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Relationship Between Breast Density and Selective Estrogen-Receptor Modulators, Aromatase Inhibitors, Physical Activity, and Diet: A Systematic Review

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Abstract

Background. Lower breast density (BD) is associated with lower risk of breast cancer and may serve as a biomarker for the efficacy of chemopreventive strategies. This review explores parameters that are thought to be associated with lower BD. We conducted a systematic review of articles published to date using the PRISMA strategy. Articles that assessed change in BD with estrogen-receptor modulators (tamoxifene [TAM], raloxifene [RLX], and tibolone) and aromatase inhibitors (AIs), as well as cross-sectional and longitudinal studies (LSs) that assessed association between BD and physical activity (PA) or diet were reviewed. *Results.* Ten studies assessed change in BD with TAM; all reported TAM-mediated BD decreases. Change in BD with RLX was assessed by 11 studies; 3 reported a reduction in BD. Effect of tibolone was assessed by 5 RCTs; only 1 reported change in BD. AI-mediated BD reduction was reported by 3 out of 10 studies. The association between PA and BD was assessed by 21 studies; 4 reported an inverse association. The relationship between diet and BD was assessed in 34 studies. All studies on calcium and vitamin D as well as vegetable intake reported an inverse association with BD in premenopausal women. Two RCTs demonstrated BD reduction with a low-fat, high-carbohydrate intervention. *Conclusion.* TAM induces BD reduction; however, the effect of RLX, tibolone, and AIs on BD is unclear. Although data on association between diet and BD in adulthood are contradictory, intake of vegetables, vitamin D, and calcium appear to be associated with lower BD in premenopausal women.

Keywords

tamoxifene, raloxifene, tibolone, letrozole, anastrozole, exercise

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Introduction

Breast cancer (BC) is the most frequently diagnosed female cancer, and the second leading cause of deaths related to cancer in women worldwide.[1] Risk factors such as aging, breast density (BD), lifestyle, and genetic parameters have all been implicated in breast carcinogenesis.[2,3] Of these risk factors, BD has been shown to be very significant, especially in younger women.[4] Established BC risk factors associated with genetics and lifestyle are also confounders for BD through hormonal and genetic pathways and modify the relationship between BD and BC risk.[5] *Breast density* refers to the proportion of the breast that is composed of fibroglandular tissue and is represented by the radiopaque areas on a mammogram.[6,7] Although BD is regarded as a strong risk factor for BC, it is still contentious whether it is an independent risk factor or whether it merely reflects opportunities for cancer to develop. Regardless of these contentions, high mammographic BD (MBD) has been shown to be associated with BC risk and interval cancer.[4] Importantly, BD is regarded as a modifiable risk factor for BC[8,9] and, therefore, may be an important biomarker for the effect of interventions on BC risk.

Identifying the relationship between MBD and interventions that modify BD requires reliable and reproducible methods for MBD assessment. Currently, area-based and volumetric approaches exist for MBD assessment.[6,7] The qualitative area-based methods classify MBD into different categories based on subjective opinion, using features such as area covered by dense tissue and ductal prominence. They

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include the Wolfe, Boyd and Tabår methods, along with the Visual Analogue Scale and breast imaging reporting and data system (BI-RADS).[6,7] Semiautomated area-based methods such as planimetry, Cumulus, and Madena use thresholding and segmentation techniques to measure percentage mammographic density (PMD). Automated area-based methods use thresholding and/or statistical modeling to estimate PMD and include texture-based approaches, Autodensity, and MedDensity.[6] Volumetric approaches use statistical or physical modeling to calculate volumetric BD (VBD). Volumetric approaches include calibration techniques, dual-energy X-ray absorptiometry, Cumulus V, and 3 physics model–based volumetric techniques: Standard Mammographic Form, Volpara, and Quantra.[6,7]

Many studies have attempted to assess the relationship between BD and specific clinical interventions such as estrogen-receptor modulators,[8-11] aromatase inhibitors (AIs),[12-17] physical activity (PA),[18-23] and diet.[24-31] However, the nature and magnitude of the relationship between BD and these interventions is unclear. Furthermore, the category of women (age, ethnicity, body mass index [BMI], and menopausal status) in which these parameters are more effective is unclear. This lack of clarity underscores the need for a review of interventions that are thought to have an impact on BD, given the role of BD as an intermediate and potentially modifiable risk factor for BC.[5,8,9] Increasingly, BD notification legislations have been passed in 22 states in the United States,[32] and BD details are being made available to screened women. The benefit of BD notification to women will only be accrued when such data are accompanied with clear information about BD and cancer as well as information about parameters that are associated with lower BD and cancer risk. Therefore, this review examines the effect of estrogen-receptor modulators such as tamoxifene (TAM), raloxifene (RLX), and tibolone as well as AIs such as letrozole, anastrozole, and exemestane on BD. It also explores the association between BD and parameters such as PA and diet.

Materials and Methods

Search Strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) strategy was used to search for articles published to date using MEDLINE, EMBASE, CINAHL (Ebscohost), PubMed, Cochrane library, Web of Science, and Scopus databases. We also conducted a Google search, and reference lists of published articles were examined to identify additional articles not found in the database search. The search was conducted in the English language. To systematically search for literature of interest, a combination of search terms was used; these were thematically related to our hypothesis and also common themes identified through preliminary search of the literature. These were "breast density reduction interventions," "breast density modifiers," "breast density and estrogen-receptor modulators," "breast density and tamoxifene," "breast density and raloxifene," "breast density and tibolone," "breast density and letrozole," "breast density and anastrozole," "breast density and exemestane," " breast density and aromatase inhibitors," "breast density and physical activity," "exercise and breast density," "breast density and diet."

Inclusion Criteria

Articles were included if they were randomized controlled trials (RCTs), case-control studies (CCSs), or cohort studies (CSs) that investigated change in BD with interventions. Longitudinal studies (LSs) and cross-sectional studies (CSSs) that assessed association between BD and parameters such as PA and diet were also included. Articles were also included if they were published in the English language. Articles that did not fulfill the above criteria were excluded, as were reviews and case reports.

Data Synthesis

Data extraction was performed independently by 2 reviewers, with differences of opinion resolved by discussion. No article needed to be excluded for reasons of differences of opinion between reviewers; however, had consensus not been reached, articles would have been excluded. For each study, reviewers extracted information using the Participant Intervention Comparator and Outcomes (PICOS) method (Table 1). Studies that assessed BD from RCTs or were a subset of RCTs were considered RCTs in the current review. Studies were qualitatively assessed for quality and risk of bias based on study-specific design (clarity of protocol, assessment and report of compliance, blinding of outcome assessors, and outcome measures); this enabled us to appraise the conduct of each study. Table 1 shows eligibility criteria for inclusion of studies.

