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ASSOCIATION OF BRCA1 AND BRCA2 GENE MUTATIONS WITH BREAST CANCER RISK AMONG WOMEN WITH POSITIVE FAMILY HISTORY: A SYSTEMATIC REVIEW

Systematic Review

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ABSTRACT

Background: Pathogenic variants in the BRCA1 and BRCA2 genes significantly elevate breast cancer risk, particularly among women with a positive family history. However, precise risk quantification for this specific, genetically predisposed subpopulation requires consolidation from the growing body of recent literature.

Objective: This systematic review aims to investigate the association between BRCA1/2 mutations and breast cancer risk among women with a confirmed positive family history of the disease.

Methods: A systematic review was conducted following PRISMA guidelines. Electronic databases (PubMed, Scopus, Web of Science, Cochrane Library) were searched for observational studies published between 2019-2024. Included studies reported breast cancer risk estimates for BRCA carriers versus non-carriers within cohorts of women with a family history. Study quality was assessed using the Newcastle-Ottawa Scale.

Results: Eight studies (n=35,842 participants) were included. The synthesis consistently demonstrated a substantially elevated risk for BRCA carriers with a family history compared to non-carrier relatives, with adjusted hazard ratios ranging from 12.5 to 28.4. Cumulative risk estimates by age 70 were high, between 66% and 72%. The strength of the family history was identified as a key effect modifier, with stronger family aggregation associated with higher penetrance.

Conclusion: The evidence confirms that BRCA1/2 mutations confer a profoundly high risk of breast cancer in women with a positive family history. These findings are critical for refining risk assessment, guiding genetic counseling, and personalizing clinical management strategies for this high-risk population. Future research should focus on standardizing family history reporting and integrating genetic modifiers into risk prediction models.

Keywords: BRCA1, BRCA2, Hereditary Breast Cancer, Family History, Systematic Review, Risk Assessment.

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women globally, with a significant proportion of cases attributable to hereditary factors (1). Among these, germline mutations in the BRCA1 and BRCA2 tumor suppressor genes represent the most penetrant genetic determinants of hereditary breast cancer, conferring a lifetime risk of developing the disease that is substantially higher than that of the general population (2). The clinical significance of these mutations is profound, as identification not only impacts risk stratification and personalized screening protocols but also informs prophylactic surgical decisions and targeted therapeutic strategies, such as PARP inhibition (3). Epidemiologically, it is estimated that 55-72% of women with a BRCA1 mutation and 45-69% of those with a BRCA2 mutation will develop breast cancer by 80 years of age, starkly contrasting with the ~13% lifetime risk in the general population (4). This elevated risk is particularly concentrated in women with a positive family history, where the aggregation of cases suggests a strong inherited predisposition, yet the precise quantification of risk in this subpopulation requires further elucidation. While the association between BRCA mutations and increased breast cancer risk is well-established, the existing body of literature presents a heterogeneous landscape of risk estimates, often varying by specific mutation, population ancestry, and modifier genes (5). Current clinical management guidelines for high-risk women are largely based on meta-analyses and large cohort studies; however, a comprehensive synthesis focusing specifically on women with a confirmed positive family history is lacking (6). This population is unique, as familial aggregation implies the potential presence of other genetic or shared environmental risk factors that may interact with BRCA mutations, potentially modifying the penetrance and overall risk profile (7). A systematic review dedicated to this genetically predisposed cohort is therefore necessary to consolidate the evidence, clarify the magnitude of risk, and resolve inconsistencies reported across smaller studies. This will provide a more nuanced and accurate evidence base that is directly applicable to genetic counseling and clinical decision-making for families with a history of breast cancer.

The primary research question, structured using the PICO framework, is: Among women with a positive family history of breast cancer (P), how do pathogenic mutations in the BRCA1 or BRCA2 genes (I) compared to no identified mutation (C) influence the lifetime risk and cumulative incidence of developing breast cancer (O)? The objective of this systematic review is to investigate and quantitatively synthesize the evidence regarding the contribution of BRCA1 and BRCA2 mutations to breast cancer susceptibility in this predefined, high-risk female population. To address this, the review will include observational studies—specifically cohort, case-control, and family-based studies—published in English between 2019 and 2024, providing a contemporary analysis of the evidence. The scope will be global to capture potential geographical and ethnic variations in risk estimates. This systematic review is expected to make a significant contribution by providing a refined and updated evidence synthesis that is specifically tailored to inform risk assessment models for women with a familial predisposition to breast cancer. By delineating more precise risk estimates, the findings will directly aid clinicians and genetic counselors in communicating personalized risk information, guiding recommendations for enhanced surveillance and prevention, and ultimately improving health outcomes. The conduct of this review will adhere rigorously to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor, transparency, and reproducibility (8).

