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# Deciphering Food-Disease Relationships Through Molecular Networks in Breast Cancer

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**ABSTRACT**

**Purpose**: Despite advances in food and disease databases, a lack of integrated resources remains that systematically elucidate molecular-level food-disease associations. This study aims to introduce a comprehensive framework for mapping associations between foods, their metabolites, molecular targets, and diseases, using breast cancer as a case study.
**Methods**: We integrated data from FooDB, HMDB, and DisGeNET to extract information on foods, food-derived metabolites, protein/gene targets, and disease associations. Data cleaning and mapping were performed in Excel 2019. Networks illustrating food-metabolite-protein/gene-disease interactions were constructed and visualized using Cytoscape 3.7.2. Functional enrichment and topological analyses (degree and betweenness centrality) identified key nodes. Additionally, a systematic literature review was conducted in PubMed to synthesize evidence from systematic reviews and meta-analyses on dietary factors and breast cancer risk.
**Results**: The integrated network included nearly 1,000 foods, 61,500 ingredients, 250,000 metabolites, and 15,000 disease variants. The breast cancer network comprised 15,966 nodes and 321,144 edges. APOE emerged as the central gene, connected to 13,628 metabolites, while major food groups also featured as key nodes. Literature synthesis confirmed that high intake of fruits and vegetables is protective against breast cancer, while alcohol, fats, and processed meats increase risk, aligning with network findings.
**Conclusion**: This study proposes a molecular framework that links foods to diseases through metabolites and pathways, enabling testable hypotheses and informing precision nutrition. It urges improved data integration, control of confounders, and experimental validation to support personalized dietary recommendations.

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## Introduction

Food plays an essential role in human life, extending beyond its fundamental nutritional function to encompass social, cultural, and religious dimensions.[1] Dietary habits have a profound impact on human health, contributing not only to disease prevention but also to symptom management and therapeutic support.[2] The concept of "food as medicine" has gained growing scientific interest, emphasizing the capacity of dietary factors to influence health and disease through molecular and physiological mechanisms.[3-5] Recent advances have provided deeper insight into interactions between dietary constituents and key biological processes, including inflammation, metabolic regulation, and cellular homeostasis. These findings highlight the potential of targeted dietary strategies to contribute to the prevention, management, and treatment of chronic diseases.[6-8] At the molecular level, nutrients and food-derived metabolites serve as sources of energy, provide structural components required for tissue growth and repair, and support the development and regulation of immune function.[9-11] Many foods also contain bioactive compounds that can interact directly or indirectly with target proteins, influencing pathways involved in the development, progression, or suppression of disease.[12-14] In addition, food-derived compounds may affect the pharmacokinetics and pharmacodynamics of drugs, further highlighting the complexity of food-disease and food-drug interactions.[15-19]

Precision nutrition (PN), highlighted in the "NIH 2020-2030 Nutrition Research Strategic Plan", represents a transformative shift in nutritional sciences by acknowledging that individuals can respond differently to the same foods. By integrating multi-omics data, including genomics, proteomics, metabolomics, and microbiome composition, along with lifestyle factors, PN aims to generate personalized dietary recommendations that optimize health outcomes. In this context, PN investigates complex relationships between dietary components and biological systems through mechanisms such as gene-diet interactions,[20] microbiome-mediated metabolic effects,[21] and metabolomics signatures.[21]

Nutritional metabolomics has attracted considerable attention in recent years because of its potential to clarify the complex relationship among dietary components, their metabolic byproducts, and health outcomes. The link between diet and metabolic formation depends on biotransformation processes involving digestion, gut microbiota metabolism, and host-mediated metabolic pathways. Dietary carbohydrates, fats, polyphenols, and other bioactive constituents can be enzymatically converted into biologically active metabolites, including short-chain fatty acids and amino-acid derivatives. These metabolites act on host proteins and signaling pathways such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptors (PPARs), modulate epigenetic regulators such as histone deacetylases (HDACs), influence gut-microbiota activity, and reshape metabolic pathways. Collectively, these mechanisms contribute to the regulation of gene expression, maintenance of energy homeostasis, and fine-tuning of inflammatory responses.[22]

The concept of functional foods, which are enriched with biologically or physiologically active compounds that provide health benefits beyond basic nutrition[23] has also gained substantial research momentum. The identification and characterization of these bioactive compounds, alongside the detection of their metabolites in biological fluids or tissues, are critical for assessing nutrient imbalances, tracking biochemical responses to dietary interventions, and guiding personalized nutritional therapies. Clearly defining the molecular relationship between dietary components, target genes or proteins, and disease states is essential for advancing nutritional sciences and developing targeted nutritional interventions.

Despite the important contributions of existing databases such as NutriChem, DietRx, and FooDisNET, several key limitations remain. First, most of these resources are primarily centered on two- or three-layer relationships, such as food–disease or food–compound–protein associations, and therefore do not capture the broader biological complexity underlying diet-disease interactions. Second, many platforms assign directional scores, weights, or probabilities to reported associations. Although these measures can be useful for prediction, they may introduce confirmation bias and constrain the discovery of unexpected or alternative links. Third, a substantial number of available resources have been developed for specific diseases or food categories, which limits their broader applicability across diverse nutritional and biomedical contexts.

To address these gaps, the present study proposes a novel four-layer integrative framework. This framework offers several innovations: (1) the simultaneous integration of foods, metabolites, proteins/genes, and diseases within unified network; (2) an unbiased association-mapping strategy that avoids directional scoring and therefore more conductive to hypothesis generation; (3) generalizable methodology that can be applied to any disease context, illustrated here through breast cancer case study; and (4) a systematic validation strategy in which network-derived associations are compared against evidence reported in 35 systematic reviews and meta-analyses.

**Related works**

In recent years, considerable attention has been given to understanding the relationships between food, dietary constituents, and human disease, in parallel with advances in the study of drug-disease interactions. The primary focus has been on identifying relationships between food constituents and various biomedical entities, including diseases, treatments, drugs, and symptoms. Table 1 summarizes representative studies that have examined food-related associations in recent years.

Broadly, two main approaches have been used to explore the relationship between food and other biological entities. The first approach relies on text-mining techniques to extract associations from the scientific literature. Examples of this approach include DietRx,[24] NutriChem,[12] FooDis,[2] and ABCkb.[25] DietRx, for instance, documented 279,103 positive and negative associations linking food, chemical compounds, genes, and disease, based on text mining of MEDLINE abstracts. Similarly, NutriChem catalogued 6242 associations, involving 1066 plants and foods linked with 751 diseases. Nutrichem2 further expanded this scope by reporting 14662 drug–food interactions and highlighting 107 proteins commonly targeted by 428 drugs and 339 foods. The second approach infers the association between food and disease based on shared biological targets, particularly proteins or genes. In this context, computational (in-silico) methodologies have emerged as powerful tools for investigating associations among diverse agents by leveraging the wide structural variety of foods, drugs, and disease entities. Studies based on this approach are also summarized in Table 1.