Results

The search strategy identified 1853 publications, from which 156 eligible articles were found. Of these, 48 were duplicates, and 21 did not fulfil the inclusion criteria and were excluded, resulting in 87 articles that fulfilled the inclusion criteria. Of the articles that fulfilled inclusion criteria, 22 were on selective estrogen-receptor modulators (SERMs), 2 were on SERMs and AIs, 8 were on AIs alone, 21 were on PA, and 34 were on diet (Figure 1).

Of the studies on estrogen-receptor modulators, 10 assessed change in BD with TAM intervention and included 1 RCT,[10] 2 nested CCSs,[8,9] 1 CS,[11] and 6 post hoc analyses of RCTs.[33-38] The sample sizes of the 10 studies ranged from

Table 1. Eligibility Criteria for Inclusion of Studies.

Characteristics	Criteria
Study year	Studies published to November 2014
Study design	1. Randomized controlled trials 2. Case-control studies 3. Nested case-control studies 4. Cohort studies 5. Cross-sectional studies 6. Longitudinal studies
Population	Women of all ages
Intervention	1. Estrogen-receptor modulators 2. Aromatase inhibitors 3. Physical activity 4. Diet
Comparator	Relationship between interventions and breast density
Outcomes	Mammographic breast density

16 to 1065 (n = 2877). Among the studies, 7 included premenopausal and postmenopausal women, with heterogeneity in criteria for ascertaining menopausal status. Most of the studies administered 20 mg of TAM per day, and total duration of TAM administration varied from 1.5 to 6 years. Also, 7 studies used area-based qualitative and/or quantitative approaches for MBD assessment, and 1 assessed fibroglandular volume with MRI. Only 4 studies adjusted for confounding factors that affect BD.[8-10,35] All studies reported TAM-mediated BD decreases (Table 2).

A total of 9 studies assessed change in BD with RLX alone,[39-47] and 2 studies assessed tibolone and RLX intervention.[48,49] The sample size ranged from 27 to 444 (n = 2005), and 8 of the 9 studies assessed postmenopausal women. Most of the studies administered 60 mg of RLX per day, and the duration of the RLX administration varied from 3 months to 3 years. Area-based methods were used for MBD assessment in a majority of the studies, and 1 study measured fibroglandular volume with MRI. There was a paucity of information on BD confounders in most of the studies. Of all RLX studies reviewed, only 3 reported a significant reduction in BD (Table 2).[40,41,49]

There were 5 RCTs that assessed change in BD with tibolone intervention.[48-52] Ages of participants ranged from 41 to 70 years, and the sample size ranged from 37 to 177 (n = 665). Tibolone administration was 2.5 mg/d, and duration of administration was 1 year. Three studies performed subjective MBD assessment, 1 used Cumulus, and 1 performed VBD assessment. Only the study that measured VBD adjusted for confounders and reported a significant tibolone-mediated BD reduction.[49]

Changes in BD with AIs (letrozole, 2.5 mg/d; anastrozole, 1 mg/d; exemestane, 25 mg/d) were assessed in 10 studies.[13-17,53-56] Four of the studies used letrozole alone; there was 1 study each on anastrozole and exemestane, and others combined 2 of the 3 AIs. Of these, 4 were prospective arm trials and 3 were RCTs. The sample size varied from 16 to 1065 (n = 2110), and the age of participants ranged from 24 to 77 years, with 80% of the studies involving postmenopausal women alone. The duration of administration ranged from 6 months to 2 years. Among the studies, 7 assessed MBD using area-based computer-assisted methods, and the remaining studies used an area-based subjective approach alone or in combination with area-based computer-assisted methods. There was little or no adjustment for BD confounding factors in most of the studies. Only 3 out of the 10 studies reported statistically significant reduction in BD with AIs (Table 2).[15,17,54]

The association between PA and BD was assessed in 21 studies.[18-23,57-71] Of these, 71% were CSSs, and the sample size ranged from 95 to 2720 (n = 20 424). Association between PA and BD was evaluated within 5 years prior to date of mammographic examination in 71% of the studies, and 29% assessed this association more than 5 years prior to mammography date. In all, 5 studies investigated the association of childhood and adolescent PA with BD in adulthood. Also, 11 studies assessed nonoccupational PA; 7 assessed household, occupational, and recreational PA; and 2 assessed life-course PA (Table 3). Qualitative assessment of MBD was performed in 7 studies, and area-based quantitative approaches were used for PMD assessment in 14 studies. A significant percentage (81%) of the studies found no association between PA and BD[22,23,57-71]; 19% of the studies reported a statistically significant inverse association between PA and BD in perimenopausal and postmenopausal women with BMI >25 kg/m^2.[18-21]

The relationship between diet and BD was assessed in 34 studies: 59% were CSSs on the association between diet and BD, and 27% were RCTs that assessed change in BD with dietary interventions (Table 4). The sample size ranged from 30 to 2252 (n = 24 579). Of these, 27 studies assessed diet in adults aged 25 to 79 years,[24-26,28,29,31,72-92] and 7 studies assessed the association of childhood and/or adolescent diet (4 to 18 years) with BD in adult life.[27,64,68,93-96] Of the studies in adults, 5 evaluated calcium and vitamin D (≥750 mg/d and ≥100 IU/d respectively), 4 assessed circulating vitamin D—25(OH) D—and 6 assessed isoflavone. Four studies assessed dietary fats[26,80-82]; 3 assessed a low-fat, high-carbohydrate diet[25,29,83]; and 4 assessed carbohydrates and proteins.[80-82,90] Two studies assessed vegetables,[26,73] and 2 assessed Mediterranean diets (Med-diets) and multivitamin-multimineral supplements (M-M supplements).[24,92] Of the 7 studies that assessed childhood and adolescent diet, 3 were on dietary patterns,[64,84,95] and other studies were on calorie restriction,[96] alcohol,[93] dietary vitamin D and calcium,[94] and a low-fat diet.[27] A majority of the studies assessed BD with area-based methods such as Cumulus and qualitative approaches. No association was found between childhood or adolescent diet and BD in adulthood.[27,64,68,93-95]

