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REVIEW

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Interactions dietary components with expression level of breast cancer-related genes

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Abstract

Background: Dietary components can influence the effects of genetic background in breast cancer (BC). This review study aimed to investigate the effect of dietary components on the expression level of BC-related genes.

Methods: In this narrative review, Embase, PubMed, PsycInfo, and the Cochrane databases were used to collect the related papers with interactions of BC, genetics, and dietary intake. Appropriate keywords such as BC, gene expression, mutation, nutrient, and diet (alone and together) were applied for data collection.

Results: The association of BC with some genes including the BC1 gene (*BRCA1*), the human epidermal growth factor receptor 2 (*HER2*), and the fat mass and obesity-associated (*FTO*) gene can be affected by dietary components. Moderate B12 supplementation may be protective against BC in people with the inherited mutation of *BRCA*. The olive oil may have a protective effect against BC through several mechanisms such as suppressing *HER-2* expression. Furthermore, high glycemic index foods may increase the risk of BC by the activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway and the up-regulation of *FTO* gene expression.

Conclusion: There are interactions between BC, BC-related genes, and dietary intake. Dietary components such as macronutrients, micronutrients, and phytochemicals may regulate the expression level of BC-related genes. Further longitudinal studies are needed to confirm the associations between BC-related genes and diet and to discover the underlying mechanisms.

Keywords: Breast cancer, Gene expression, Dietary intake

Introduction

Breast cancer (BC) is one of the main health challenges worldwide [1, 2] and is considered the most prevalent type of malignancy [3–5] and the second cause of cancer-related mortality in women [4, 6]. Annually, there are about 14 million diagnosed BC cases and 8 million cancer-related deaths around the world [7]. However, developed countries are more prone to BC and cancer-related deaths, which are likely to be due to an unhealthy environment and lifestyle [8]. Thus, comprehensive preventive approaches are needed to suppress these predisposing factors [9]. Generally, the etiology of BC is highly complex [4, 10] and refers to multifactorial causes, which can be genetic non-modifiable factors, non-genetic non-modifiable factors (e.g., age, race, menstrual/menopausal age, breast characteristics, and reproductive factors), and non-genetic modifiable factors (e.g., lifestyle) [2, 8].

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Some genes were reported to have crucial roles in the development of BC. For example, *BRCA1* (breast cancer type 1) is a tumor suppressor gene in humans [11] that plays a key role in deoxyribonucleic acid (DNA) repair [12]. *BRCA1* mutations exist in nearly 2% of BC patients [8] and increase the risk of mortality in their carriers compared to the others [13]. Further, human epidermal growth factor receptor 2 (*HER2*) is a human proto-oncogene [14] that controls cell division and repair in breast tissues [15] The overexpression of *HER2* was found in 15–20% of BC [14] and was associated with a more invasive form of BC with less recovery [2, 14, 16, 17]. Furthermore, the fat mass and obesity-associated (*FTO*) gene, as a strong genetic predictor of obesity [18], is a protein-coding gene [19] and recent studies identified its possible role in several types of malignant cancers such as BC [20]. The *FTO* gene up-regulation in human breast tissues is reported to be related to the higher breast cell proliferation that can lead to the development and progression of BC [21].

On the other hand, diet, environment, physical activity, body mass index (BMI), smoking, and alcohol use are among non-genetic modifiable risk factors [10, 22–24] that have significant roles in BC [25, 26] and represent 30–35% of all types of cancers [7, 9]. Interestingly, dietary factors can regulate the expression of some cancer-related genes [27]. In addition, the mutations of some specific genes may influence the level of nutrient requirements and body response to cancer-related dietary compounds. For example, it was reported that lifestyle and diet have the potential to alter the level of *FTO* gene expression [27]. However, the effect of the modification of a diet on the consequences of BC is unclear [28]. Nutrition is considered to play a key role in the inhibition and excitation of BC-related genes [1, 5]. Dietary components can influence the expression of genes that are involved in critical metabolic pathways [29] through epigenetic mechanisms [29, 30] including transcription, maturing, and stability of ribonucleic acids (RNAs), translation into proteins, and post-translational modifications (PTMs) [31].