Table 1. Summary of key studies on the extraction of food-related associations via text mining and computational (in-silico) approaches.

| Name (year) Type | Associations | Technique | Data volume | Specificity | URL Address, Ref. No. |
|---|---|---|---|---|---|
| NutriChem (2015) Database<br><br>NutriChem 2.0 (2017) | - Food - phytochemical associations<br>- Food-disease associations<br><br>NutriChem2.0<br>- Diet–drug–disease interactions | Text mining of over 21 million MEDLINE abstracts | -18478 pairs of 1772 plant-based foods and 7828 phytochemicals<br>- 6242 pairs of 1066 plant-based foods and 751 diseases<br>- Predicted Associations: 1,549 predicted links between 548 phytochemicals and 252 diseases<br>NutriChem2.0<br>- 7898 small molecule components<br>- 751 human diseases<br>- 14662 drug–food interactions<br>- 107 proteins targeted by 428 drugs and 339 foods | - Scope and Scale<br>- Data Integration<br>- Prediction Capabilities<br>- Visualization and Usability | http://cbs.dtu.dk/services/NutriChem-1.0[12]<br><br>http://sbb.hku.hk/services/NutriChem-2.0[14] |
| DietRx (2024) platform | - Disease-Chemical associations<br>- Chemical-Gene associations<br>- Disease-Gene associations<br>- Food-Disease associations | -Text-mining from biomedical literature (27 million MEDLINE abstracts)<br>- A deep learning-based relation classification model | - 279103 positive /negative food-disease associations<br>- 2222 food entities belonging to 24 categories (vegetable, plant, fruit, meat & egg, herbs & spices, etc)<br>-7610 disease entities<br>- 20550 gene entities<br>-6992 food chemicals | - Using machine learning algorithms to analyze associations | https://cosylab.iiitd.edu.in/dietrx/index[24] |
| FooDisNET (2020) Database | Direct Associations:<br>- Food-Compound<br>- Compound-Protein<br>- Compound – Disease associations<br>Indirect Associations:<br>- Food-Protein<br>- Compound-Disease<br>- Food –Disease associations | Identifying target proteins and affecting the disorder through natural products, food-compound-protein-disorder interaction through InChiKey | - 6329 plant foods<br>- 18689 diseases<br>- 53,920 compounds<br>- 22,865 proteins<br>- 332 KEGG biochemical pathways<br>- 2,105 reaction pathways (Reactome)<br>- 16,885 Gene Ontology terms | - Scope<br>- Approach<br>- Relation Types<br>- Dynamicity<br>- Precision | http://140.113.120.248/FooDisNET/[13] |
| ABCkb (2021) Database | - Direct Associations: Plant-Chemical<br>- Chemical-Gene<br>- Gene-Pathway<br>- Pathway-Phenotype<br>Indirect Associations: Plant-Disease | Text mining associations from MEDLINE abstracts using Linguamatics' I2E NLP text mining platform | - 2337 foods belonging to 25 food categories (plant, fruit, meat, etc.)<br>- 957,000 nodes with over 11 million edge relationships | - User-friendly interface<br>- Attention to precision nutrition | https://abckb.charlotte.edu[25]<br><br>Source code on Github https://github.com/atrautm1/ABCkb |
| SAFFRON (2021) Dataset | - Food-Disease Relation | Detecting the cause and treatment relations | Two datasets (the CrowdTruth and the ADE dataset were used. The best macro-average F1 scores were | - Its ability to accurately detect and classify food- | https://github.com/gjorgjinac/food-disease-dataset[26] |

| | | | | | |
|---|---|---|---|---|---|
| | | between food and disease entities from raw text | 0.847 and 0.900 for the cause and treatment relations. | disease relationships | |
| FooDis (2023) Pipeline | - Food-Disease relation<br>- Both causal and treatment relations between foods and diseases | Semi-automatic food-disease relation mining | - <1800 plant-based foods<br>- <4,000 dietary components<br>- food-disease relations: 931<br>- 931 cause<br>- 2059 treat relations<br>- In total, 79,941 abstracts | | Source code https://github.com/gjorgjinac/foodis_pipeline[2] |
| NutriFD (2023) Dataset | -Disease-miRNA associations<br>- Disease-Gene associations<br>- Disease Ontology | Developing a dataset for exploring the relationship between foods and Diseases from the perspective of nutrients<br>- Scoring the associations and therapeutic relationships | - 3,237,640 connections between foods and diseases<br>- 591 foods<br>- 2,208 diseases | | https://nutrifd.dedyn.io[11] |

After extracting the main items of some relevant studies in food-disease associations, as shown in Fig. 1, we presented the food-disease databases' data sources.

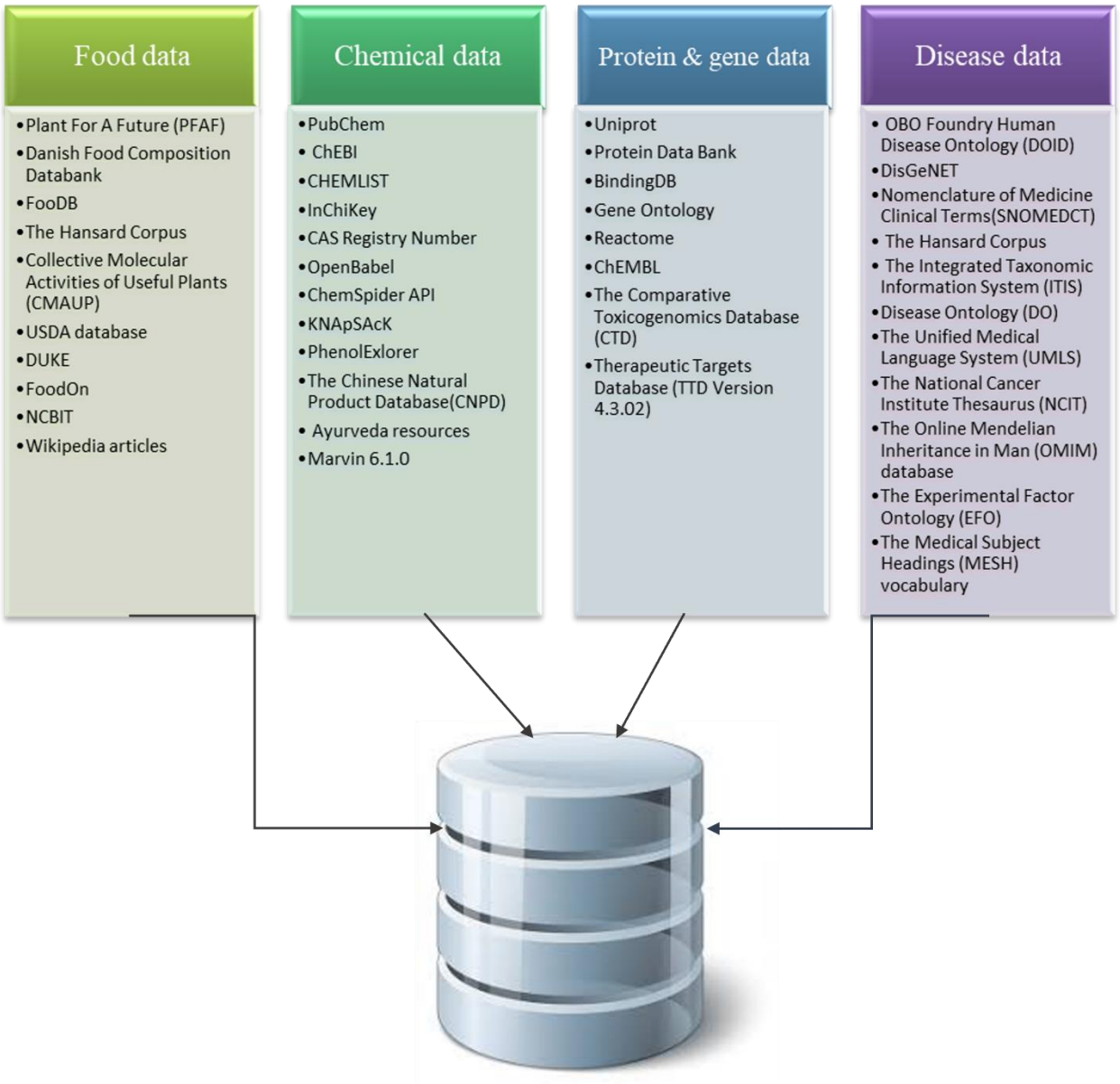


**Fig. 1.** The data sources of the food databases

## Methods and materials

This study investigates associations between dietary components and diseases by analyzing shared molecular targets. Our approach integrates bioinformatics databases and network-based analytical tools to illustrate the potential molecular mechanisms underlying the effects of specific food-derived compounds on disease pathways. In Fig. 2, we illustrated the overall framework.