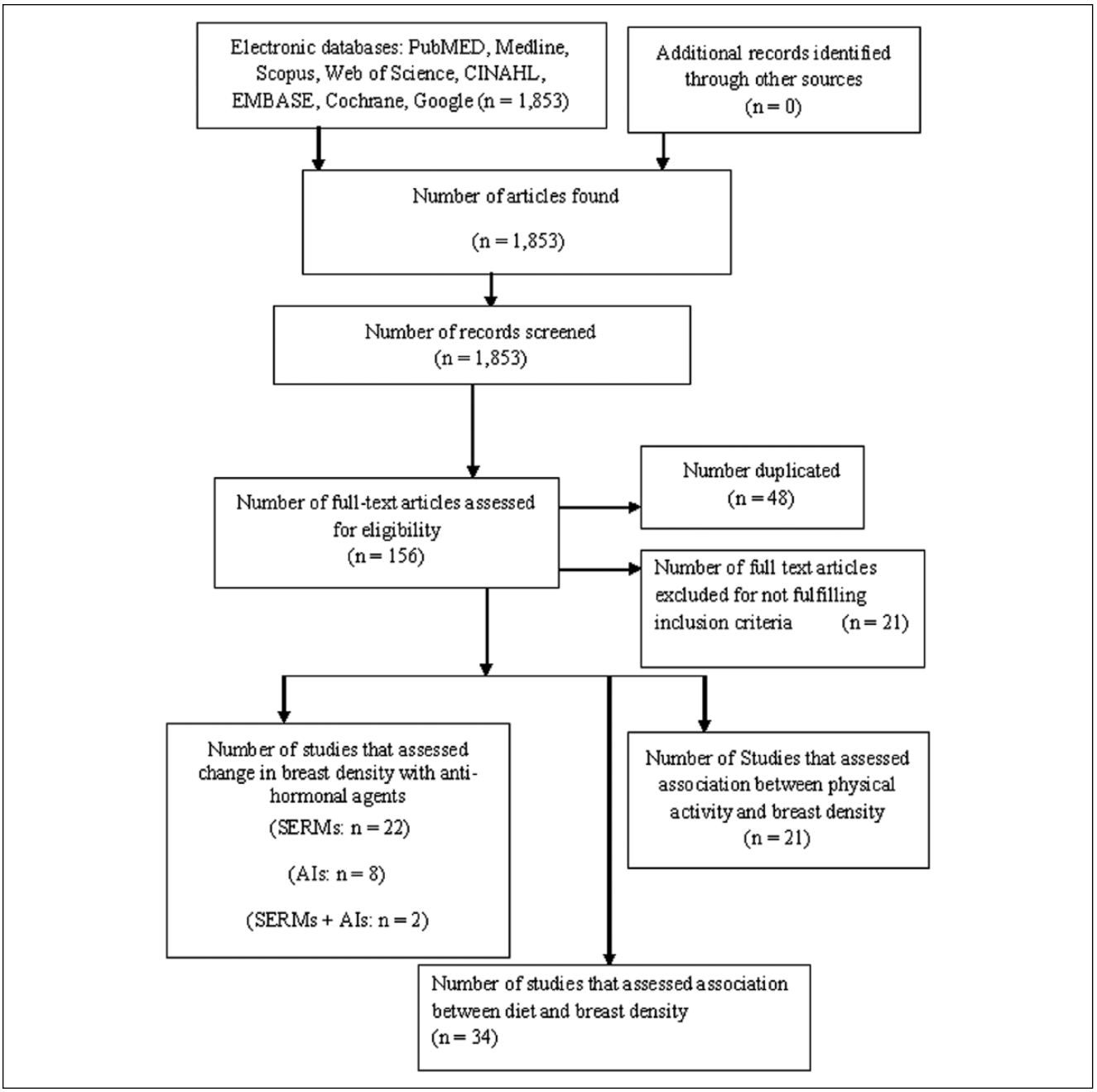

Figure 1. Chart of studies identified on search.
Abbreviations: AI, aromatase inhibitor; SERMs, selective estrogen-receptor modulators.

In adults, all 5 studies on calcium and vitamin D reported an inverse association with BD in premenopausal women but not in postmenopausal women.[72,73,76,77,84] All RCTs of isoflavone demonstrated no change in BD,[31,86-89] and all CSSs reported no inverse association between dietary fat and BD.[26,80-82] The 2 RCTs on low-fat, high-carbohydrate intervention found statistically significant BD decreases,[25,83] and no further change was noted in a 4-year post hoc analysis of 1 RCT.[29] Studies on protein and carbohydrate intake and BD generated conflicting results, with 2 reporting higher BD,[82,90] 1 demonstrating an inverse association,[80] and 1 reporting no association with BD.[81] The 2 studies on vegetable intake in adulthood reported an inverse association with BD.[26,73] Intake of Med-diets and M-M supplements also demonstrated conflicting results, with one reporting lower BD for Med-diet and M-M supplements in

Table 2. Characteristics of Studies on the Effects of Estrogen-Receptor Modulators and Aromatase Inhibitors on BD.

