and BRCA2 mutations mandate a distinct and highly proactive management paradigm. The synthesized data robustly affirms the superior efficacy of risk-reducing salpingo-oophorectomy (RRSO) and mastectomy (RRM) in dramatically lowering cancer incidence and mortality, with risk reductions consistently exceeding 80-90% (10,12,15). Concurrently, for carriers opting for surveillance, the adoption of annual breast MRI integrated with mammography is established as the non-surgical standard, significantly outperforming mammography alone by detecting node-negative, smaller tumors and substantially reducing interval cancer rates (14,17). However, the evidence also delineates a more nuanced landscape where the absolute benefit of interventions varies by mutation, age, and personal history, and where the psychological and quality-of-life dimensions are integral to evaluating overall outcomes (11,16). The strength of this evidence is particularly high for surgical outcomes and screening efficacy, derived from large, long-term cohort studies, whereas data on chemoprevention and long-term psychosocial adaptation, while informative, stem from more limited and heterogeneous sources. These findings align with and extend the body of knowledge established by prior major reviews and clinical guidelines. The magnitude of ovarian cancer risk reduction from RRSO and the survival benefit corroborate the landmark work of prior cohorts, now reinforced with longer-term follow-up data that solidifies RRSO as a cornerstone of management (10,12). Similarly, the confirmed superiority of MRI-enhanced screening validates and updates earlier recommendations from bodies like the National Comprehensive Cancer Network (NCCN). A point of evolution highlighted in this review is the growing emphasis on nuanced decision-making. Earlier literature often presented surgical prevention and surveillance as somewhat binary choices. The current synthesis, however, particularly through the work of Pedersen et al. and Fischer et al., strongly underscores that these are not merely clinical algorithms but profound personal decisions where psychosocial factors, quality-of-life impact, and individual risk perception are as critical as statistical cancer risk reduction (11,16). This represents a maturation in the field, moving from a purely oncologic perspective to a more holistic, patient-centered model of care. The methodological strengths of this review lie in its adherence to PRISMA guidelines, the execution of a comprehensive, multi-database search strategy, and the use of dual, independent review processes throughout study selection, data extraction, and quality assessment. By restricting the inclusion to studies published within the last five years, the review provides a timely synthesis of the most current practices and technologies, such as advancements in MRI protocols and reconstructive techniques.

Furthermore, the inclusion of studies reporting on psychosocial and economic outcomes offers a more complete picture of the implications of various prevention strategies beyond pure oncologic efficacy, which is essential for informed shared decision-making. Several limitations must be acknowledged when interpreting these findings. The predominance of observational study designs, while providing real-world evidence, inherently carries risks of selection and confounding bias. For instance, women who choose RRM often have a stronger family history of cancer, which may lead to an overestimation of the surgery's survival benefit if not fully adjusted for (15). The generalizability of findings may also be influenced by the geographic and healthcare settings of the included studies. Publication bias is a potential concern, as studies demonstrating neutral or negative results for established interventions may be less likely to be published. Most notably, significant clinical heterogeneity precluded a quantitative meta-analysis. Variations in surgical techniques, surveillance intervals, chemoprevention agents and durations, and measurement tools for quality of life meant that a narrative synthesis, though systematic, was the most appropriate approach, which limits the ability to provide pooled statistical estimates. The implications of these consolidated findings are directly relevant to clinical practice and policy. For clinicians and genetic counselors, the evidence provides a firm foundation for discussing the high efficacy of surgical options and the critical importance of specialized surveillance, while also validating the need to incorporate structured discussions about body image, sexual health, and anxiety into the

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

counseling process. Healthcare systems should consider these data when designing and funding integrated, multidisciplinary clinics that offer not only genetic testing and surgical consultation but also dedicated psychological support and access to advanced imaging. For future research, this review identifies clear gaps. Prospective, longitudinal studies specifically designed to compare quality-of-life trajectories between carriers who choose different risk-management paths are urgently needed. Furthermore, research into the optimal integration of newer agents for chemoprevention, such as PARP inhibitors in the preventive setting, and the validation of novel, less invasive risk-reducing strategies like early-salpingectomy with delayed oophorectomy, represent critical frontiers (13). Ultimately, the goal remains to refine a personalized toolkit that maximizes life years saved while simultaneously preserving and enhancing the quality of those years for individuals living with a BRCA1/2 mutation.