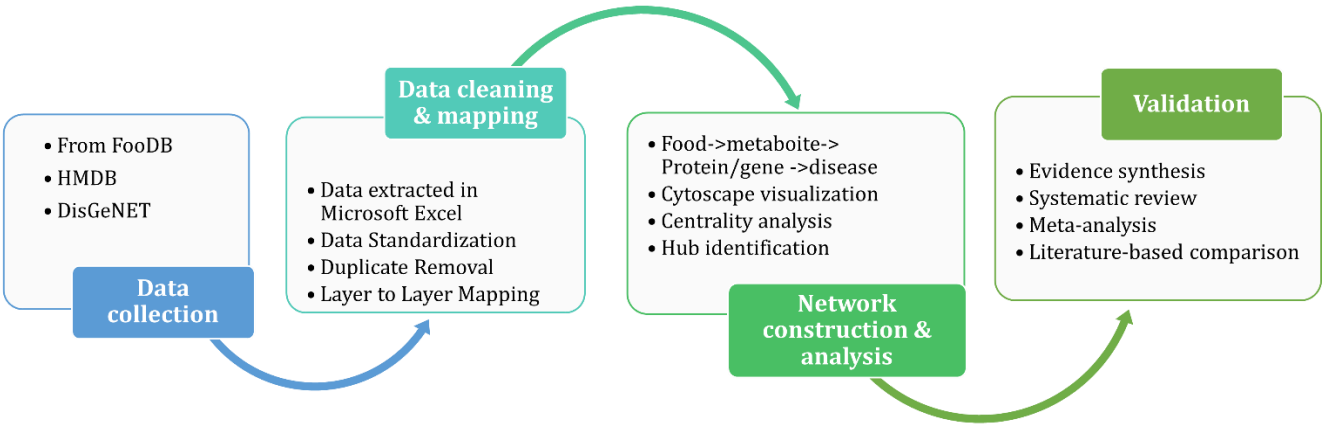


**Fig. 2.** Overall Framework for Deciphering Food-Disease Relationships through Molecular Networks

## Data Collection

Food items and their constituent compounds were identified from the FooDB.[27] These food-derived compounds were then mapped to corresponding nutritional metabolites known to occur in the human body. Data on metabolites, proteins, and metabolite-protein interactions were obtained from the Human Metabolome Database (HMDB) version 4.0.[28] Additionally, disease-associated proteins and genes were retrieved from the DisGenet database.[29,30] Breast cancer was selected as the case study because it is the second most prevalent cancer worldwide.[31] Fig. 3 shows a thematic network linking food metabolites, target proteins/genes, and associated diseases.

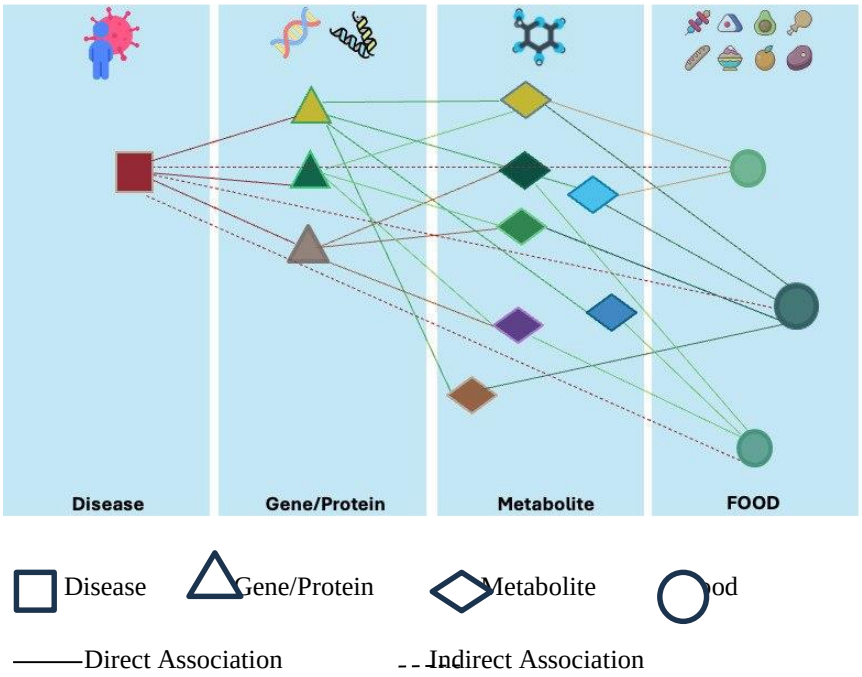


**Fig. 3.** Thematic network of associations between food metabolites, protein/gene targets, and diseases

**Mapping and cleaning**

The metabolites corresponding to each protein were systematically extracted. Proteins linked to disease-related mechanisms- such as key receptors, enzymes, and signaling molecules- were specifically identified for further in-depth analysis. Data importation and initial cleaning were performed using Microsoft Excel 2019.

**Network construction**

In the final phase of analysis, a multi-layer network was constructed to show direct and indirect relationships among foods, metabolites, proteins/genes, and diseases. Interactions among foods, metabolites, proteins/genes, and disease entities, along with the results of functional enrichment analyses, were visualized using Cytoscape software (version 3.7.2).[32] Cytoscape is a widely used platform for integration, analysis, and interactive visualization of complex biological network data, enabling the exploration of intricate relationships and identification of significant biologically meaningful patterns.[32-34]

**Evidence synthesis**

A literature review was conducted to identify and summarize existing systematic reviews and meta-analyses examining the associations between dietary intake and breast cancer outcomes. Dietary exposure of interest included specific foods, food groups, and overall dietary patterns, while outcomes included breast cancer incidence, recurrence, and mortality. The findings of included studies were qualitatively synthesized, with particular attention to the consistency, quality, and volume of evidence supporting reported associations between dietary factors and breast cancer risk or recurrence.[35]

The review question was structured according to the PICO framework as follows:

Population, women with breast cancer or women at risk of developing breast cancer; Intervention/Exposure, dietary intake including specific foods, food groups, or dietary patterns; Comparison (no pre-defined comparison group); and Outcome, breast cancer incidence, recurrence, or mortality.

A comprehensive literature search was conducted in Medline via PubMed, with no restrictions on publication date or language. The following search strategy was used:

("breast neoplasm" (MeSH Terms) OR "breast cancer" OR "breast tumor") AND ("diet" (MeSH Terms) OR "food" OR "nutrition") AND ("systematic review" (MeSH Terms) OR "meta-analysis" (MeSH Terms) OR "systematic review*" OR "meta-analysis"). Study selection was conducted in two steps: first, screening titles and abstracts, followed by full-text assessment of potentially eligible articles. Systematic reviews and meta-analyses were included if they evaluated the association between dietary patterns, specific foods, or food groups and breast cancer outcomes. Reviews examining broader dietary interventions, including Mediterranean or Western dietary patterns, were also eligible for inclusion. Table 2 presents a summary of the included studies.

**Results**

Based on data extracted from the FooDB, HMDB, and DisGenet databases, we identified approximately 1000 foods and up to 61,500 dietary components from the FooDB, around 250000 metabolites from HMDB, and 15000 disease-associated variants from DisGenet. Figure 4 (A) summarizes the data retrieved from these biomedical

databases. Given the large volume of data on disease-associated genes and food-derived metabolites, a comprehensive analysis across all disease categories was not feasible. Therefore, breast cancer was selected as a representative case study for detailed investigation, as it is among the most prevalent cancers worldwide. To our knowledge, this study represents the first four-layer food–metabolite–protein/gene–disease network for breast cancer that explicitly avoids directional scoring, thereby supporting unbiased hypothesis generation.