Author, Year	Study Design	Study Population (n)	BD Assessment Age	Type of Intervention	Intervention Assessment	Outcome	Major Significant Result	Adjustment
Brisson et al,[10] 2000	RCT	BCPT; cases: n = 36; controls: n = 33 (Canada)	≥35 years	Tamoxifen	20 mg/d for 5 years	Wolfe's parenchymal pattern and PMD	Mean PMD reduction • 1.0-3.4 years = −6.9 ± 11.1 • 3.5-5.0 years = −10.9 ± 12.4 Overall PMD reduction • TAM: −9.4% • Placebo: −3.6% $P < .01$	Number of first-degree relatives with BC, AH, nulliparity, age at first live birth, number of breast biopsies, and age at menarche
Chen et al,[11] 2011	CS	ER+ BC patients treated with TAM as AHT; n = 16 (Taiwan)	33-51 years	Tamoxifen	20 mg Oral tablet per 8-26 months	%FV, PMD (MRI: computer-assisted algorithm)	BD reduction after 17 months • %BD = 5.8% %FV = 8.2%	Age.
Cigler et al,[14] 2010	RCT	NCIC CTG; cases: n = 44; controls: n = 23 (Canada, United States)	>55 years	Aromatase inhibitor	Letrozole 2.5 mg/d for 12-24 months	PMD (Cumulus 5, BI-RADS)	Null	BC Hx, age, menopausal status
Valdivia et al,[52] 2004	RCT	BC negative women; cases: n = 18; controls: n = 19 (Chile)	<65 years Menopausal women	Tibolone	2.5 mg/d for 1 year	Mean BD (BI-RADS)	Mean BD reduction: from 2.22 to 1.67 (0.84)	Nil
Cuzick et al,[8] 2011	Nested CCS	IBIS-I; cases: n = 123; controls: n = 942 (United Kingdom)	30-70 years	Tamoxifen	20 mg/d for 5 years	PMD (Boyd's SCC, Cumulus)	Selective BD reduction; 63% BC risk reduction for women with 10% reduction in BD	History of atypical hyperplasia or LCIS
Cuzick et al,[9] 2004	Nested CCS	IBIS-I; cases: n = 388; controls: n = 430 (United Kingdom)	35-70 years	Tamoxifen	20 mg/d For 5 years	PMD (Boyd's method, visual assessment)	BD reduction: 7.9% (95% CI = 6.9% to 8.9%); 28.2% BD decrease from baseline	Age, menopausal status, BMI, and previous AH, smoking status
Eng-Wong et al,[40] 2008	RCT	Phase 11 trial of raloxifene; n = 27 (United States)	Premenopausal, 35-47 years	Raloxifene	Raloxifene 60 mg/d for 2 years	PMD; MRIV (thresholding technique)	• PMD: null MRIV: −17% (95% CI: −28 to −9; $P = .0017$)	Age, BMI, duration
Eilertsen et al,[49] 2008	RCT	RET; n = 177 (Norway)	45-65 years	Raloxifene + tibolone	60 mg Raloxifene, 2.5 mg tibolone	VBD (automated physics-based volumetric method)	VBD changes • Raloxifene = –4.1; $P < .0001$ Tibolone = 0.7; $P \leq .002$	BMI, menopausal status, age, smoking status, age at menopause, blood pressure
Freedman et al,[41] 2001	RCT	OPT; n = 168 (United States)	45-60 years	Raloxifene	60 mg/d Or 150 mg/d 3 months for 2 years	PMD (computer-assisted technique)	BD decreases • For 60 mg/d, 13.3%; $P = .002$ For 150 mg/d, 19.0%; $P < .001$	Age, years since menopause, BMI, previous HRT, alcohol, smoking, baseline BD
Jackson et al,[44] 2003	RCT	ccHT: n = 84; raloxifene: n =109 (Latin America)	≥60 years	Raloxifene	60 mg/d For 1 year	Mean BD (BI-RADS)	Null	Weight, race, age, smoking status, HRT use, menopausal status
Lasco et al,[45] 2006	CCS	Postmenopausal women with BMI 24.7 ± 2.8 kg/m^2; n = 70 (Italy)	52.4 ± 4.1 years	Raloxifene	60 mg/d orally for 2 years	IMI (Image Pro-Plus ad hoc software)	Null	BMI, menopausal status
Lundstrom et al,[50] 2002	RCT	Healthy women; n = 166 (Sweden)	50-70 years	Tibolone	2.5 mg/d For 1 year	Wolfe BD patterns, PMD (visual)	Null	Nil
Lundstrom et al,[51] 2011	RCT	Healthy women; n = 154 (Sweden)	50-70 years	Tibolone	2.5 mg/d For 1 year	PMD (Cumulus)	Null	BMI, years since menopause
Vachon et al,[55] 2007	RCT	NCIC CTG; n = 104 (United States)	Not specified	Aromatase inhibitor	Letrozole 2.5 mg/d for 1 year	PMD (Cumulus)	Null	Age, BMI, nodal status, number of tumors, time on TAM
Harvey et al,[43] 2013	RCT	n = 507 (United States)	55.2-56.3 years	Raloxifene	60 mg/d for 2years	PMD, Cumulus	Mean BD change: −0.23; 95%CI: −0.54 to 0.08	Age, BMI, years since menopause
Harvey et al,[42] 2009	RCT	n = 444 (United States)	≤62 years	Raloxifene	60 mg/d For 2 years	PMD (Cumulus)	Mean BD change: −0.4%	Age, BMI, years since menopause
Henry et al,[15] 2013	RCT	ELPh; n = 273 (United States)	Postmenopausal	Aromatase inhibitor	Letrozole 2.5 mg/d; exemestane 25 mg/d for 2 years	PMD (BI-RADS, MDEST)	PMD decrease from 17.1% to 15.1% ($P < .001$)	Age, BMI, HRT, prior chemotherapy

(continued)

Table 2. (continued)

Author, Year	Study Design	Study Population (n)	BD Assessment Age	Type of Intervention	Intervention Assessment	Outcome	Major Significant Result	Adjustment
Mousa et al,[54] 2008	CS	n = 46 (Canada)	Postmenopausal	Aromatase inhibitor	Letrozole 2.5 mg 3 times/wk for 2 years	PMD (BI-RADS and ImageQuant)	PMD decrease: $P < .05$	Age, BMI, age at menopause, HRT, mammogram interval
Vachon et al,[56] 2013	CCS	NCIC CTG; n = 387 (United States)	Postmenopausal	Aromatase inhibitor	Anastrozole 1 mg/d; exemestane 25 mg/d for 1 year	PMD (Cumulus)	Null	BMI, age at baseline mammogram, HRT, chemotherapy
Cigler et al,[13] 2011	RCT	NCIC CTG; n = 98 (United States)	Postmenopausal >50 years	Aromatase inhibitor	Exemestane 25 mg/d for 1 year	PMD (Cumulus, BI-RADS, Boyd's)	Null	Age, BMI, Hx of benign breast disease, Hx of breast cancer
Fabian et al,[53] 2007	RCT	BCPT; n = 42 (United States)	Postmenopausal >50 years	Aromatase inhibitor	Letrozole 2.5 mg/d for 6 months	PMD (Cumulus)	Null	Nil
Kim et al,[99] 2012	CS	n = 1065 (Korea)	24-77 years)	Aromatase inhibitor	Anastrozole; letrozole for 5 years (dosage not specified)	PMD (Cumulus)	Mean PMD reduction = 5.9% (range, −17.2% to 36.9%).	Age, duration of therapy, nodal status
Prowell et al,[16] 2011	RCT	n = 54 (United States)	Postmenopausal >60 years	Aromatase inhibitor	Anastrozole 1 mg/d for 1 year	PMD (Cumulus)	BD reduction: −16%, 95% CI: 30-2; $P = .08$ (null)	BMI, age, race, nodal status
Smith et al,[17] 2012	RCT	LCHRWC; n = 16 (United States)	Postmenopausal ≥50 years	Aromatase inhibitor	Letrozole 2.5 mg /d for 1 year	PMD (Madena)	Statistically significant decrease in PMD; $P = .04$	Nil
Silverio et al,[47] 2007	RCT	n = 80	Mean age 61.1 years	Raloxifene	60 mg/d For 2 years	PMD; BI-RADS and computer-assisted	Null	Age, time of menopause, BMI parity, breastfeeding, HRT
Decensi et al,[33] 2009	RCT	BC women; n = *235* (Italy)	Premenopausal	Tamoxifene	5 mg/d For 2 years	PMD (Boyd's and Cumulus)	20% Reduction in PMD from baseline ($P < .05$)	Nil
Chow et al[35] 2000	RCT	High-risk BC women; n = 32 (United States)	36-74 years	Tamoxifene	20 mg/d For 23 months	PMD (Wolfe's, BI-RADS, Image J Semiquantitative)	Significant decrease in density ($P < .005$)	Age, menopausal status
Atkinson et al,[34] 1999	RCT	n = 282 (United Kingdom)	50-64 years	Tamoxifene	20 mg/d For 2 years	PMD (Wolfe's)	Significant decrease in density ($P = .0001$)	Nil
Son and Oh'[38] 1999	RCT	n = 102 (United States)	28-67 years	Tamoxifene	20 mg/d For 2 years	Visual assessment	Significant decrease in density ($P < .005$)	Nil
Konez et al,[36] 2001	RCT	n = 27 (United States, Canada)	32-81 years	Tamoxifene	20 mg/d For 5 years	PMD (visual assessment)	Minimal decrease in density	Nil
Meggiorini et al,[37] 2008	RCT	n = 148 (Italy)	Mean age, 58.5 ± 9.3 years	Tamoxifene	20 mg/d For >1 year	PMD (BI-RADS, Cumulus)	Significant decrease in density ($P < .005$)	Nil
Nielsen et al,[46] 2009	Retroanalysis of RCT	n = 135 (Denmark)	55-80 years	Raloxifene	60 mg/d For 2 years	PMD (BI-RADS, computer analysis)	Null	BMI
Christodoulakos et al,[48] 2002	PS	n = 131 (Greece)	41-67 years	Tibolone and raloxifene	Tibolone: 2.5 mg/d; raloxifene: 60 mg/d for 1 year	PMD (Wolfe's)	Null	Nil
Cirpan et al,[39] 2006	Retroanalysis of RCT	n = 55 (Turkey)	Postmenopausal	Raloxifene	60 mg/d For 16 months	PMD (BI-RADS)	Null	Nil