METHOD

The systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and reproducibility (8). A comprehensive and systematic literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials, from January 2019 to May 2024. The search strategy employed a combination of controlled vocabulary terms, such as Medical Subject Headings (MeSH), and free-text keywords related to the core concepts. Key terms included "BRCA1", "BRCA2", "breast neoplasms", "genetic predisposition to disease", "familial breast cancer", "family history", and "risk assessment". These terms were combined using appropriate Boolean operators (e.g., AND, OR) to maximize sensitivity and specificity. The reference lists of all included studies and relevant review articles were also manually screened to identify any additional eligible publications that may have been missed in the initial electronic search. Eligibility criteria were established a priori to guide the study selection process. The review included observational studies, specifically prospective and retrospective cohort studies, case-

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control studies, and family-based studies, that reported on breast cancer risk estimates for women with a positive family history who carried a pathogenic or likely pathogenic variant in the BRCA1 or BRCA2 genes. The population of interest was defined as adult women with at least one first- or second-degree relative with breast cancer. The comparator was women from similar familial backgrounds without a identified BRCA mutation.

The primary outcome was the incidence or cumulative lifetime risk of developing breast cancer. Studies were excluded if they were editorials, commentaries, case reports, or reviews; if they were not published in English; if they involved animal models or cell lines; or if they did not provide extractable quantitative data on the risk association. The study selection process was managed using the Covidence systematic review software, which facilitated the removal of duplicates and streamlined the screening phases (9). All identified records were independently screened by two reviewers based on their titles and abstracts. The full texts of potentially relevant articles were then retrieved and assessed for eligibility against the predefined inclusion and exclusion criteria. Any discrepancies between the reviewers at either stage were resolved through discussion or, if necessary, by consultation with a third senior researcher. This process was documented using a PRISMA flow diagram, which detailed the number of records identified, included, and excluded at each stage, along with the specific reasons for exclusions. Data from the eight included studies were extracted independently by two reviewers using a piloted, standardized data extraction form to ensure consistency and accuracy (7, 10, 11, 12, 13, 14, 15, 16). The extracted variables encompassed bibliographic details (e.g., first author, publication year), study characteristics (e.g., design, country, follow-up duration), participant demographics (e.g., sample size, age, family history criteria), genetic testing methodology, BRCA mutation types, and key outcome data.

The latter included hazard ratios (HRs), odds ratios (ORs), risk ratios (RRs), cumulative incidence estimates, confidence intervals, and any adjusted covariates in the analyses. The risk of bias and quality of the included observational studies were critically appraised by two independent reviewers using the Newcastle-Ottawa Scale (NOS), a validated tool for non-randomized studies (17). The NOS assesses studies across three domains: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. Each study was awarded a star rating, with a higher number of stars indicating higher methodological quality. Studies were not excluded based on quality assessment alone, but the findings were interpreted with consideration of the individual study's risk of bias. Given the anticipated heterogeneity in study designs, populations, and methods of outcome measurement, a quantitative meta-analysis was deemed inappropriate. Instead, the results were synthesized qualitatively using a narrative approach. The findings are presented in a structured summary, detailing the study characteristics, risk estimates, and key conclusions from each included paper. The evidence is grouped and discussed thematically to provide a comprehensive overview of how BRCA1 and BRCA2 mutations contribute to breast cancer susceptibility in women with a positive family history.

RESULTS

The initial systematic search across the four electronic databases yielded a total of 2,347 records. Following the removal of 588 duplicates, the titles and abstracts of 1,759 unique articles were screened for relevance. From this pool, 1,732 records were excluded as they did not meet the predefined population or outcome criteria. The full texts of the remaining 27 articles were thoroughly assessed for eligibility. After this detailed evaluation, 19 studies were excluded with reasons, primarily for not providing stratified risk data for women with a family history (n=11), lacking a clear comparator group without mutations (n=5), or for being review articles (n=3). Ultimately, eight studies met all inclusion criteria and were selected for qualitative synthesis in this systematic review (7, 10, 11, 12, 13, 14, 15, 16). The eight included studies, published between 2020 and 2024, encompassed a total of 35,842 participants, with sample sizes ranging from 512 to 12,550 women. The research was conducted across diverse geographical regions, including Europe, Asia, and North America. The study designs consisted of four retrospective cohort studies (12, 12, 13, 16), three case-control studies (11, 14, 15), and one prospective cohort study (7). The definition of a positive family history varied but consistently required at least one first- or second-degree relative with breast cancer. All studies utilized next-generation sequencing panels for the identification of pathogenic variants in BRCA1 and BRCA2. The primary outcome across all studies was the cumulative incidence or odds of breast cancer development, with most studies reporting adjusted hazard ratios (aHR) or odds ratios (aOR) to quantify the risk associated with BRCA mutations while controlling for potential confounders such as age, parity, and hormonal factors. The key characteristics of the included studies are summarized in Table 1.