In general, there are contradictory results on the association between diets and BC risk, [32] and the overall impact of diet on the risk of BC is unknown [25, 31]. For example, Farvid et al. concluded that the higher intake of fruits and vegetables is associated with a lower *HER2* overexpression and lower risk of BC [4]. However, Pierce et al. reported that a diet high in vegetables, fruit, and fiber had no effect on prognosis following treatment for BC [33]. Also, most of the previous studies investigated the relationship between dietary components and cancer-related gene expression with BC risk in isolation, and thus few studies assessed the interactions between dietary intake, BC-related genes, and BC. Therefore, this study aimed to evaluate the associations between the risk of BC, dietary intake, and BC-related genes expression.

Methods

Embase, PubMed, PsycInfo, and the Cochrane databases were used for identifying the related articles. Appropriate keywords including gene or expression or regulation or genetic or mutation or polymorphism AND nutrient or diet or nutrition or macronutrient or micronutrient or vitamin or mineral or protein or carbohydrate or fat or lipid AND breast cancer or breast malignancy or breast tumor were used. All articles published in English from June 1990 to August 2022 which examined the interaction of BC with gene expression and diet were included in the present study. Studies of other cancers, have focused on factors other than gene expression (such as genotype and gene polymorphisms), that only focused on BC and diet, or that only considered BC and genes were excluded from the present study. Also, only genes were included which their interactions with both BC and diet were already investigated at least in two original research. Based on the collected studies, *BRCA1*, *HER2*, and *FTO* genes have been identified. The interactions of nutrients with BC and the expression of BC related genes as well as the mechanisms of their effects were explored.

Results

BRCA1 gene

The breast cancer 1 gene (*BRCA1*) encodes a tumor suppressor protein that is involved in DNA repair and maintenance of gene stability. Women carrying a mutated copy of *BRCA1* gene have 45–70% elevated risk of developing BC [34].

Some nutrients may influence the association between *BRCA1* and BC [35]. For example, moderate B12 supplementation may be protective against BC, particularly in a person who has an inherited mutation of *BRCA* [36]. Vitamin B12 is essential for DNA synthesis, repair, and methylation by participating in one-carbon metabolism, and B12 deficiency causes chromosome breaks. Thus, sufficient B12 levels may prevent aberrant gene expression, DNA instability, and cancer development. Also, folic acid may have similar effects in the prevention of chromosomal inconsistency, DNA repair, and neoplastic transformation, especially in a person who has an inherited mutation of *BRCA* [37].

In human BC cells in which aromatic hydrocarbon receptors (AhR) are activated, the hypermethylation of *BRCA1* was associated with reduced *BRCA-1* and estrogen receptor alpha (ERα) expression. Accordingly, some studies proposed a causative role for AhR in the etiology of breast tumorigenesis. Genistein (GEN), as a common dietary isoflavone, exerts antagonistic

effects on DNA methyltransferase (DNMT) enzymes. GEN may have a protective effect against cell proliferation through AhR-mediated *BRCA1* CpG methylation in ERα-positive BC cells. Several mechanisms have been proposed for the association between GEN and *BRCA1*–related BC including rescued *BRCA-1* protein expression, reduced *DNMT-1* and cyclin D1 expression, reduced *BRCA1* CpG methylation, and increased p53 levels [38] (Fig. 1).

Moreover, BC is potently inhibited by vitamin D3's active form, 1α,25-dihydroxy vitamin D3. *BRCA1* and vitamin D3 are both linked to the up-regulation of another tumor suppressor gene, *CDKN1A*, encoded by p21waf1, the G1 cell cycle inhibitor. The *BRCA1* gene can bind to the vitamin D receptor (VDR) and co-occupies the vitamin D responsive elements (VDRE) at the *CDKN1A* promoter (p21waf1), where acetylation of histone H3 and H4 is increased. Cooperation between *BRCA1* and vitamin D may have a crucial role for histone acetylation of the p21waf1 promoter and for growth inhibition of BC cells [39].

HER2 gene

Approximately 10–35% of all types of BC have the overexpression of the human epidermal growth factor receptor 2 (*HER2*) oncogene which is associated with BC prognosis and response to treatment [40].