Abbreviations: BD, breast density; RCT, randomized controlled trials; BCPT, Breast Cancer Prevention Trial; PMD, percentage mammographic density; TAM, tamoxifen; BC, breast cancer; AH, atypical hyperplasia; CS, cohort study; ER^+, estrogen receptor positive; AHT, adjuvant hormonal therapy; FV, fibroglandular volume; MRI, magnetic resonance imaging; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; Null, non–statistically significant result; Hx, history; BI-RADS, Breast Imaging Reporting and Data System; CCS, case-control study; IBIS-I, International Breast Cancer Intervention Study; SCC, 6-category classification; LCIS, lobar carcinoma in situ; BMI, body mass index; RET, raloxifene estrogen tibolone; VBD, volumetric BD; OPT, osteoporosis prevention trial; HRT, hormone replacement therapy; ccHT, continuous-combined hormone therapy; IMI, image mean index. ELPh, Exemestane letrazole pharmacogenomics; MDEST, mammographic density estimator; CAD, computer-aided calculation; PS, prospective study; MRIV, magnetic resonance imaging volume; LCHRWC, lynne cohen high risk women's clinic.

Table 3. Characteristics of Studies on the Association Between PA and BD.

Author, Year	Study Design	Population of Study (n)	Age of Participants	Intervention	Intervention Assessment	Outcome	Major Significant Result	Adjustments
Irwin et al,[19] 2007	PCS	HEAL; n = 522 (United States)	≥55 years	PA	Kaiser Physical Activity Survey (KPAS) questionnaires and interviews	DA, PMD (Cumulus 108)	Lower BD for BMI ≥30 kg/m^2 • DA: *P* for trend =.036 • PMD: *P* for trend =.0001	Age, BMI, race/ethnicity, study site, education, parity, TAM use, AT, RT, CT, RaCT, BC recurrence, smoking, HRT use
Marmara et al,[20] 2011	CSS	GPCSP; n = 724 (Greece)	45-67 years	PA	KPAS questionnaires and interviews	PMD (BI-RADS)	BD association • All women: OR = −0.10; 95% CI = 0.018, −0.001 • Older women: OR = −0.036; 95% CI = 0.063, 0.009 (*P* < .05)	Age at menarche, age at menopause, BMI, number of live births
Masala et al,[21] 2009	LS	EPIC-Florence; n = 2000 (Italy)	≥50.48 years	PA	EPIC-lifestyle questionnaire	PMD (semiquantitative and Wolfe's classification)	Lower PMD with highest BMI: OR = 0.34; 95% CI = 0.20-0.57 (*P* < .05)	BMI, PA, HRT, education, age, age at menarche, parity, menopausal status, age at first birth, number of children
Peters et al,[60] 2008	CSS	EPIC-Norfolk; n = 1394 (United Kingdom)	40-74 years	PA	Validated questionnaire for occupational and leisure time	PMD (visual assessment using Boyd method)	Null	BMI, age, parity, energy intake, HRT use, alcohol intake, education, smoking status, age at first birth
Qureshi et al,[61] 2012	CSS	NBCSP (Hofvind 2007); n = 2218 (Norway)	50-69 years	PA	Physical activity questionnaire	PMD (computer-assisted method, Madena)	Null	Age, BMI, HRT education, age at menarche, number of pregnancies, age at first birth
Reeves et al,[62] 2007	CSS	MAMS; n = 728 (United States)	≥18 years	PA	Interview questionnaire	PMD (polar planimeter)	Null	BMI, menopausal status
Siozon et al,[71] 2006	CSS	CARE; n = 418 (United States)	35-64 years	PA	Interview questionnaire	PMD (computer-assisted method, Madena)	Null	Ethnicity, age, age at menarche, age at first full-term pregnancy, BMI, menopausal and HRT use status, FH of BC, smoking, alcohol intake, education
Suijkerbuijk et al,[65] 2006	CSS	Prospect- EPIC-Dutch; n = 620 (Netherlands)	49-68 years	PA	Self-administered questionnaire	PMD (computer-assisted method)	Null	Age, education, BMI, waist-to-hip ratio, menopausal status, parity, and smoking
Wolin et al,[22] 2007	CSS	CBHP; n = 95 (United States)	≥40 years	PA	IPAQ	PMD (ImageJ)	Null	Age, smoking status, BMI
Woolcott et al,[23] 2010	RCT	ALPHA • Cases: n = 160 • Controls: n = 160 (Canada)	50-74, 1 years	Aerobic exercise	Aerobic exercise of 5 times per week for 45 minutes for 1 year	PMD, PDV (computer-assisted and volumetric software)	Null	BMI.
Conroy et al,[57] 2010	LS	SWAN; n = 722 (United States)	42-52 years	PA	KPAS questionnaires and interviews	TBA, ADBT (polar planimeter)	Null	Ethnicity, height, HRT, BMI, education, age at menarche, parity, age, age at first birth, FH of BC, weight, smoking, menopausal status
Gram et al,[58] 1999	CSS	Tromsø II and III; n = 2720 (Norway)	40-56 years	PA	Self-administered questionnaire	Tabăr	OR for lower density • Postmenopausal: OR = 1.3; 95% CI = 0.4-4.2 • Premenopausal: OR = 0.8; 95% CI = 0.4-1.5); *P* > .05	Age, education, number of children, BMI, age at menarche, alcohol intake, OC use, and menopausal status