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Table 1: Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size (N)	Family History Definition	BRCA Testing Method	Key Outcome Measure
Giacomini (2024) (7)	Brazil	Prospective Cohort	2,150	≥1 first-degree relative	NGS panel	aHR for breast cancer incidence
Lakeman (2023) (10)	Netherlands	Retrospective Cohort	12,550	≥1 first or second-degree relative	NGS panel	Cumulative risk by age 80
Palermo (2022) (11)	Italy	Case-Control	1,024	≥1 first-degree relative	NGS panel	aOR for BRCA carrier status
van der Kolk (2022) (12)	Netherlands	Retrospective Cohort	985	Families with known BRCA mutation	NGS panel	Penetrance estimates
Whitworth (2021) (13)	USA	Retrospective Cohort	8,741	Varied (clinic-based)	NGS panel	aHR by family history strength
Cini (2021) (14)	Italy	Case-Control	512	≥2 relatives across generations	NGS panel	aOR for mutation detection rate
Terasawa (2020) (15)	Japan	Case-Control	3,210	≥1 first or second-degree relative	NGS panel	aOR for BRCA association
Sun (2021) (16)	China	Retrospective Cohort	6,670	≥1 first-degree relative	NGS panel	Cumulative incidence

The assessment of methodological quality using the Newcastle-Ottawa Scale revealed that the overall quality of the included studies was moderate to high. The cohort studies generally scored well on the selection and outcome domains but demonstrated variability in the comparability domain, often due to incomplete adjustment for all relevant confounding variables. The case-control studies were effective in selecting appropriate cases and controls but occasionally lacked clarity regarding the non-response rate between groups, potentially introducing selection bias. A common source of potential performance bias across several studies was the lack of blinding of genetic status during outcome assessment, though the objective nature of a breast cancer diagnosis likely mitigated this risk. No studies were deemed to be of low quality to the point of warranting exclusion from the synthesis. The synthesis of results consistently demonstrated a substantially elevated risk of breast cancer among women with a positive family history who carried a pathogenic BRCA1 or BRCA2 variant, compared to both the general population and familial non-carriers. The reported adjusted hazard ratios for breast cancer development in carriers versus non-carriers ranged from 12.5 (95% CI: 9.8–15.9) to 28.4 (95% CI: 22.1–36.5) across the studies (7, 10, 13). The cumulative risk estimates by age 70 were notably high; for instance, Lakeman et al. reported a risk of 68% (95% CI: 62–74%) for BRCA1 and 66% (95% CI: 59–73%) for BRCA2 carriers within high-risk families (10). This trend was corroborated by van der Kolk et al., whose penetrance analysis showed a cumulative incidence of 72% for BRCA1 and 69% for BRCA2 by age 80 (12). Furthermore, the strength of the family history was identified as a significant effect modifier. Whitworth et al. found that the penetrance was highest among carriers with a strong family history (e.g., two or more first-degree relatives affected), with an aHR of 32.1 (95% CI: 24.5–42.0), compared to an aHR of 14.2 (95% CI: 10.5–19.2) for those with a more moderate family history (14). The case-control studies by Palermo et al. and Cini et al. provided complementary evidence, showing significantly higher odds of being a BRCA carrier among cases with familial breast cancer compared to controls, with aORs exceeding 15.0 (11, 14).

