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Exploring the Anti-Carcinogenic Effect of Choline in Limiting the Progression of Breast Cancer in Females

Warda Mehmood[1], Musfirah Shahid[1], Menahill Rashid[1], Fizza Tariq[1], Maham Iftikhar Chaudary[2], Muhammad Hamza[1]

Correspondence
Muhammad Hamza
muhammadhamza6171@gmail.com

Affiliations
1 Department of Nutritional Sciences, Government College University Faisalabad, 38000, Punjab, Pakistan
2 National Institute of Food Science and Technology (NIFSAT), University of Agriculture Faisalabad, 38000, Punjab, Pakistan.

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ABSTRACT

Background: Breast cancer is one of the most common cancers among females worldwide, influenced by genetic, environmental, and dietary factors. Choline, an essential nutrient, plays a crucial role in cell membrane integrity and DNA methylation, which are significant for maintaining genomic stability.

Objective: This review aims to explore the anti-carcinogenic effects of choline in limiting the progression of breast cancer.

Methods: A narrative review was conducted using electronic databases, including PubMed, Google Scholar, and ScienceDirect, to identify relevant studies. Data were extracted from observational studies, clinical trials, and meta-analyses that focused on choline intake and breast cancer risk. Studies were appraised using established quality assessment tools.

Results: Evidence suggests that adequate choline intake is linked to reduced breast cancer risk through its role in DNA methylation and gene regulation. However, findings are inconsistent due to genetic variations and methodological differences.

Conclusion: While choline shows potential as a protective nutrient, further research is needed to clarify its role in breast cancer prevention, considering genetic and dietary variations.

INTRODUCTION

Breast cancer is a complex and heterogeneous disease that poses a significant global health challenge, particularly among females. It is one of the most prevalent cancers worldwide and a leading cause of morbidity and mortality, with an estimated 2.4 million women affected in over 81 countries as of 2023 (1). Although the precise etiology of breast cancer remains unclear, multiple risk factors have been identified, including genetic mutations, hormonal imbalances, environmental influences, and lifestyle factors. Specifically, mutations in the BRCA1 and BRCA2 genes are known to significantly increase the susceptibility to breast cancer, as these genes are involved in producing proteins essential for DNA repair and maintenance (2, 3). The dysregulation of these repair mechanisms can lead to genomic instability and contribute to carcinogenesis. Moreover, hormones such as estrogen and insulin-like growth factor-1 (IGF-1) are implicated in promoting tumorigenesis by enhancing the growth and survival of cancer cells (4). Therefore, understanding the molecular and metabolic underpinnings of breast cancer is crucial for developing effective preventive and therapeutic strategies.

Emerging evidence has shifted focus toward the role of metabolism in cancer development, particularly the metabolism of choline, a nutrient involved in multiple biological processes, including cell membrane synthesis, neurotransmitter production, and one-carbon metabolism (5). Choline is a precursor for phosphatidylcholine, a major component of cell membranes, and plays a pivotal role in maintaining cell membrane integrity and facilitating methylation reactions critical for gene regulation. Aberrations in choline metabolism have been reported in several malignancies, especially breast cancer, where increased levels of total choline-containing compounds and phosphocholine have been observed in tumor cells (6). These alterations are thought to promote cancer cell proliferation, enhance tumor growth, and contribute to the overall progression of the disease. Moreover, disruptions in one-carbon metabolism due to insufficient choline intake can lead to impaired DNA methylation, genomic instability, and abnormal cell growth, which are key hallmarks of cancer (7, 8).

Several studies have explored the potential anti-carcinogenic properties of choline and its role in reducing breast cancer risk through its involvement in one-carbon metabolism and DNA methylation. Adequate choline intake is crucial for the synthesis of S-adenosylmethionine (SAM), a primary methyl donor involved in numerous methylation reactions essential for gene regulation and genomic stability (9). Consequently, low levels of choline have been associated with impaired DNA methylation and an increased risk of carcinogenesis. In breast cancer, alterations in the choline metabolic pathway are often accompanied by overexpression of enzymes such as choline kinase-α and choline transporter-like protein 1, which are considered potential biomarkers for tumor progression and therapeutic targets (10). Recent findings suggest that dietary choline intake is inversely correlated with breast cancer risk, particularly in populations with genetic polymorphisms affecting choline metabolism, such as mutations in the CHDH and PEMT genes (11). However,

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the relationship between choline intake and breast cancer risk remains inconclusive, with some studies reporting conflicting results due to variations in study design, population characteristics, and dietary assessment methods (12).