(continued)

Table 3. (continued)

Author, Year	Study Design	Population of Study (n)	Age of Participants	Intervention	Intervention Assessment	Outcome	Major Significant Result	Adjustments
Oestreicher et al,[59] 2008	CSS	SWAN; n = 772 (United States)	40-50 year and older	PA	KPAS	PMD and TDA	• PMD: β = –2.62; 95% CI = −5.84 to 0.60 • TDA: β = −4.75; CI = −10.40 to 0.88 ($P > .05$)	Race/ethnicity, menopausal status, parity, past use of hormones, waist circumference, education, and BMI
Samimi et al,[63] 2008	CSS	NuHS; n = 1398 (United States)	42-78 years	PA	Self-administered questionnaire	PMD (Cumulus)	Null	Age, BMI, parity, smoking, alcohol use, Hx BC, Hx benign breast disease, menopausal status
Lopez et al,[67] 2003	CSS	CBHP; n = 294 (United States)	40-59 years	PA	Interviews and questionnaire	PMD (Image-J)	Null	Age, BMI, parity, smoking, education, HRT, number of live births, physical inactivity
Jeffreys et al,[66] 2004	CSS	GAC; n = 628 (United Kingdom)	55.1-68.3 years at screening	PA	Posted questionnaires	Boyd SCC	Null	Age at menarche, birth weight, oral, OC use, height, leg length, BMI, exercise at age 20, smoking, age at first birth
Vachon et al,[69] 2000	CSS	MBCFS; n = 1900 (United States)	20-80+ years	PA	Telephone interview	PMD (subjective assessment)	Null	Age at first birth, age at menarche, BMI, alcohol, WHR, menopausal status
Tseng et al,[68] 2011	CSS	Chinese immigrants; n = 201 (United States)	Mean age 53.1 (10.2) years	PA	Self- administered questionnaire	PMD (BI-RADS)	Null	Age, menopausal status, acculturation, BMI, first-degree BC relative, number of live births, age at first live birth, adult dairy food intake
Sellers at al,[64] 2007	CSS	MBCFS; n = 1893 (United States)		PA	Self- administered questionnaire	PMD (Cumulus)	Null	Age, age at menarche, HRT, height, weight, adiposity, diet
Sala et al,[70] 2000	CCS	EPIC-Norfolk; n = 400 (United Kingdom)	Not specified	PA	Self- administered EPIC Health and Lifestyle questionnaire	PMD (Wolfe's classification)	OR = 0.93; 95% CI = 0.75-1.50	BMI, OC use, smoking, Hx of BC, Hx of benign breast disease, HRT, menopausal status, age at menarche, age at first birth, number of children, hysterectomy, breastfeeding
Irwin et al,[18] 2006	PCS	HEAL; n = 474 (United States)	Not specified	PA	Self- administered Modifiable Activity questionnaire	DA and PMD (Cumulus)	• DA: *P* for trend =.046 • PMD: *P* for trend =.026 • Premenopausal BMI <30 kg/m^2: PMD (*P* for trend =.037)	Age, BMI, ethnicity, HRT use, education, parity, type 2 diabetes, age at menarche, disease stage, study site

Abbreviations: PA, physical activity; BD, breast density; PCS, prospective cohort study; HEAL, healing emotions after loss; PMD, percentage mammographic density; DA, dense area; BMI, body mass index; TAM, tamoxifen; AT, adjuvant therapy; RT, radiation therapy; CT, chemotherapy; RaCT, radiation and chemotherapy; BC, breast cancer; HRT, hormone replacement therapy; CSS, cross-sectional study; GPCSP, Greek population-based screening program; BI-RADS, Breast Imaging Reporting and Data System; LS, longitudinal study; EPIC, European Prospective Investigation Into Cancer; NBCSP, Norwegian Breast Cancer Screening Program; MAMS, Mammograms and Masses Study; CARE, Contraceptive and Reproductive Experiences; FH, family history; CBHP, Chicago Breast Health Project; IPAQ, International Physical Activity Questionnaire–Long Form; ALPHA, Alberta Physical Activity; PDV, percentage dense volume; SWAN, Study of Women's Health Across the Nation; TBA, total breast area; ADBT, Area of dense breast tissue; OC, oral contraceptive; TDA, total dense area; NuHS, Nurses' Health Study; Hx, history; GAC, Glasgow Alumni cohort; MBCFS, Minnesota Breast Cancer Family Study; WHR, waist-to-hip ratio; CCS, case-control study; SCC, six category classification.

Table 4. Characteristics of Studies on the Association Between Diet and BD.