DISCUSSION

This systematic review provides a contemporary synthesis of evidence confirming that among women with a positive family history of breast cancer, pathogenic variants in the BRCA1 and BRCA2 genes confer a substantially elevated risk of developing the disease. The analysis of eight observational studies consistently demonstrated high hazard ratios, indicating that carriers within these high-risk

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families are over twelve times more likely to develop breast cancer compared to their non-carrier relatives. The cumulative risk estimates by age 70 were notably high, ranging from 66% to 72%, underscoring the profound penetrance of these genetic mutations in a familial context. A key nuanced finding was the role of family history strength as a significant effect modifier, with risk estimates markedly higher for women from families with a greater aggregation of breast cancer cases. These findings solidify the position of BRCA1/2 mutations as the principal genetic drivers of inherited breast cancer susceptibility.The results of this review are largely congruent with the foundational literature on BRCA penetrance, such as the seminal work by Kuchenbaecker et al., which established lifetime risk estimates in large, international cohorts (2). However, this review adds a critical layer of specificity by focusing exclusively on women with a confirmed familial predisposition, a population that is inherently distinct from unselected carriers identified through population screening. The risk estimates reported herein align with but tend to be on the higher end of the spectrum compared to older meta-analyses, a finding potentially attributable to the more advanced genetic testing methodologies used in recent studies, which reduce misclassification bias, and the explicit focus on families where genetic susceptibility is more concentrated.

The consistency of findings across diverse geographical populations, from North America and Europe to Asia, enhances the generalizability of the conclusion that family history significantly amplifies the inherent risk posed by BRCA mutations. A principal strength of this review lies in its rigorous adherence to PRISMA guidelines, which bolsters the transparency and reproducibility of the methodology (8). The implementation of a comprehensive, multi-database search strategy mitigated the risk of missing relevant studies, while dual, independent review processes at the screening, selection, and data extraction stages minimized potential for reviewer bias. The application of the Newcastle-Ottawa Scale provided a structured and objective assessment of the methodological quality of the included observational studies, allowing for a nuanced interpretation of the findings within the context of each study's limitations. By restricting the inclusion to studies published within the last five years, the review offers an analysis that reflects current genetic testing practices and contemporary risk assessment models. Despite these strengths, several limitations warrant consideration. The inherent heterogeneity in the operational definitions of a "positive family history" across the included studies introduces a degree of clinical variability that complicates direct comparisons and precluded a quantitative meta-analysis. While all studies adjusted for key confounders, residual confounding from unmeasured genetic, environmental, or lifestyle factors cannot be entirely ruled out.

The exclusive inclusion of English-language publications may have introduced a language bias, potentially omitting relevant studies from non-English speaking regions. Furthermore, as with all systematic reviews, the potential for publication bias exists, wherein studies with null or negative findings may be less likely to be published and thus missed by the search strategy. The reliance on observational study designs, while necessary for investigating this research question, inherently limits the ability to infer causality definitively. The implications of these findings are immediately relevant for clinical practice and genetic counseling. The quantifiably high risk estimates reinforce the necessity of offering enhanced, personalized surveillance strategies to BRCA-positive women from familial backgrounds, which may include commencing breast MRI at an earlier age and considering risk-reducing interventions. For clinicians, these results provide a robust evidence base to support shared decision-making discussions regarding the intensity of screening and the pros and cons of prophylactic surgeries. From a research perspective, future studies should strive to standardize the reporting of family history to facilitate more precise risk stratification. Investigations into the complex interplay between BRCA mutations, other genetic modifiers, and familial environmental factors are warranted to explain the observed variation in penetrance. Ultimately, this review consolidates evidence critical for refining risk prediction models and optimizing management pathways for this high-risk population.

CONCLUSION

In conclusion, this systematic review robustly demonstrates that among women with a positive family history of breast cancer, pathogenic variants in the BRCA1 and BRCA2 genes are associated with a profoundly elevated risk of developing the disease, with hazard ratios exceeding 12 and cumulative lifetime risk estimates ranging between 66% and 72%. These findings hold significant clinical import, as they provide genetic counselors and clinicians with quantifiable, high-quality evidence to better communicate personalized risk and to strongly advocate for adherence to enhanced surveillance protocols and discussions of risk-reducing strategies for this vulnerable population. While the overall evidence is reliable and consistent across recent studies, the observed variability in risk estimates, partly attributable to differences in family history strength, underscores the necessity for future research to develop more refined, individualized risk prediction models that integrate specific familial patterns with genetic and modifiable lifestyle factors.

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AUTHOR CONTRIBUTION

Author	Contribution
Imad Hassan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Asmat Nawaz	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
Shehroz Nafees	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Kifayat Ullah	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Irfan Ishaque	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Momtaz Akter Mitu	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Rehana Shaheen	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Javeria Naz	Writing - Review & Editing, Assistance with Data Curation

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