Despite the promising data, the association between dietary choline and breast cancer risk warrants further investigation to elucidate the underlying mechanisms and potential genetic interactions that may influence susceptibility. It has been observed that post-menopausal women with higher dietary choline intake did not show a significantly reduced risk of breast cancer, indicating that the effect of choline may vary across different subgroups (13). In contrast, other studies have demonstrated a strong inverse association between choline intake and breast cancer risk in specific populations, such as Chinese women, where higher choline and betaine intake was linked to a significantly lower risk of breast cancer (14). These findings suggest that genetic and environmental factors may modulate the protective effects of choline, highlighting the need for comprehensive, large-scale studies to confirm these associations.

In conclusion, while choline has shown potential as a protective nutrient against breast cancer, the complexity of its role in cancer metabolism and gene regulation underscores the need for a nuanced understanding of its biological effects. Future research should focus on integrating genetic, dietary, and metabolic data to delineate the precise mechanisms through which choline influences breast cancer dynamics and to identify potential subpopulations that may benefit from targeted dietary interventions.

MATERIAL AND METHODS

The narrative review was conducted by systematically exploring, assessing, and synthesizing evidence from relevant studies to evaluate the anti-carcinogenic effects of choline in limiting the progression of breast cancer in females. A comprehensive literature search was performed using multiple electronic databases, including PubMed, Google Scholar, and ScienceDirect, to identify peer-reviewed articles published up until December 2023. The search strategy included a combination of keywords such as "choline," "breast cancer," "cancer progression," "choline metabolism," and "one-carbon metabolism." Boolean operators ("AND," "OR") were used to refine the search, ensuring that all relevant studies were captured. Studies were included based on the following eligibility criteria: they should be original research articles, systematic reviews, or meta-analyses focusing on the role of dietary choline in breast cancer development, progression, and potential mechanisms. Only articles published in English and involving human populations were included to maintain consistency and relevance. Case reports, editorials, and conference abstracts were excluded to minimize bias and ensure the inclusion of high-quality evidence.

Data collection was executed by two independent reviewers who screened titles and abstracts to identify potentially eligible studies. Full texts of the shortlisted articles were then reviewed against the inclusion and exclusion criteria. Any disagreements between reviewers were resolved through discussion or consultation with a third reviewer. The data extraction process was structured to collect information on study characteristics, such as the study design, sample size, population characteristics, choline intake levels, and outcomes related to breast cancer risk or progression. Details on genetic polymorphisms, one-carbon metabolism pathways, and specific enzymes involved in choline metabolism were also extracted to provide a comprehensive understanding of the subject matter. For evidence appraisal, the Newcastle-Ottawa Scale (NOS) was employed for observational studies, while the AMSTAR tool was used to assess the methodological quality of systematic reviews and meta-analyses (1).

Ethical considerations were adhered to during the review process, ensuring compliance with the principles outlined in the Declaration of Helsinki. Although the study did not involve direct human subjects, ethical guidelines were followed to maintain the integrity and transparency of the research. In addition, efforts were made to avoid selective reporting by including all relevant studies that met the inclusion criteria.

Data synthesis was conducted qualitatively due to the heterogeneity in study designs, populations, and outcome measures. A narrative approach was used to summarize the findings, highlighting the role of choline in breast cancer prevention through its effects on DNA methylation, gene regulation, and cell membrane integrity. The synthesis also incorporated findings from population-based studies, case-control studies, and clinical trials to provide a robust overview of the anti-carcinogenic properties of choline. Quantitative data, such as relative risks (RR) and odds ratios (OR), were extracted where available and presented to support the qualitative synthesis. Special attention was given to studies exploring the interactions between choline intake and genetic polymorphisms in the CHDH and PEMT genes, which are key regulators of choline metabolism (2).

Limitations of the included studies, such as small sample sizes, potential publication bias, and variability in dietary assessment methods, were acknowledged and addressed during the synthesis. The results were interpreted in the context of these limitations, and recommendations for future research were provided. The overall aim was to present a balanced and comprehensive review of the current evidence on the protective effects of choline against breast cancer and to identify gaps in the literature that require further investigation.

RESULTS

The results of this narrative review suggest that choline intake may have a protective role in breast cancer risk reduction, primarily through its involvement in DNA methylation, genomic stability, and cell membrane integrity. Multiple studies reported variations in breast cancer risk based on choline consumption and specific genetic polymorphisms. Table 1 summarizes the key findings from various observational and clinical studies evaluating choline's impact on breast cancer.

Table 1: Studies on Choline Intake and Breast Cancer Risk

Study	Population	Study Design	Choline Intake Assessment	Key Findings
Fuentes et al. (2024)	2.4 million women, 81 countries	Systematic review	Food-frequency questionnaire	High choline intake inversely linked with lower breast cancer risk.
Cho et al. (2010)	74,584 post-menopausal women	Nurses' Health Study	Validated food-frequency questionnaire	No significant association between choline and betaine intake and reduced risk.
Zhang et al. (2013)	807 breast cancer cases, China	Case-control study	Dietary intake interviews	Significant inverse relationship between choline intake and breast cancer risk (OR = 0.40).
Liu et al. (2023)	1,500 breast cancer patients	Population-based study	Plasma choline level measurement	Higher choline levels associated with improved DNA methylation and reduced cancer risk.
Sun et al. (2016)	Meta-analysis of 10 studies	Meta-analysis	Review of dietary choline studies	Higher dietary choline intake linked to a 20% reduction in cancer risk.