**Case study on breast cancer**

Breast cancer (BC) is the second most common cancer worldwide and remains a leading cause of cancer-related deaths among women.[36] In this study, we evaluated the dietary components potentially associated with breast cancer. Increasing evidence on dietary patterns, micronutrients, and bioactive compounds suggests that nutrition-based strategies may contribute to improved treatment outcomes in patients with breast cancer, both during and after therapy.[37-39]

To identify key food groups and related molecular components, we constructed a gene-metabolite association network. Data on breast cancer-related metabolites were extracted from FooDB, HMDB, and DisGenet databases as summarized in Fig. 4 (B). We visualized the molecular-level associations between foods and disease phenotypes using Cytoscape. The disease-gene network is presented in Fig. 4. At the same time, the detailed associations among genes, metabolites, and foods related to breast cancer are shown in Fig. 5. The resulting network comprised 15966 nodes and 321144 edges.

Further network analyses were conducted based on key topological parameters (centrality), specifically node degree and betweenness centrality. Comprehensive details of these associations are provided in the supplementary materials.

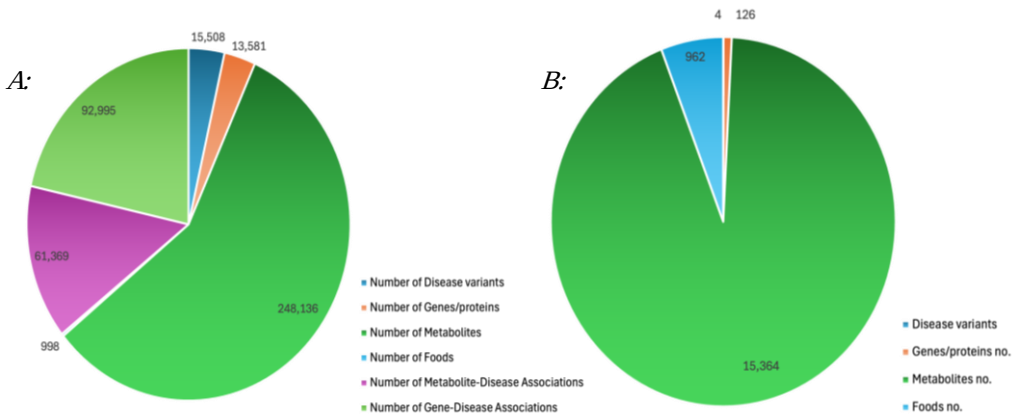


**Fig. 4.** Data extracted from biomedical databases for diseases, disease-associated genes, foods, and food-derived metabolites (A), and breast cancer-related data (B)

Fig. 5 demonstrates the network of genes involved in different breast cancer phenotypes, while Fig. 6 shows the identification of the top 10 nodes with the highest degree values in the network. Among these, Apolipoprotein E (APOE) emerged as the most prominent node, representing a key gene linked to 13628 metabolites. The remaining nine major hub nodes identified through network analysis corresponded to food groups including fruits, animal foods, herbs & spices, vegetables, pulses, cereals & cereal products, teas, nuts, and soy foods. Based on the network analysis, degree values for these hub-bottleneck nodes ranged from 745 to 13595.