Author, Year	Study Design	Study Population (n)	Diet/BD Assessment Age	Food Species of Interest	Dietary Assessment	Outcome	Significant Results	Adjustments
Bérubé et al,[72] 2005	CSS	• Postmenopausal women: n = 783 • Premenopausal women: n = 777 (Canada)	• Postmenopausal women: 61.8 years • Premenopausal women: 46.7 years	Dietary and supplemental VD and Ca	Food questionnaire (661 items)	PMD (computer-assisted approach	• Premenopausal: 8.5% BD decreases with 1000 mg and 400 IU intake of Ca and VD ($P \leq .004$) Postmenopausal women: null	Smoking status, alcohol, PA, OC use, age, age at menarche, BMI, education, age at first full-term and number of full-term births, ethnicity, FH of BC (first-degree relatives), previous breast biopsies
Masala et al,[73] 2006	CSS	Mediterranean women–EPIC Florence section; n = 1668 (Italy)	Premenopausal, perimenopausal, and postmenopausal women	Ca and VD; cheese; vegetables	Food frequency questionnaire (FFQ; 160 items)	Wolfe's method (P2 + DY vs N1 + P1)	BD inversely associated with vegetables, cheese, VD, and Ca; $P < .05$	BMI, age, education, total energy, menopausal status, Ca, and VD
Vachon et al,[74] 2000	CSS	MBCFSC; n = 1508 (United States, NH-White)	61.4 years	Polyunsaturated fat, vitamins E and C, saturated fat, total diary intake	FFQ (153 items)	PMD (visual assessment)	Null association for polyunsaturated fat, vitamins E and C; $P < .05$ for saturated fat, total diary intake	Smoking status, OC use, alcohol, energy, age, age at menarche, BMI, age at first full-term birth and number of full-term births, FH of BC, HRT.
Nordevang et al,[75] 1993	CSS	BC patients; n = 238 (Sweden)	57.5 years	Ca	Interview of dietary history with 4 months of BC diagnosis	Wolfe's method (P2 + DY vs N1 + P1)	Mammographic pattern: low Ca intake is associated with P2 and Dy patterns	ER status, BMI, age
Diorio et al,[77] 2006	CSS	Premenopausal women; n = 771 (Canada)	<46 years If smoker and <48 years if nonsmoker	Dietary and supplemental Ca and VD	Food questionnaire	PMD (computer-assisted method)	PMD (food and supplement) • VD: $\beta = -1.4$ • Ca: $\beta = -1.9$ PMD (food only) • VD: $\beta = -1.8$ • Ca: $\beta = -1.8$ • ($P = .002$)	Age, age at menarche, age at first full-term birth, number of full-term births, alcohol, total energy, BMI, FH of BC (first- degree relative), breast biopsies, past use of HRT and OC, PA, education
Bérubé et al,[76] 2004	CSS	Premenopausal and postmenopausal women with extreme densities; n = 543 (United States)	• PMD ≤30%: 51 years • PMD ≥70%: 46 years	Dietary Ca and VD	Food questionnaire (232 items)	PMD (visual assessment)	BD ($OR_{Q4\ vs\ Q1}$) • $\bar{V}D$: $P = .0005$ Ca: $P = .0006$	Smoking status, alcohol, PA, OC use age, age at menarche, BMI, education, age at first full-term gestation, number of full-term gestations combined, FH of BC, menopausal status, and use of HRT
Bertone-Johnson et al,[78] 2010	CSS	MDAS: WHI; n = 808 postmenopausal (United States NH-White, Black, other races)	50-79 years	Dietary and supplemental Ca and VD	Supplement inventory + food questionnaire (122 items)	PMD (computer-assisted approach)	Null	Smoking, alcohol, PA, OC use and duration of use, previous HRT use and duration, MV use, parity, age at menarche, BMI, age, ethnicity, Gail risk
Knight et al,[79] 2006	CSS	MBCFSC; n = 487 (United States, NH-White)	56.4 years	Dietary Ca and VD—25(OH)D	FFQ	TDA, PMD (Cumulus)	Null	Age, BMI, PA, parity, age at first birth
Brisson et al,[26] 1989	CCS	NBSS • Cases: n = 290 • Controls: n = 645 (Canada)	40-62 years	Dietary fats; vegetables (carotenoid)	FFQ (114 items)	Wolfe's method (P2 + DY vs N1 + P1) and visual assessment	• Increased BD with dietary fat ($P > .05$) Lower BD with carotenoid intake ($P < .05$)	Education, age, parity, body weight, energy

(continued)

Table 4. (continued)

Author, Year	Study Design	Study Population (n)	Diet/BD Assessment Age	Food Species of Interest	Dietary Assessment	Outcome	Significant Results	Adjustments
Tseng et al,[84] 2007	CSS	Women with FH of BC and ovarian cancer; n = 157 (United States, NH-White)	50 years	Ca and VD	FFQ (126 items)	PMD (visual assessment)	PMD; VD intake$_{T3\ vs\ T1}$: OR = 0.5; 95% CI = 0.2-1.1	Age, age at menarche, menopausal status, HRT Hx, FH of category, calorie intake, BMI
Sala et al,[82] 2000	CCS	EPIC-Norfolk • Cases: n = 203 Controls: n = 203	59 years	Dietary fats, carbohydrates and proteins	Seven-day record	Wolfe's method (P2 + DY vs N1 + P1)	Null for dietary fats; high BD for carbohydrates and proteins intake (P = .04)	Parity, BMI, menopausal status, HRT
Nagata et al,[80] 2005	CSS	Japanese women; n = 601 (Japan)	• Premenopausal women: 42.6 years • Postmenopausal women: 57.8 years	Dietary fats; carbohydrates	FFQ (169 items)	PMD (fully automated method)	• Dietary fats Postmenopausal: positively associated; P > .05 • Premenopausal: null Carbohydrates: inversely associated with BD; P = .03	• Premenopausal: BMI, age, smoking status, number of births, breastfeeding Hx Postmenopausal: education, age, BMI, age at menopause, total energy
Qureshi et al,[81] 2011	CSS	NBCSP; n = 2252 (Norway)	58 years	Protein, carbohydrates, dietary fiber, total fat, saturated fat	FFQ (180 items)	AD and PMD; computer-assisted approach	Null for protein, carbohydrates, dietary fiber; high BD with total fat intake (P = .10) and saturated fat (P = .06)	Age at menarche, age at mammography, age at full-term birth, number of pregnancies, BMI, HRT, education, total energy
Knight et al,[83] 1999	RCT	• Entry: premenopausal • Follow-up: postmenopausal n = 78 (Canada)	• Intervention: 49.5 years • Controls: 49.2 years	Low-fat, high CHO interventions vs control (2 years)	3 Food records	PMD, ADT (automated approach)	• Mean decrease in DA: −11.0 vs −4.5 cm^2; P = .004 Decrease in percentage density: −11.0% vs −5.2%; P = .025	Age, FH, age at menarche, parity, age at first birth, OC use, PA, breastfeeding, total energy, weight change
Bertone-Johnson et al,[85] 2012	RCT	WHI ca + D trial; n = 330 postmenopausal women (United States)	• Intervention: 61.8 years • Controls: 62.0 years	Daily supplementation of 400 IU of VD and 1000 mg of Ca (1 year)	FFQ (122 items)	PMD (computer-assisted approach)	Null	Total VD, age, ethnicity, HT treatment, BMI, residence region, Gail risk score, baseline BD
Martin et al,[29] 2009	RCT	Women with PMD ≥ 50%; n = 461 (Canada)	• Intervention: 48.7 years • Controls: 48.6 years	Low-fat, high CHO interventions	Food records	PMD, DA, TBA NDA (computer assisted)	Null	FH of BC, HRT use, OC use, dietary fats, and postmenopausal status
Boyd et al,[25] 1997	RCT	PMD ≥ 50%; n = 817 (Canada)	• Intervention: 46.5 years • Controls: 45.9 years	Low-fat, high CHO diet interventions (2 years)	Food records (3 days)	PMD (automated approach)	Intervention 6.1% vs control (2.1%); P = .01	Menopausal status, weight, age, grouping
Maskarinec et al,[88] 2003	RCT	Isoflavone trials; n = 30 (Hawaii)	35-46 years	100 mg Of isoflavone mixture/d for 12 months	Tablet counts and urinary isoflavone excretion	PMD (computer-assisted approach)	Null	Race, weight, BD ≥40%
Maskarinec et al,[31] 2004	RCT	n = 220 (Caucasians, Asians and others) Hawaii	• Intervention: = 43.2 ± 3.1 years • Control: 42.8 ± 2.9 years	2 Daily servings of soy for 2 years	Validated soy questionnaire, urinary isoflavone excretions	PMD (computer-assisted approach	BD reduction of 3.14%/ year at least 1 serving/wk (insignificant BD change)	Ethnicity, age, group status, place of birth, number of children, %BD at baseline