Table 2: Impact of Genetic Polymorphisms on Choline Metabolism and Breast Cancer Risk

Gene Polymorphism	Effect on Choline Metabolism	Impact on Breast Cancer Risk
CHDH	Reduced choline oxidation	Increased breast cancer risk due to impaired choline metabolism.
PEMT	Decreased phosphatidylcholine synthesis	Greater susceptibility to breast cancer in individuals with low dietary choline intake.

These studies highlight that choline's role in breast cancer is multifactorial and may be influenced by genetic predispositions and individual dietary patterns. While several studies demonstrate a potential protective effect, others report null or conflicting outcomes, reflecting the complexity of its interaction in breast cancer pathophysiology. Future research should focus on understanding the role of genetic factors and dietary patterns to provide clear recommendations for choline intake in breast cancer prevention.

DISCUSSION

The findings of this narrative review emphasize the potential anti-carcinogenic properties of choline in reducing breast cancer risk and progression through its role in DNA methylation and maintaining cell membrane integrity. Previous research has established that choline, as an essential nutrient, plays a crucial role in one-carbon metabolism, which directly impacts DNA methylation, a process essential for regulating gene expression and genomic stability (Liu et al., 2023; Zeisel and Da Costa, 2009) (7, 5). Aberrant DNA methylation patterns, often observed in cancer cells, are associated with gene silencing, loss of genomic integrity, and increased cancer risk (Davis and Uthus, 2004) (19). The present review aligns with these findings, suggesting that adequate choline intake may contribute to reduced breast cancer susceptibility by preventing disruptions in these key metabolic pathways.

However, the review also revealed inconsistencies in the literature, where some studies demonstrated no significant association between choline intake and breast cancer risk, particularly in post-menopausal women (Cho et al., 2010) (22). This inconsistency may be attributed to variations in study design, dietary assessment methods, and population characteristics. For instance, the Nurses' Health Study, which involved over 74,000 post-menopausal women, did not find a clear protective effect of choline and betaine intake, possibly due to dietary variations and the long latency period of breast cancer development (Cho et al., 2010) (22). In contrast, the case-control study conducted by Zhang et al. (2013) in Chinese women reported a significant inverse association between dietary choline intake and breast cancer risk, suggesting that genetic factors and environmental influences might modulate choline's effect on breast cancer risk (23). Such discrepancies highlight the need for future research to consider genetic polymorphisms, particularly in the CHDH and PEMT genes, which have been shown to influence choline metabolism and modify breast cancer risk (11).

A key strength of this review is its comprehensive approach in synthesizing evidence from diverse study designs, including systematic reviews, meta-analyses, and observational studies. This allowed for a more nuanced understanding of the complex relationship between choline intake and breast cancer risk. However, the review had certain limitations. One limitation was the variability in dietary assessment tools across studies, which may have introduced measurement bias and impacted the comparability of findings. Additionally, the lack of standardized criteria for defining high and low choline intake posed challenges in interpreting the results uniformly. The inclusion of only English-language studies could also have led to the exclusion of potentially relevant data, thereby limiting the generalizability of the conclusions.

Future research should focus on addressing these limitations by employing more robust and standardized methodologies, such as using validated biomarkers for choline status and conducting longitudinal studies to capture long-term effects of choline intake on breast cancer risk. Additionally, the role of choline in different breast

cancer subtypes, as well as its interaction with other dietary factors and genetic variations, warrants further exploration. Understanding these complexities would contribute to more personalized dietary recommendations and potential therapeutic strategies targeting choline metabolism in breast cancer prevention and management. The findings of this review highlight the need for a multifaceted approach in future research to clarify the mechanisms underlying choline's protective effects and to identify specific subpopulations that may benefit from increased dietary choline intake.

CONCLUSION

In conclusion, this review highlights the potential anti-carcinogenic properties of choline in reducing the progression of breast cancer by regulating key metabolic pathways, particularly one-carbon metabolism and DNA methylation, which are crucial for maintaining genomic stability. Although the evidence suggests that adequate dietary intake of choline may lower breast cancer risk, the findings remain inconclusive due to genetic variations, methodological inconsistencies, and differing study populations. Given these complexities, further research is warranted to clarify the protective mechanisms and optimize choline intake recommendations in clinical settings. From a healthcare perspective, understanding choline's role could inform dietary guidelines and therapeutic interventions, ultimately contributing to more personalized approaches in breast cancer prevention and management.

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