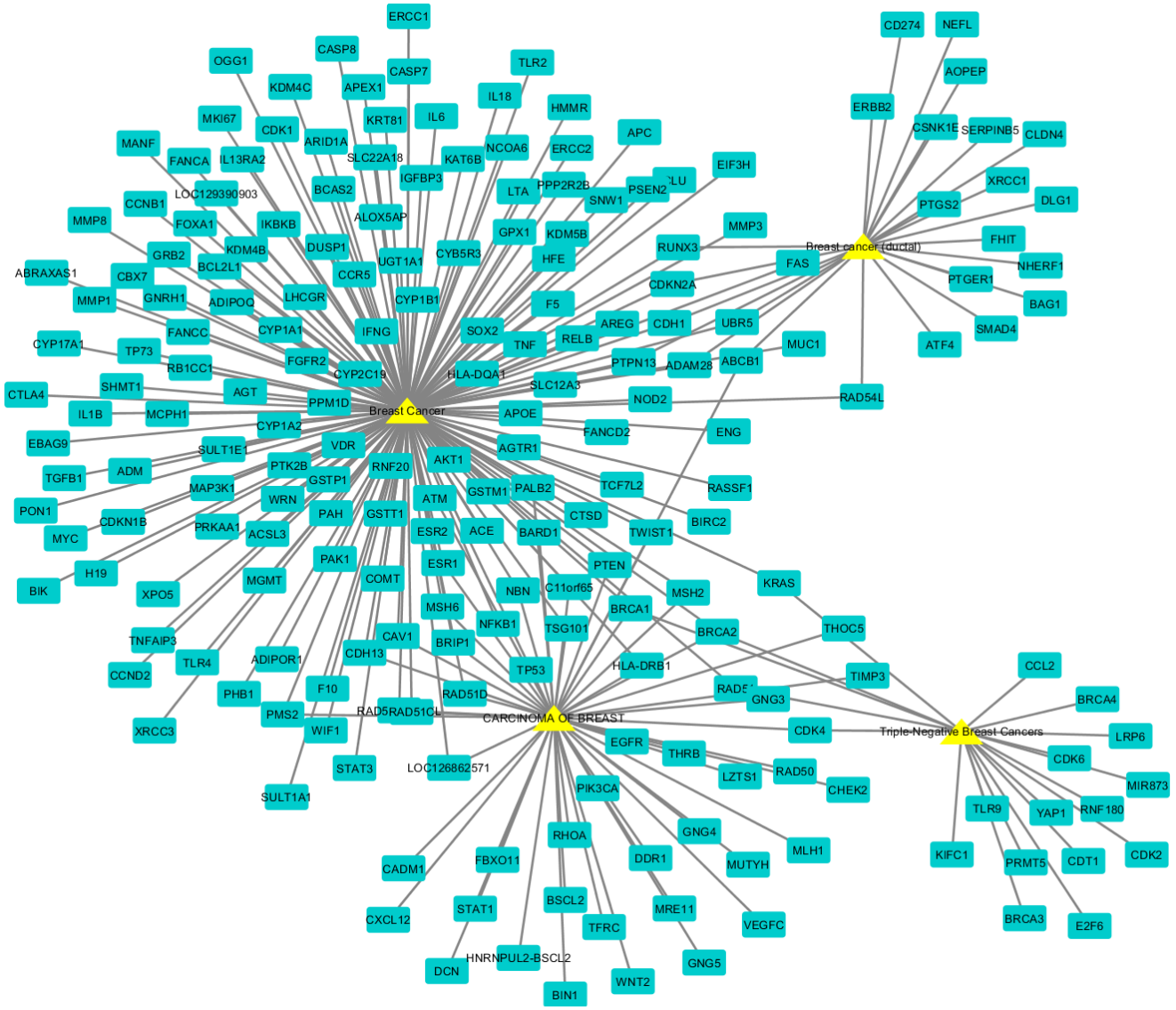


**Fig. 5.** The network of genes involved in breast cancer

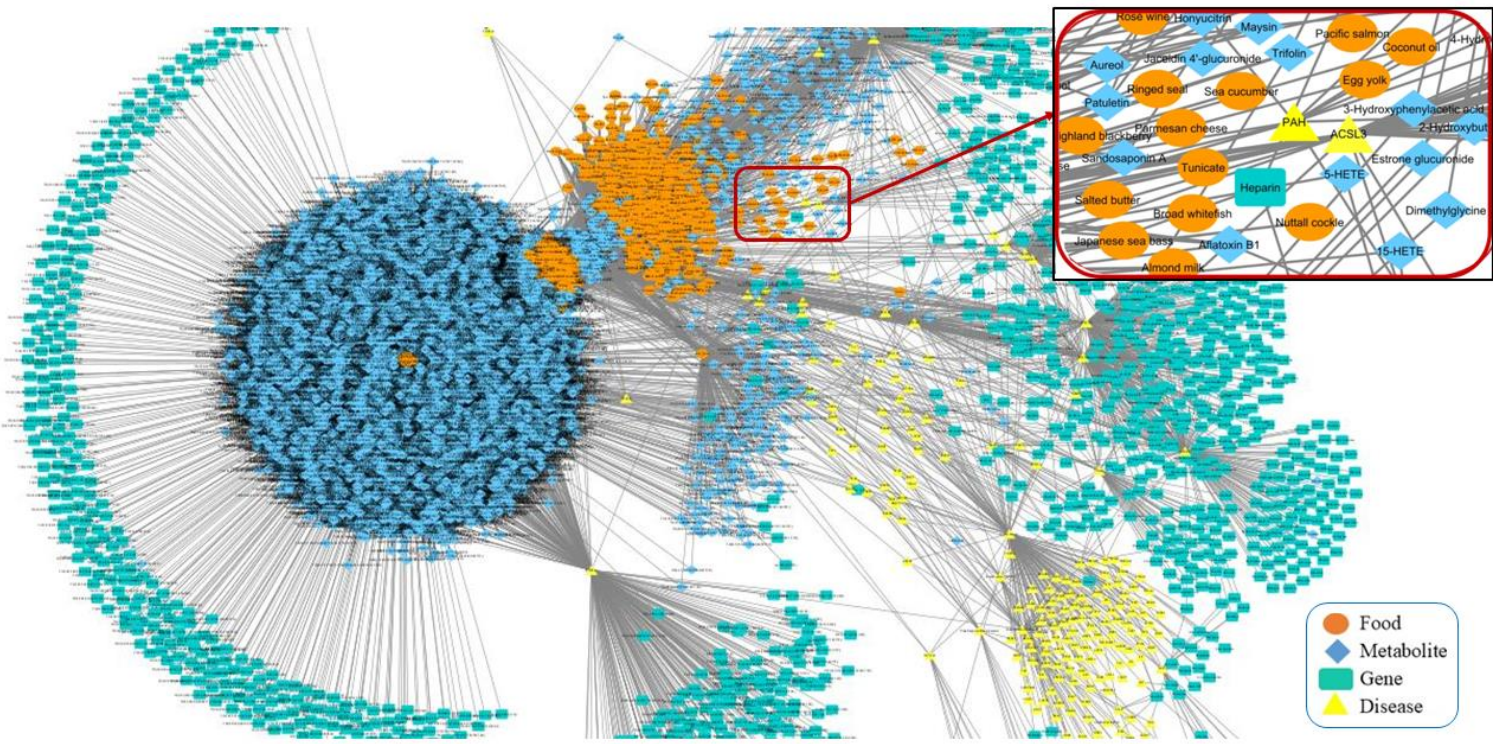


**Fig. 6.** The network of genes, metabolites, and food associations in breast cancer.

Supplementary files S5-S6 contain Fig. 5 & Fig. 6 as exported files from Cytoscape software.

**Evidence linking food groups to breast cancer**

To summarize the current evidence on associations between specific foods or food groups and breast cancer risk, recurrence, or mortality, we reviewed published systematic reviews and meta-analyses. A structured literature search in PubMed on December 25, 2024, identified 227 articles. Eligible studies were those examining associations between dietary exposures, including foods or food groups) and breast cancer risk, mortality, or disease recurrence. Initial screening based on titles and abstracts yielded 86 potentially relevant reviews. After full-text evaluation, 35 systematic reviews and meta-analyses met all inclusion criteria and were included for detailed assessment. The key descriptive characteristics of these studies are summarized in Table 2.

**Table 2.** Key descriptive characteristics of systematic reviews and meta-analyses examining the association of dietary exposures and breast cancer

| Author | Year | Region/ Country | Study Type/No. | Results in brief | Results | Molecular level |
|---|---|---|---|---|---|---|
| Jadwiga Konieczna, et al.[40] | 2024 | Spain | 84 (77 observational, 7 RCT) | Vegetarian/Mediterranean dietary ☺ Western/Meat/Alcohol dietary ☹ | Prudent/Vegetarian/Mediterranean dietary patterns may reduce BC risk in all females A posteriori, Western dietary patterns, meat-rich, and alcohol-inclusive diets may elevate the risk of breast cancer (BC) in postmenopausal women. Conversely, dietary patterns that are prudent, vegetarian, or Mediterranean in nature could potentially lower the risk of breast cancer across all females. | |
| Heba Mohammed Arafat, et al.[41] | 2023 | Malaysia | 18 (9 Prospective, 7 Retrospective, 2 Cross-Sectional) | Dairy consumption ☺ | Negative correlations were observed between dairy consumption and the risk of breast cancer | |
| Jiajie Zang, et al.[42] | 2015 | China | 27 (22 prospective cohort studies, 5 case-control studies) | Yogurt and low-fat dairy ☺ | Yogurt and low-fat dairy products were linked to a decreased risk of breast cancer. Among Asians, the highest levels of dairy consumption were also associated with a lower risk of developing breast cancer. | |
| E Vidal García, et al.[43] | 2020 | Spain | 18 (10 case-control, 8 cohort studies) | Dairy products ☺ | The consumption of dairy products was negatively correlated with the risk of breast cancer. | |
| Xue-Ou Liu, et al.[44] | 2014 | China | 33 (31 case-control studies, 2 | Soy and fruit ☺ Fat ☹ | Soy and fruit intake were strongly linked to a reduced risk of breast cancer, while fat consumption was associated with an increased risk. | |

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| | | | cohort studies | Vegetables 😐 | Additionally, vegetables appear to offer protective benefits against breast cancer. | |
| Sangah Shin, et al.[45] | 2023 | South Korea | 49 (15 cohort studies and 34 case-control studies) | Fruits and vegetables 🙂 Alcohol ☹ Meat, soy foods, and green tea 😐 | Eating fruits and vegetables was linked to a 29% lower risk of breast cancer. No significant relationship was observed between the consumption of meat, soy foods, or green tea and breast cancer risk. Following a healthy dietary pattern was associated with a 38% to 51% reduction in breast cancer risk, whereas adherence to an unhealthy dietary pattern correlated with a 44% increase in risk. Additionally, alcohol consumption was associated with a 75% increase in breast cancer risk. | Isoflavone 🙂 |
| Rita CR Albuquerque, et al.[46] | 2014 | Brazil | 26 (11 cohort studies, 15 case-control studies) | Vegetables, fruit, fish, and soy 🙂 Alcohol ☹ | The Mediterranean dietary pattern, along with diets rich in vegetables, fruits, fish, and soy, is linked to a lower risk of breast cancer. In contrast, traditional dietary patterns showed no significant association with breast cancer risk, although one study indicated that a Western dietary pattern may increase this risk. | |
| Alessandra Buja, et al.[47] | 2020 | Italy | 48 (32 meta-analyses, 4 pooled analyses, 5 systematic reviews, and 7 qualitative reviews) | Vegetables, citrus fruit, soy, and mushrooms 🙂 Meat, red or processed meats, and eggs ☹ | A higher intake of total meat, or red or processed meats, foods with a high glycemic index, or eggs, would seem to be associated with a higher risk; vegetables, citrus fruit, and mushrooms would seem instead to have an inverse association. | polyunsaturated fatty acids (PUFA) 🙂 vitamin D and calcium 🙂 flavonoids and flavones 🙂 Folate 😐 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | α-carotene and β-carotene ☺ |
| Jung-Kook Song, et al.[48] | 2013 | Korea | 6 case-control studies out of five articles | Citrus fruits ☺ | Higher intake of citrus fruits may decrease breast cancer risk. | β-carotene, vitamin C, ☺ |
| Niki Mouroutsi, et al.[49] | 2015 | Greece | - | Soy ☺<br>Dietary Fat ☹<br>Fruit, vegetables, and meat 😐 | Soy food consumption appears to be linked to a lower risk of breast cancer. In contrast, higher dietary fat intake may indicate an increased risk of developing breast cancer. However, research on the impact of fruits, vegetables, meat, and overall dietary patterns on breast cancer risk has produced mixed findings. | |
| Sarah F. Bernnan, et al.[50] | 2017 | UK | 15 prospective cohorts | Saturated fat 😐 | There was no difference in risk of breast-cancer-specific death or all-cause death; there was a higher risk for women in the highest versus the lowest category of saturated fat intake. | |
| Akhila Dandamudi, et al.[51] | 2018 | USA | 17 case-control studies | Vegetables ☺<br>Saturated fat, red or processed meats ☹ | Vegetables were consistently identified as part of dietary patterns that protect against breast cancer, while saturated fats, red meats, and processed meats were linked to patterns associated with a higher risk of breast cancer. | |
| Mei-Yuan Xing, et al.[52] | 2014 | China | 3 (2 RCTs and one large multi- | Low-fat diet ☺ | Post-diagnostic low-fat diet reduced the risk of recurrence of breast cancer by 23%, and all- | |