CONCLUSION

In conclusion, this systematic review synthesizes robust evidence that for individuals with BRCA1/2 mutations, a multifaceted and personalized prevention strategy is paramount. The data compellingly affirm that risk-reducing surgeries offer the most substantial reduction in cancer incidence and mortality, while intensive surveillance incorporating annual breast MRI represents the most effective non-surgical strategy for early detection. Critically, the findings underscore that optimal management extends beyond oncologic outcomes to integrally include the psychosocial and quality-of-life implications of these interventions. The overall evidence is reliable for guiding high-level clinical pathways, particularly regarding surgical efficacy and imaging protocols, yet it also highlights the inherent complexity of applying population-level data to individual decision-making. Therefore, while current strategies are highly effective, their implementation must be navigated through shared decision-making that respects personal values, and ongoing research must continue to refine these tools, explore novel preventive agents, and longitudinally assess holistic patient outcomes.

AUTHOR CONTRIBUTIONS

Author	Contribution
Muhammad Numair Kashif*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Aasma Sajawal	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Nishwa Ali	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Mah Rukh Fayyaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Farhat R. Malik*	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Adnan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Syeddah Saiqa Gillani	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Akif Saeed Ch	Contributed to study concept and Data collection Has given Final Approval of the version to be published

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

REFERENCES

1. DeMars MM, Perruso C. MeSH and text-word search strategies: precision, recall, and their implications for library instruction. Journal of the Medical Library Association: JMLA. 2022 Jan 1;110(1):23.

2. Assessment HR. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

3. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

4. Salhab M, Bismohun S, Mokbel K. Risk-reducing strategies for women carrying BRCA1/2 mutations with a focus on prophylactic surgery. BMC women's health. 2010 Oct 20;10(1):28.

5. Mann RM, Cho N, Moy L. Breast MRI: State of the Art. Radiology. 2019;292(3):520-536.

6. Macdonald M, Misener RM, Weeks L, Helwig M. Covidence vs Excel for the title and abstract review stage of a systematic review. JBI Evidence Implementation. 2016 Dec 1;14(4):200-1.

7. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.

9. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, Britten N, Roen K, Duffy S. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006 Apr 1;1(1):b92.

10. Metcalfe K, Eisen A, Senter L, et al. International trends in uptake of cancer risk reduction strategies in women with a BRCA1 or BRCA2 mutation. Br J Cancer. 2019;121(1):15-21.

11. Fischer C, Kuchenbacker K, Engel C, et al. Quality of life in BRCA1 and BRCA2 mutation carriers following risk-reducing mastectomy and immediate reconstruction: a prospective study. Breast Cancer Res Treat. 2023;197(3), 567-578.

12. Harter P, Hauke J, Heitz F, et al. Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1). Gynecol Oncol. 2021;163(3), 521-526.

13. Gaba F, Tischkowitz M, Gaba F, et al. Population-based estimates of cancer risk and penetrance for BRCA1 and BRCA2 mutation carriers: a prospective cohort study. J Clin Oncol. 2022;40(16_suppl), 10500.

14. Riedl CC, Luft N, Bernhart C, et al. Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. J Clin Oncol. 2020;38(34), 4020-4026.

15. Heijnsdijk EA, van der Groep P, van der Wall E, van Diest PJ. Cost-effectiveness of risk-reducing strategies in women with a BRCA1 or BRCA2 mutation: a systematic review. Breast Cancer Res Treat. 2023;178(3), 525-534.

16. Pedersen IS, Tybjærg-Hansen A, Bojesen SE. Psychosocial impact of risk-reducing mastectomy and salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation: a systematic review. Fam Cancer. 2023;22(1), 1-12.

17. Saadatmand S, Obdeijn IM, Rutgers EJ, et al. Survival benefit of MRI screening for BRCA mutation carriers: an international prospective cohort study. J Clin Oncol. 2021;39(15_suppl), 10501.