HER2 and fatty acids

Some studies indicated that HER2 positive BC cells contain large amounts of endogenous saturated fatty acids (FAs) and neutral fats and generally exhibit a pro-lipogenic phenotype. Small amounts of exogenous palmitate were reported to be toxic to *HER2*-positive BC cells; thus their effects were studied in Michigan Cancer Foundation-7 (*MCF7*) and *SKBR* which are *HER2*-negative and *HER2*-positive BC cell lines, respectively. In *HER2*—positive SKBR3 cells, exogenous palmitate induces a partial estrogen receptor (ER) stress response through the activation of Inositol-requiring enzyme 1 (IRE1) and activating transcription factor 6 (ATF6), two of the three major regulators of ER stress [41]. IRE1 was activated in response to ER-stress, resulting in a non-canonical splicing mechanism wherein the mRNA transcript of X-box binding protein 1 (XBP1) is spliced to give rise to a transcriptionally active variant that up-regulates many genes that are involved in the UPR/ER-stress including many resident ER protein folding chaperones. In addition, ATF6 activity, which is a transmembrane ER protein, was induced by ER-stress [42]. Interestingly, no changes in protein levels or relative phosphorylation rates were detected for the third major regulator of ER stress, namely, the endoplasmic reticulum kinase such as PKR (PERK). This ER stress response was accompanied by a significant reduction in *HER2* and *HER3* protein levels by interfering with FA synthesis, without creating any

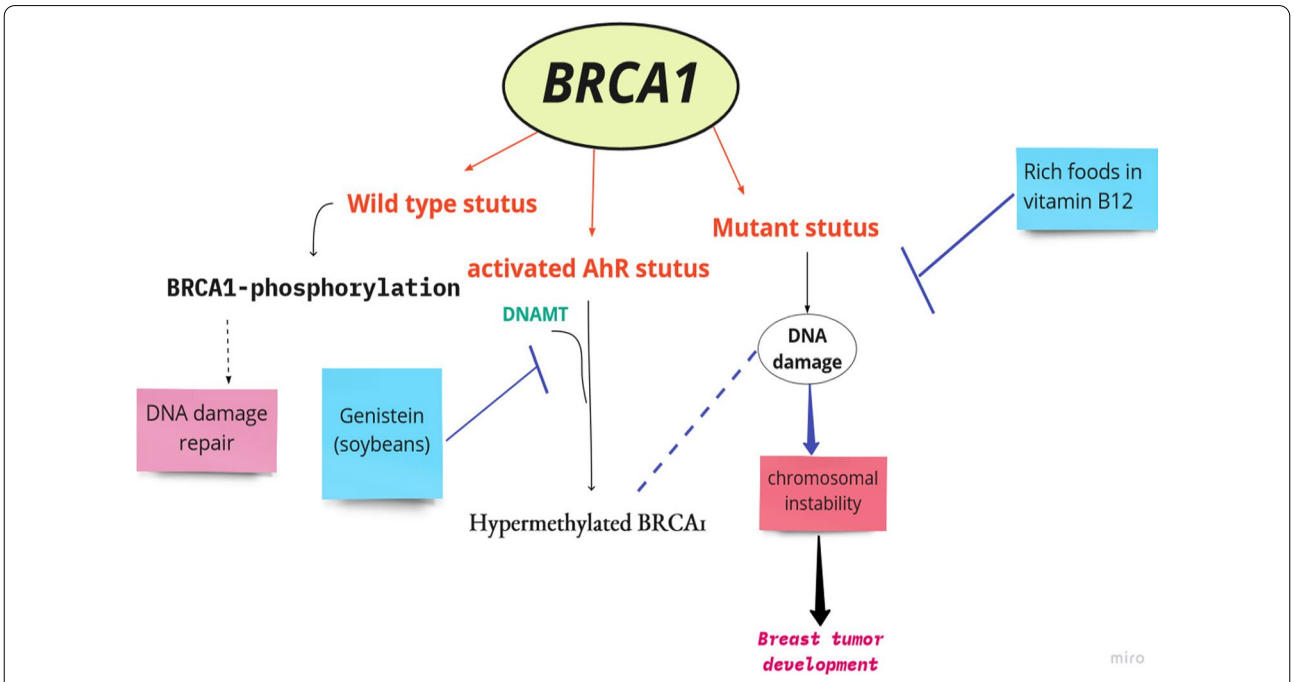

Fig. 1 Interactions between dietary intake and *BRCA1* (breast cancer 1) gene. *DNAMT* DNA Methyltransferases; *AhR* Aromatic hydrocarbon receptors

changes in phosphorylation [41]. Further, high intensity or prolonged duration of ER-stress can lead to apoptosis through the induction of the pro-apoptotic regulator DNA-damage-inducible transcript 3 (DDIT3/CHOP), thus the increase in DDIT3/CHOP expression with palmitate treatment is responsible for the increase in cell death in the SKBR3 cell line [42]. On the other hand, exogenous palmitate sensitizes *HER2*-positive BC cells to trastuzumab treatment [41].