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|---|---|---|---|---|---|---|
| | | | center prospective cohort study) | | cause mortality of breast cancer by 17%. | |
| Jalal Poorolajal, et al.[53] | 2021 | Iran | 92 studies (56 Alcohol drinking, 22 Red meat, 14 Fruit/ Vegetable) | Vegetables, fruit ☺ Alcohol ☹ Red meat 😐 | Alcohol drinking significantly increased the risk of breast cancer by 10%, and fruit/vegetable consumption significantly reduced the risk of breast cancer by 23%. Red meat had no significant effect. | |
| Paula Tâmara Vieira Teixeira Pereira, et al.[54] | 2018 | Brazil | 8 studies (7 articles, 1 dissertation) | Guarana ☺ fruits and vegetables ☺ | The most commonly used supplements that improve fatigue were guarana, acetyl-L-carnitine, and coenzyme Q10. | acetyl-l-carnitine with co-enzyme Q10 ☺ CoQ10 with vitamin E 😐 |
| Djibril M Ba, et al.[55] | 2021 | USA | 17 Observational studies, 6 cohort studies, 11 case-control studies | Mushroom ☺ | Higher mushroom consumption of 18 g/d was associated with a 45% lower risk of total cancer compared with 0 g/d. | Ergothioneine ☺ |
| A Gopinath, et al.[56] | 2022 | USA | 22 articles (7 systematic reviews with meta-analysis, 7 reviews, 2 RCTs, 6 observational studies) | Dietary fat ☹ | There was a significant correlation between dietary fat and an increased risk of breast cancer development and a worsening prognosis | |

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| Sylvia H J Jochems, et al.[57] | 2018 | UK | 38 studies (2 RCTs and 36 cohort studies) | Dietary fat ☹ | Reducing the amount of fat after diagnosis appears to decrease the risk of breast cancer recurrence. Adherence to a Western diet, before and after diagnosis, appears to increase the risk of overall mortality from other causes among breast cancer survivors. | |
| Shikha Virani, et al.[58] | 2024 | USA | 11 studies (3 RCTs, 4 observational studies, 4 reviews and systematic reviews) | Mediterranean diet ☺ legumes, fruits, and vegetables ☺ Olive oil ☺ | Following the Mediterranean diet is associated with better quality of life and lower mortality rates in women with breast cancer, especially among older individuals. Additionally, certain unsaturated fats, particularly omega-3 polyunsaturated fatty acids (PUFAs), exhibit anti-cancer effects. | Docosahexaenoic acid (DHA), Eicosapentaenoic acid (EPA) ☺ β-carotene, lycopene ☺ Polyphenols ☺ Calcium ☺ |
| Laurah B Turner[59] | 2011 | USA | 57 published studies | Dietary fat 😐 | Post-menopausal women indicated a significant association between total fat, PUFA intake, and breast cancer. A non-significant inverse relation between intakes of all fat types was identified in premenopausal women. | |
| S Gandini, et al.[60] | 2000 | Italy | 26 published studies | Vegetables, fruit ☺ Olive oil ☺ | This analysis confirms the association between the intake of vegetables and, to a lesser extent, fruits and breast cancer risk from published sources. | β-carotene ☺ Linoleic acid and tocopherol ☺ |
| Lu Chen, et al.[61] | 2019 | China | 8 publications | Milk or milk products 😐 | The results of all milk models and the available epidemiologic evidence do not support a strong association between the consumption of milk or milk products and breast cancer risk. | |

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|---|---|---|---|---|---|---|
| Luisa Hardt, et al.[62] | 2022 | Germany | 30 studies (seven meta-analyses and 23 primary studies) | Fruit, vegetable, and soy  | For breast cancer survival, a higher intake of fruit, vegetables, and fibre and a moderate intake of soy/ isoflavone were associated with beneficial outcomes. | |
| Feng Chi, et al.[63] | 2013 | China | 5 cohort studies | Soy food  | Pooling the comparisons of highest vs. lowest dose, soy food intake after diagnosis was associated with reduced mortality and recurrence. | |
| Paula A Oliveira, et al.[64] | 2023 | Portugal | 4 studies (3 in vitro studies, 1 mixed study with in vivo and in vitro approach) | Quercus spp. Extract  | The results suggested a positive impact of Quercus spp. extract by reducing cancer development | |
| Dennis A. Savaiano, et al.[65] | 2021 | USA | 16 studies (1 RCT, 11 cohort studies, 5 case-control) | Yogurt, other fermented milk products  | A causal relationship exists between lactose digestion and tolerance and yogurt consumption, and consistent associations exist between fermented milk consumption and reduced risk of breast cancer | |
| Shiva Nasr, et al.[66] | 2023 | Iran | - | Soy products  | The effect of flavonoids on changes in IGF1 and IGFBP-3 was not statistically significant. A high soy diet has beneficial effects on IGF system components, which might be useful in breast cancer. | Flavonoids  |
| Dominik D. Alexander, et al.[67] | 2010 | USA | 8 prospective cohorts | Animal fat  | No significant association was observed comparing the highest category of animal fat intake with the lowest. Similarly, no significant association between a 5% increment of energy from animal fat intake and breast cancer. | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Heidi Fritz, et al.[68] | 2013 | Canada | 131 articles: 40 RCTs, 11 uncontrolled trials, and 80 observational studies | Soy 🙂 Red clover 😐 | Soy intake consistent with that of a traditional Japanese diet (2-3 servings daily, containing 25- 50 mg isoflavones) may be protective against breast cancer and recurrence. | |
| Jana J. Anderson, et al.[69] | 2018 | UK | 10 cohort studies | Red meat, 😐 processed meat ☹ | Processed meat consumption was associated with overall and post-menopausal, but not pre-menopausal, breast cancer. Red meat consumption was not associated with breast cancer. | |
| Naria Sealy, et al.[70] | 2021 | USA | 10 observational studies (2 prospective studies, 8 case-control studies) | Olive oil 😐 | Comparing women with the highest intake to those with the lowest category of olive oil intake was 0·48 in case-control studies, with evidence of substantial study heterogeneity. | |
| Xia Ye, et al.[71] | 2023 | China | 5 studies (2 case-control studies, 3 cohort studies) | Sweeteners 😐 | Exposure to artificial sweeteners was not related to the risk of BC. | |
| Asma Kazemi, et al.[72] | 2021 | Iran | 75 studies reported ≥1 of the 13 food groups | Vegetables, fruit, cheese, soy products 🙂 Red meat, processed meat ☹ | Inverse linear associations were observed for vegetables, fruit, cheese, and soy, while positive associations were observed for red and processed meat. None of the other food groups was significantly associated with breast cancer risk. | |
| Amir Shamshirian, et al.[73] | 2020 | Iran | 39 studies (35 case-control, 4 cross- | Vegetables 🙂 Sweets ☹ | A significant harmful effect of sweets consumption and inverse linear associations were observed for vegetable consumption. | |

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|---|---|---|---|---|---|---|
| | | | sectional studies) | | | |

We compared the food-metabolite associations related to breast cancer in our network with the findings of the systematic review (Table 3). In this table, the "Category" column demonstrates food categories derived from the USDA fact sheets,[74] while the "Food categories" column reflects the food groups identified through the association network (Fig. 6). Vegetables and fruits were the most frequently investigated food groups, appearing in 17 and 13 systematic reviews, respectively. In contrast, sugars, snacks, and sweet foods were each examined in only one systematic review.