Furthermore, alpha-linolenic acid (ALA) supplementation specifically suppresses the overexpression of *HER2* in cultured *HER2*-amplified BC cells [43]. A randomized, double-blind, placebo-controlled study assessed the effects of dietary flaxseed, which is high in ALA (57% of total fatty acids), on tumor biological markers in postmenopausal BC patients. According to the results of this study, flaxseed consumption of 25 g per day significantly reduced the proliferation, apoptosis, and cell signaling by reducing *HER2* expression in breast tumors. A decrease in *HEB2* expression (71%) and an increase in apoptosis (30.7%) were observed in the flaxseed group but not in the placebo group [44]. Flaxseed oil and *n*-3 fatty acids were also reported to exert further anticancer effects including reducing the expression of other growth factor receptors such as epidermal growth factor receptors (EGFR) and insulin-like growth factor I receptors (IGF-IR) as well as reducing the expression and activity of fatty acid synthetases (FASN) and enhancing the expression of the tumor suppressor phosphatase and tensin homologs (PTEN) [45]. In summary, these findings suggest that Flaxseed oil reduces tumorigenesis and modulates *HER2* expression and growth factor receptor signaling pathways.

HER2 and olive oil

Olive oil was reported to act as a protective factor against several malignancies, especially BC. The fundamental characteristics of olive oil are a high $\omega - 9$ MUFA level, a low $\omega - 6/\omega - 3$ PUFA ratio, and the presence of a large number of phenolic compounds including simple phenols, lignans, and secoiridoids such as deacetoxy oleuropein aglycone, oleuropein aglycone, and ligstroside aglycone [46]. A recent study found that olive oil suppressed Her-2 expression and synergistically enhanced the trastuzumab efficacy by promoting DNA fragmentation associated with apoptotic cell death, and dramatically increased both the expression and the nuclear accumulation of p27Kip1 (a cyclin-dependent kinase) in BC cells with *HER-2* oncogene amplification. Finally, olive oil co-exposure significantly enhanced the ability of trastuzumab to inhibit the signaling pathway downstream of *HER-2*, including phosphoproteins such as protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) [47]. Oleuropein aglycone was reported to be the strongest extra virgin olive oil phenol, which reduces the viability of BC cells. It was found that BC cells with *HER2* oncogene-overexpression exhibit an exacerbated sensitivity to oleuropein aglycone-induced cytotoxicity. Oleuropein aglycone preferentially induces apoptotic cell death and synergistically enhances trastuzumab-efficacy in *HER2*-overexpressing BC cells [46] (Fig. 2).

HER2 and phytochemicals

Green tea contains polyphenolic catechin epigallocatechin-gallate (EGCG). Regular consumption of green tea was associated with the prevention of BC through induce apoptosis and inhibit cell proliferation. EGCG may inhibit *HER2* and *STAT3* phosphorylation in *HER2*-overexpressing BT-474 BC cells lead to enhanced apoptosis due to loss of nuclear integrity, DNA fragmentation, and further dispersion in the cytoplasm [48].

Genistein treatment of BT-474 *HER2*-positive cells for five days inhibited total and phosphorylated *HER2* protein independently of ER status in vitro experiments [49]. Furthermore, genistein treatment of *MCF-7/HER2* and *BT-474 BCE* cells inhibited the growth of cells by deregulating *HER2* [48].The natural flavonol kaempferol is found in a variety of plants and plant-derivatives, including broccoli, tea, and tomato. The administration of 10 mM Kaempferol or 50 mM Kaempferol to MDAMB453 BC cells resulted in cell cycle arrest and apoptosis, which was associated with phosphorylated *p53* upregulation [48].

The chemopreventive and therapeutic effects of resveratrol have been observed in *HER2*-positive BC [50]. In human and mouse *HER2*-positive BC cells, resveratrol 4.4–50 mM for 4 h inhibited proliferation through inhibition of the FASN signaling pathway and by downregulating *HER2* and *p185HER2/neu* [48].

FTO gene

The fat mass and obesity-associated (*FTO*) gene expression in BC cells was reported to be significantly higher compared to the normal breast cells, which represents *FTO* as a potential new marker for the early diagnosis of BC. The findings of a recent study demonstrated that the ATP levels, pyruvate kinase hexokinase activity, and the content of lactic acid significantly decreased in cells that were transfected with the *FTO* mRNA inhibitor. The overexpression of the *FTO* gene could promote glycolysis in BC cells (the Warburg effect). Furthermore, the expression of the *FTO* gene can influence the energy metabolism of BC cells through the PI3K/AKT signaling pathway [51].

Some studies suggested that the level of calories and the level of macronutrients intake have the potential to change the *FTO* gene expression level. For instance, one

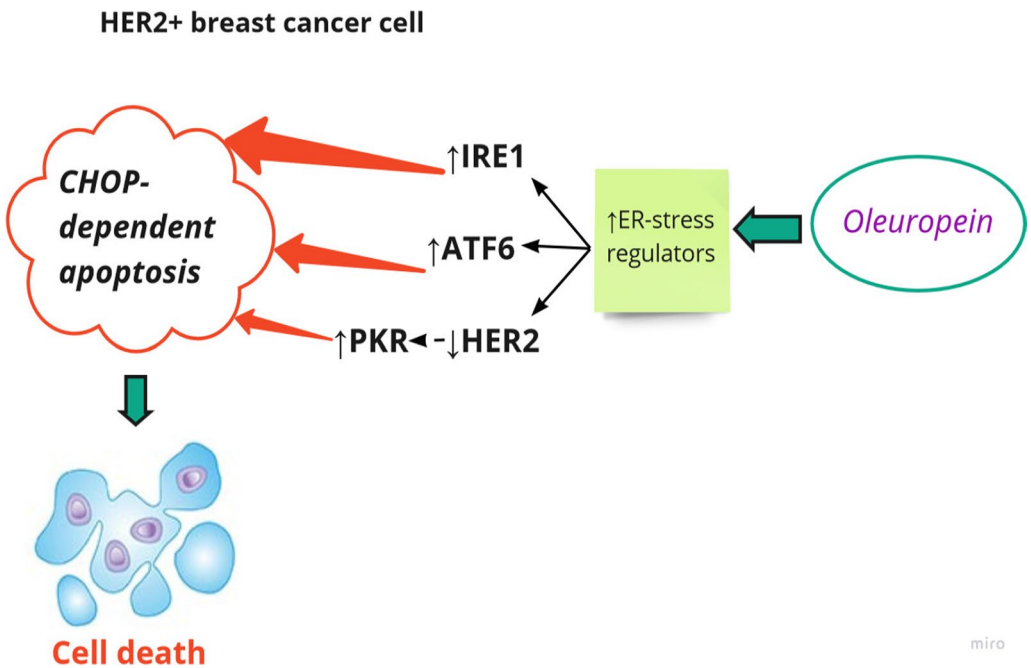

Fig. 2 Interactions between dietary intake and *HER2* (human epidermal growth factor receptor2) gene. *ER* Estrogen receptor; *IRE1* Inositol-requiring enzyme 1; *ATF6* Activating transcription factor 6; *PKR* Protein kinase R; ↑: Increase; ↓: Decrease

study indicated that increasing glucose administration increased *FTO* gene expression at 48 h post-intervention [52]. High levels of blood glucose and insulin apply some of their effects through the steady activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway that is involved in cell survival, and eventually, increase the risk of cancer. However, the underlying mechanism of the effect of carbohydrates on PI3K/AKT pathway is unclear [53].

Moreover, recent studies found that there is a mutual interaction between the *FTO* gene and the intake of protein. According to some clinical trial studies higher protein intake was significantly associated with the up-regulation of the *FTO* gene. *FTO* may be involved in pairing cell accessibility to amino acids with the mammalian Target of Rapamycin Complex 1 (MTORC1) signaling pathway. *MTORC1* mTOR signaling which is over active in multiple cancer types including BC [54] was reported to be impaired in the absence of *FTO* [55, 56]. Regarding the effects of micronutrients on *FTO* gene, a recent study reported that B12 supplementation influences regulation of *FTO* gene through methylation of microRNA 21 (miR21) [57].

In general, the results of the present study showed that dietary components may change the expression of some BC-related genes and thereby cause a change in the risk of BC. Future research in this field of nutritional genomics can help provide practical nutritional recommendations to prevent BC. However, this study had some limitations. First, few genes were investigated on the interaction of BC with genes and diet. Second, the number of papers examining the interaction of these genes with BC and diet was not sufficient for meta-analysis. Further longitudinal studies on the effects of dietary components on the expression level of different BC-related genes are required to confirm the interactions between BC, genes, and diet and to uncover the underlying mechanisms (Fig. 3 and Table 1).