**Table 3.** Dietary dos and don'ts in systematic reviews & extracted from a network for breast cancer based on USDA food categories

| **Category** | **Subcategory** | **Evidence** ☺ | **Evidence** 😐 | **Evidence** ☹ | **Food categories** |
|---|---|---|---|---|---|
| MILK AND DAIRY | Dairy products | 41, 42,43 | 61 | | Milk and milk products |
| | Yogurt and Fermented milk | 42, 65 | 61 | | |
| | Low-fat dairy | 42 | 61 | | |
| | Cheese | 72 | | | |
| PROTEIN FOODS | Fish | 46 | 72 | | Animal foods<br>Aquatic foods<br>Eggs<br>Nuts<br>Pulses<br>Soy |
| | Legumes | 58 | 72 | | |
| | Poultry | | 72 | | |
| | Nuts | | 72 | | |
| | Red meat | | 45, 49, 53, 69 | 40, 47, 51, 72 | |
| | Processed meat | | | 40, 47, 51, 69, 72 | |
| | Soy | 44, 46, 49, 62, 63, 68, 72 | 66 | | |
| | Acorn | 64 | | | |
| | Egg | | 72 | 47 | |
| GRAINS | Carbohydrates | | 49 | | Cereals and cereal products |
| | Whole grains | 40 | 72 | | |
| SNACKS AND SWEETS | Sweets | | | 73 | Snack foods<br>Confectioneries |
| FRUIT | Fruits | 40, 44, 46, 53, 54, 58, 60, 62, 72 | 49 | | Fruits<br>Gourds |

| | | | | | |
|---|---|---|---|---|---|
| | Citrus fruits | 47, 48 | | | |
| | Guarana | 54 | | | |
| VEGETABLES | Vegetables | 40, 45, 46, 47, 51, 53, 54, 58, 60, 62, 72, 73 | 44, 49 | | Vegetables<br>Gourds<br>Herbs and Spices |
| | Mushroom | 47, 55 | | | |
| | Red clover | | 68 | | |
| MIXED DISHES | | | | | Dishes |
| BEVERAGES, NONALCOHOLIC | Green tea | | 45 | | Beverages<br>Coffee and coffee products<br>Teas |
| | Fruit juice | | 72 | | |
| ALCOHOLIC BEVERAGES | Alcohol | | | 40, 45, 46, 53 | Alcoholic beverages |
| FATS AND OILS | Dietary fat | | 50, 59, 67 | 44, 49, 51, 52, 56, 57 | Fats and oils |
| | Olive oil | 58, 60, 70 | | | |
| WATER | | | | | Water |
| CONDIMENTS AND SAUCES | | | | | Baking goods |
| SUGARS | | | 71 | | Confectioneries |
| INFANT FORMULA & BABY FOOD | | | | | Baby food |
| OTHER | | | | | Cocoa and cocoa products<br>Theobroma cacao |

**Discussion**

This study introduces a novel four-layer framework for exploring molecular-level associations between foods and diseases. Rather than assigning scores or interpreting directional effects, positive or negative, we focused on uncovering potential associations between foods and diseases through shared metabolites and protein targets. This non-directional and exploratory strategy supports the generation of testable hypotheses regarding the mechanistic links between dietary components and disease processes, mediated through genes or protein targets. We applied this framework to breast cancer as a case study and constructed a network of food-derived metabolites and their potential interactions with genes implicated in the disease. The resulting associations were further examined in relation to existing evidence from systematic reviews and meta-analyses by existing literature, as summarized in

Fig. 4 (B). Importantly, the proposed methodology is not limited to breast cancer and can be extended to other diseases, phenotypes, or clinical conditions.

By identifying foods and their bioactive metabolites that may interact with genes associated with breast cancer, this study provides a framework for constructing hypothetical food–metabolite–gene–disease networks. Such networks may serve as a starting point for future experimental studies aimed at validating dietary interventions, identifying molecular mechanisms, or discovering novel nutrition-related therapeutic targets.

Based on results (Fig. 5), APOE emerged as the largest and most connected node in the association network. APOE is a key protein involved in lipid metabolism and has been previously linked to the progression of several cancer types,[75-77] including breast cancer.[78] Evidence suggests that elevated levels of APOE may promote tumor growth by supplying essential lipids required for cancer cell proliferation.[79-81] Furthermore, serum APOE has been proposed as a promising non-invasive biomarker for the diagnosis and prognosis of breast cancer.[82]

The remaining nine major nodes in the network represented distinct food groups, each of which has been reported to have either protective or risk-associated relationships with breast cancer risk (Fig. 6). Numerous studies have consistently reported the protective associations between higher intake of vegetables and fruits, and reduced breast cancer risk and improved survival outcomes.[45-48,51,53-55,60,62,72,73] These findings are consistent with associations observed in our network analysis. Additionally, the systematic reviews included in our evidence synthesis did not report adverse associations between breast cancer risk and intake of fruits, vegetables, soy, grains, or dairy products (Table 2). In contrast, substantial evidence supports an association between alcohol intake, dietary fats, red and processed meat consumption, and an increased risk of breast cancer and several other cancer types.[40,44-47,49,51,53,56,57,69] Processed red meat contained relatively high concentrations of added nitrites and nitrates, amines, and heme iron- a combination previously shown to promote the endogenous formation of N-nitroso compounds (NOCs).[83] In our evidence synthesis, four systematic reviews reported a significant association between alcohol consumption and an increased risk of breast cancer.[40,45,46,53] Alcohol may increase breast cancer risk through several mechanisms, including its metabolism into carcinogenic compounds, particularly acetaldehyde, and the generation of free radicals such as hydroxyl radicals. Alcohol intake may also elevate serum estrogen concentration, thereby increasing estrogen-mediated carcinogenic activity in breast tissue.[45]

In contrast to other dietary fats, current evidence suggests that olive oil intake may exert a protective effect against breast cancer.[58,60] Potential anti-cancer properties of olive oil are largely attributed to its high content of monounsaturated fatty acids, especially oleic acid, as well as squalene. Furthermore, several bioactive compounds present in olive oil, including lignans, oleocanthal, oleuropein, and hydroxytyrosol, may contribute to its potential role in breast cancer prevention.[58]

Although many studies have examined the relationship between overall diet and breast cancer, research focusing on individual bioactive food components remains comparatively limited. Existing evidence suggests potential protective roles for nutrients and bioactive compounds such as vitamin D, calcium,[47,58,84,85] isoflavones,[45,47] vitamin A,[86] vitamin E,[87] and coenzyme Q10.[88] However, the biological mechanisms underlying these associations are not yet fully understood. Further investigation is therefore needed to clarify how these compounds influence breast cancer-related pathways and to inform the development of targeted dietary interventions for breast cancer prevention and management.

**Integration with multi-omics for precision nutrition**

The "2020-2030 NIH Nutrition Research Strategic Plan" emphasizes the importance of advancing precision nutrition to address the fundamental question: "What should we eat to stay healthy?".[89] Contemporary perspectives on food and health have introduced a paradigm shift in nutrition research and practice, giving rise to precision nutrition as a promising approach for delivering personalized, dynamic, and multidimensional dietary recommendations.[90,91] Similar to precision medicine, precision nutrition strives to understand the complex interactions among genetic makeup, microbiome composition, antibiotic and probiotic exposure, metabolic processes, food environment, physical activity, and broader economic, social, and behavioral determinants of health.[92,93] Emerging research has begun to demonstrate the potential of precision nutrition strategies in disease prevention and management. For example, Fabozzi et al. proposed a precision nutrition approach to reduce the risk of Alzheimer's disease in individuals carrying the APOE4 allele, a well-established genetic risk factor.[94] To further advance personalized nutrition, continued investigation is needed into how dietary factors interact with genetic, epigenetic, and microbiome-related variables.