Conclusion

BRCA1, *HER2*, and *FTO* may have mutual associations with BC and dietary intake. The expression level of *BRCA1*, *HER2*, and *FTO* genes play important roles in the development of BC and may be regulated by dietary components. The results of this study, if confirmed in future research, can help provide nutritional strategies to regulate the expression of genes related to BC and ultimately prevent BC. Further longitudinal studies are required to confirm the associations between BC-related genes and diet and to uncover the underlying mechanisms.

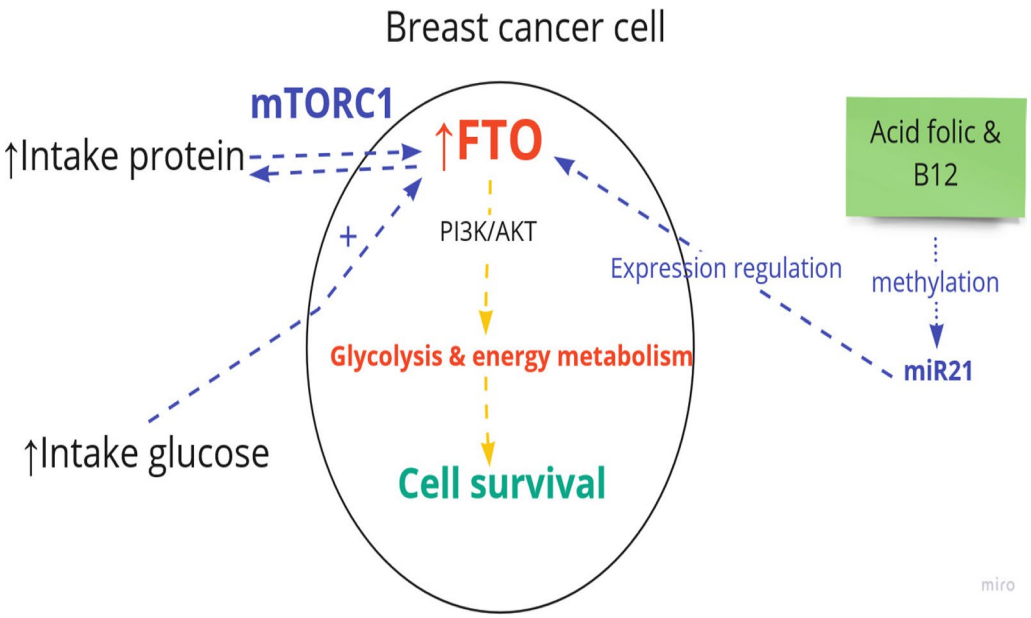

Fig. 3 Interactions between diet intake and fat mass and obesity-associated (*FTO*) gene expression. *PI3K/AKT* Phosphoinositide 3-kinase/protein kinase B; *mTORC1* Mammalian Target of Rapamycin Complex 1; ↑: Increase; +: Promote

Table 1 Summary of the effects of nutrients on breast cancer-related genes

Author (year)	Nutrients	Cancer-related gene	Design	The mechanism of effect
Kim et al. [36]	Folic acid	*BRCA1*	Case–control	The moderate use of folic acid can prevent DNA strand breaks, chromosomal inconsistency, impaired DNA repair, and neoplastic transformation, in particular in a person who has inherited a mutation of *BRCA*
Kim et al. [36]	Vitamin B12	*BRCA1*	Case–control	Protective effect by several mechanisms such as participating in synthesis, repair, and methylation of DNA and also preventing aggregation Uracil and chromosome breaks
Romagnolo et al. [38]	Genistein	*BRCA1*	Experimental	Protective effect by several mechanisms such as rescued *BRCA*-1 protein expression, reduced DNMT-1, and cyclin D1, reduced *BRCA*1 CpG methylation, and reduced cell proliferation associated with increased *p53* level
Pickholtz et al. [39]	Vitamin D	*BRCA1*	Experimental	It is similar to *BRCA1*. Vitamin D receptor (VDR) and vitamin D responsive elements (VDRE) are co-occupied by *BRCA1* at the *CDKN1A* promoter (p21waf1), where acetylation of H3 and H4 is increased

Table 1 (continued)

Author (year)	Nutrients	Cancer-related gene	Design	The mechanism of effect
Baumann et al. [41]	Exogenous palmitat	*HER2*	Experimental	Protective effect by several mechanisms such as inducing ER stress response through the activation of *IRE1* and *ATF6* that accompany with a reduction in *HER2* and *HER3* protein levels, increasing in *DDIT3/CHOP* expression that causes cell death, sensitizing *HER2*-positive breast cancer cells in trastuzumab treatment
LeMay-Nedjelski et al. [47] and Menendez et al. [46]	Olive oil	*HER2*	Experimental	Olive oil had a protective effect by several mechanisms such as suppressing *HER-2* expression and increasing the trastuzumab efficacy by oleic acid of olive oil, inducing apoptotic cell death, and synergistically enhancing trastuzumab-efficacy by Oleuropein aglycone phenol of olive oil
Menéndez et al. [43] and Thompson [44]	Alpha-linolenic acid	*HER2*	Experimental & RCT	The molecular mechanism by which ALA inhibits breast cancer cell growth and metastasis formation may involve suppressing the overexpression of *HER2*
Mason [45]	Flaxseed oil	*HER2*	Experimental	Tumorigenesis is inhibited by flaxseed oil and growth factor receptor signaling pathways are modulated. Its protective mechanisms include reducing the expression of other growth factor receptors, such as EGFR and IGF-IR, as well as reducing the activity of FASN and enhancing the expression of the tumor suppressor PTEN
Zabaleta [48]	Epigallocatechin-gallate	*HER2*	Systematic review	Several mechanisms are responsible for this protective effect, such as inducing apoptosis and inhibiting cell proliferation
Zabaleta [48] and Sakla [49]	Genistein	*HER2*	Systematic review & Experimental	Genistein inhibits the growth of cells by deregulating *HER2*
Zabaleta [48]	Kaempferol	*HER2*	Systematic review	This protective effect is due to several mechanisms such as cell cycle arrest and apoptosis, which are correlated with phosphorylated *p53* upregulation
Zabaleta [48]	Resveratrol	*HER2*	Systematic review	By inhibiting FASN signaling and downregulating *HER2* and *p185HER2/neu*, resveratrol inhibits proliferation
Doaei et al. [53]	Carbohydrate	*FTO*	Systematic review of experimental studies	High levels of blood glucose and insulin can worsen the risk of cancer by activation of phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway Also, higher glucose intake upregulated *FTO* gene expression
Doaei et al. [53]	protein	*FTO*	Population-based trial	Protein intake significantly upregulated the *FTO* gene
Yadav et al. [57]	B12	*FTO*	cohort	B12 supplementation can influence the regulation of *FTO* through methylation of miR21

Abbreviations
ATF6: Activating transcription factor 6; ALA: Alpha-linolenic acid; AhR: Aromatic hydrocarbon receptors; BMI: Body mass index; BC: Breast cancer; BRCA1: Breast cancer 1 gene; DNA: Deoxyribonucleic acid; DNMT: DNA methyltransferase; DDIT3/CHOP: DNA-damage-inducible transcript 3; EGFR: Epidermal growth factor receptors; EGCG: Epigallocatechin-gallate; ERα: Estrogen receptor alpha; FTO: Fat mass and obesity-associated gene; FASN: Fatty acid synthetases; FA: Fatty acids; GEN: Genistein; HER2: Human epidermal growth factor receptor 2; IGF-IR: Insulin-like growth factor I receptors; MTORC1: Mammalian target of rapamycin complex 1; MCF7: Michigan cancer foundation-7; MAPK: Mitogen-activated protein kinase; OA: Oleic acid; PTEN: Phosphatase and tensin homologs; PI3K/AKT: Phosphoinositide 3-kinase/protein kinase B; PTMs: Post-translational modifications; AKT: Protein kinase B; RNAs: Ribonucleic acids; VDR: Vitamin D receptor; VDRE: Vitamin D responsive elements; XBP1: X-box binding protein 1.

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Author contributions
FB, SD, KA, NHA, AH, SA, and MGH designed the study, and carried out the data collection. AEB, MA, AH, and SD were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. This study was conducted at the Shahid Beheshti University of Medical Sciences, Tehran, Iran. All authors read and approved the final version of the manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by The Shahid-Beheshti University of Medical Sciences (code: IR.SBMU.NNFTRI.REC.1400.041).

Consent for publication
Institutional consent forms were used in this study.

Competing interests
The authors declare that they have no competing interests.

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