The four-layer framework proposed in this study provides a foundation for incorporating multi-omics data into precision nutrition strategies. By linking foods, metabolites, genes/proteins, and diseases, this approach can help identify biologically meaningful pathways through which dietary components may influence disease risk or progression. Precision nutrition aims to provide individualized dietary recommendations by accounting for variability among individuals in genetic, metabolic, and microbial profiles.[95,96] Evidence from large-scale prospective cohorts and multi-omics studies has increasingly shown that each omics layer can contribute to a more refined understanding of diet–breast cancer associations.

**Genomics and nutrigenetics:** Nutrigenomics examines how genetic variation influences responses to bioactive dietary components and how nutrients modulate gene expression.[97] In the breast cancer network, the APOE gene emerged as the central hub (Fig. 6). In the context of breast cancer, existing evidence suggests that genotype-guided dietary recommendations based on APOE status may represent a viable precision nutrition strategy.[98] More broadly, adherence to the Mediterranean dietary pattern has been shown to interact with genetic variants to modify breast cancer risk, with certain genotypes demonstrating differential responses to polyphenols and micronutrients commonly found in this dietary pattern.[99] These findings imply that a "one-size-fits-all" dietary recommendation may be suboptimal and support the development of dietary interventions tailored to individual genetic profiles.[97]

**Metabolomics**

Unlike genomics, which provides relatively stable information about inherited risk, metabolomics captures dynamic and real-time metabolic responses to diet, lifestyle, and disease states.[100] Nutritional metabolomics has emerged as a powerful tool for identifying metabolites and metabolic pathways associated with breast cancer risk and progression.[101]

In this context, integrating metabolomics data into food-disease networks may help clarify how food-derived compounds influence disease- related molecular processes.

**Microbiome**

The gut microbiome plays a critical role in converting dietary components into bioactive metabolites that can influence host physiology.[102] In breast cancer, growing evidence indicates that nutritional intervention may

modulate both the composition and functional capacity of the gut microbiome, with microbiome-mediated mechanisms potentially contributing to cancer prevention and therapeutic responses.[2] Therefore, convergence of genomics, metabolomics, and microbiome data within a unified framework may enable systems-level approaches to precision nutrition.

The concept of "Food as Medicine" (FAM) has also emerged as an innovative strategy in coronary disease management, connecting diet choices to health outcomes by integrating nutrition-based therapies with conventional medical care. As the implementation of FAM programs expands, robust scientific evidence is increasingly required to validate their potential health benefits. To this end, it has become essential to characterize and define the association between foods and diseases more clearly. In recent years, several databases have been developed to explore food-disease interactions. The reliability and validity of these resources depend largely on the methods used to establish connections between dietary factors and disease outcomes.[11] One commonly used approach involves text mining methods that directly extract associations from clinical studies and biomedical literature. Alternatively, other databases infer food-disease relationships indirectly by linking foods to diseases through intermediary entities, such as chemical compounds. Integrating molecular-level data into food-disease networks enables a more comprehensive analysis and provides deeper insight into the biological mechanisms underlying these interactions.[103] For example, Su et al. developed NutriFD,[11] a database that scores therapeutic associations between foods and diseases. Unlike earlier food-disease databases, NutriFD employs machine learning algorithms to predict the therapeutic effects of nutrients, offering a systematic and data-driven approach for nutritional therapy. Similarly, FooDisNET uses specific metrics- termed "FooDis" and "DisFood" scores- to rank food-disease interactions based on the food prevalence, compound rarity, protein specificity, and disease universality. The remaining databases - NutriChem, FooDis, DietRx, SAFFRON, and ABCkb - also rely largely on text-mining methodologies. These resources systematically extract and analyze data from large-scale scientific literature, primarily MEDLINE abstracts, to identify associations between dietary components and diseases, as well as food-compound interactions.

Recent studies have highlighted the critical role of nutrients and metabolites in regulating gene expression and cellular processes.[104,105] These compounds function not only as essential components of cellular structures and sources of energy, but also as modulators of protein activity and signaling molecules[106,107] and regulators of gene expression through activation and repression mechanisms.[108-110] Many metabolites can directly influence transcription factor activity and induce changes in epigenetic markers across the genome.[9] Despite significant efforts over recent decades to identify associations among foods, diseases, drugs, and their interactions, the number of well-established and experimentally validated connections remains limited. High-throughput experimental techniques have been developed to explore these associations; however, such methods remain costly, time-consuming, labor-intensive, and technically challenging to perform routinely. Consequently, computational strategies have become increasingly valuable for leveraging existing biological data and prior knowledge to identify novel associations and improve our understanding of complex biomedical processes.

At present, several databases provide detailed information on plant-based food constituents,[12-14] traditional Chinese medicine compounds[23-26] and their corresponding molecular targets.[29,30,32] However, a comprehensive database explicitly linking foods, their compounds, associated proteins or genes, and related diseases remains unavailable. The associations identified through this study could serve as a foundational resource for the future development of such a database.

**Limitations**

While this study introduces a novel four-layer framework for mapping food–disease associations, several methodological limitations must be acknowledged. These limitations pertain to database coverage, network construction, validation status, and generalizability. The main limitations are: incomplete coverage of source databases, network simplification and thresholding, absence of experimental validation, a single disease case study, and a trade-off of unbiased association mapping.

**Future directions for food-disease associations databases**

Further research is needed to strengthen and expand the proposed approach. Bringing data on foods, their constituent compounds, proteins/genes, and diseases can improve our understanding of the diet-health relationship and support the development of more comprehensive food-disease databases. Future platforms should integrate multi-omics data, such as genomics, metabolomics, and microbiome profiles, to better capture the molecular effects of diet on disease pathways.

There is also a clear need for unified databases that systematically organize information on foods, nutrients, disease states, and drug interactions. Adding advanced analytics and machine learning could help identify meaningful patterns and generate testable hypotheses. More detailed food classification, including subspecies and preparation methods, would further improve the precision and practical value of dietary recommendations. As precision nutrition continues to evolve, future databases should also account for inter-individual variability, particularly gene-diet and microbiome-diet interactions. Ongoing curation, data standardization, and transparent scoring of associations will be essential to ensure data quality, reproducibility, and clinical relevance. Ultimately, such resources could support both personalized nutrition and the identification of food-derived compounds with therapeutic potential.

**Conclusion**

This study highlights the potential of diet and dietary bioactive compounds to reduce disease risk, improve treatment outcomes, and lower recurrence. By linking foods and their metabolites to molecular targets, the proposed framework provides a structured, mechanism-informed approach to studying the diet-disease relationship. Although demonstrated here using breast cancer, the approach can be readily extended to other diseases. In addition, our workflow establishes a discovery-to-validation pipeline for prioritizing natural compounds with drug-like features. Candidate bioactive compounds are triaged computationally (e.g., target and pathway relevance, predicted ADMET and bioavailability, potential for synergy with standard-of-care), then advanced to targeted experimental studies, including protein-specific assays, CRISPR- or RNAi-based perturbation, and disease-relevant cell models or organoids to confirm target engagement and functional effects. Subsequent work can address formulation and delivery (e.g., encapsulation to improve stability and uptake), pharmacokinetics, dose–response, and safety profiling, followed by well-designed clinical evaluations. Taken together, this framework operationalizes nutrition as a modifiable, mechanism-informed intervention and provides a rational path to identify, prioritize, and test bioactive nutrients as complements to conventional therapies. The novelty of this work lies in its four-layer integration (food → metabolite → protein/gene → disease), unbiased association mapping, generalizable methodology, and systematic literature validation—collectively offering a scalable, hypothesis-generating platform for precision nutrition and food-as-medicine research.

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**Competing Interests**

The authors have no competing interests to declare.

**Ethical Approval**

Not applicable.

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**Data Availability Statement**

Supplementary files S5-S6 contain Fig. 5 & Fig. 6 as Cytoscape files. Cytoscape software can be downloaded from the link: https://cytoscape.org/. The availability of data and content can be sent as a supplementary file in Excel format.

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