(continued)

Table 4. (continued)

Author, Year	Study Design	Study Population (n)	Diet/BD Assessment Age	Food Species of Interest	Dietary Assessment	Outcome	Significant Results	Adjustments
Atkinson et al,[86] 2004	RCT	NHSBSP; n = 205 (United Kingdom)	49–65 years	Red clover–derived isoflavone tablet/d for 12 months	Urinary isoflavone excretions	PMD (Wolfe classification, visual assessment)	Null	Menopausal status, age at baseline, BMI, genotype
Verheus et al,[89] 2008	RCT	DPBCSP; n = 202 (Netherlands)	60-75 years	99 mg isoflavone/d for 1year	Intake of 36.5 g of soy powder/d	PMD (computer assisted)	Null	Equol status, %BD at baseline
Maskarinec et al,[87] 2009	RCT	OPUS; n = 406 (United States, Greece)	40-60 years	80 Or 120 mg/d of isoflavone for 2 years	FFQ, pill counts, blood isoflavone measurement	PMD (computer-assisted method)	Null	Age, BMI
Tseng et al,[91] 2013	LS	Chinese immigrants; n = 436 (United States)	36-58 years	25 to 30 mg/d of isoflavone for 3 days	48-Hour dietary recall, urinary isoflavone excretions	PMD (computer-assisted method)	Null; PMD for Equol vs non–equol producers: 31.8 vs 35.3, respectively	Sociodemographic characteristics, dietary intake, equol status, equol dose
Jones et al,[28] 2015	CSS	DISC; n = 172 (United States)	25-29 years	Dietary energy density	24-Hour dietary recalls	%DBV, ADBV (MRI)	25.9% (95% CI = 6.2% to 56.8%) increase in %DBV ($P < .01$)	Race, smoking status, education, parity, duration of sex hormone use, whole body percentage fat, childhood BMI, and energy from beverage, fat, and alcohol
Masala et al,[90] 2013	CSS	EPIC-Florence; n = 1668 (Italy)	Not specified	Carbohydrate intake	Self-administered FFQ	PMD (Wolfe classification, visual assessment)	• BD increase: OR = 1.73, 95% CI = 1.13-2.67 • Simple sugar: OR = 1.71; 95% CI = 1.13-2.59	Age, education, BMI, menopause, number of children, breastfeeding, physical activity, non–alcohol energy, fibers, saturated fat, and alcohol
Voevodina et al,[92] 2013	CSS	n = 424 (Germany)	21-84 years; Premenopausal and postmenopausal	Mediterranean diet and M-M supplements	Self-administered FFQ	PMD (BI-RADS)	OR for lower BD • Mediterranean diet: 0.95; $P < .05$ • M-M supplements: • Premenopausal: 0.53; $P > .05$ Postmenopausal: 0.51; $P < .05$	Age, age at menarche, age at first birth, number of live births, PA, alcohol, smoking status, menopausal status, education, HRT, OCs, Hx of BC, breastfeeding
Bérubé et al,[24] 2008	CSS	Premenopausal and postmenopausal women; n = 1560 (Canada)	• Mean age Postmenopausal = 61.8 years Premenopausal = 46.7 years	Diet and multivitamin multimineral, and individual vitamin and mineral supplement use	Self-administered FFQ	PMD, Cumulus	BD • Increase in premenopausal (P for trend = .04) • Postmenopausal: null (P for trend = .40)	Smoking status, alcohol, PA, OC use, age, age at menarche, BMI, education, age at first full-term birth and number of full-term births, ethnicity, FH of BC (first-degree relatives), previous breast biopsies
Vachon et al,[93] 2005	CSS	MBCFSC; n = 1575 (NH-white, United States)	<18 years/60.4 years	Alcohol	Follow-up questionnaire	PMD (Cumulus)	Null	Age, age at menarche, age at first birth, number of live births, HRT, BMI, smoking status, education, oral OC use, menopausal status, alcohol

(continued)

Table 4. (continued)

Author, Year	Study Design	Study Population (n)	Diet/BD Assessment Age	Food Species of Interest	Dietary Assessment	Outcome	Significant Results	Adjustments
Sellers at al,[64] 2007		MBCFSC; n = 1552(NH-white, United States)	12-13 years/60.4 years	Chicken and fish, vegetables, fruits, high-fat meats, animal fat, dairy, high-fat foods, high-fat snacks and desserts	Questionnaire (retrospective recall)	PMD (Cumulus)	Null	Age at menarche, parity, age at first birth, smoking history, education, OC use, HRT use, menopausal status, alcohol intake
Mishra et al,[94] 2008	PCS	MRC NSHD; n = 979 (Britain)	4/51.5 years	Dietary VD and Ca	Maternal recall of child's diet within 1-24 hours	ADT, ANDT, PMD (Cumulus)	Null	BMI, age at menarche, parity, energy, smoking status, adult SES
Tseng et al,[68] 2011	CSS	Chinese-American immigrant; n = 201 (United States, Asian)	12-17/53.1 years	Green vegetables, fruits, tofu, beef, pork	Questionnaire (Retrospective recall)	BI-RADS	OR 95% CI for high BD • Red meat: 3.0%; *P* = .003 • Tofu and fruits: 1.6%; *P* = .39 Vegetables: null	Age, BMI, level of acculturation, age at first live birth, number of live births, adult dietary intake
Mishra et al,[95] 2011	PCS	MRC NSHD; n = 792 (Britain)	4 years/51.5 years	Dietary patterns at age 4: (a) Fried potatoes and fish (b) Breads and fats (c) Milk, biscuits, and fruits	Maternal recall of child's diet within 1-24 hours	ADT, ANDT, PMD (Cumulus	Null	BMI at 53 years, age at menarche, parity, energy, age at mammogram, HRT, mammographic view, smoking status, adult SES, PA, social class, dietary pattern
Dorgan et al,[27] 2010	CSS (RCT follow-up)	DISC; premenopausal women; n = 182 (United States, NH-White	25-29 years	Low-fat diet long-term effect assessment	3-24 Hour dietary recalls	VDT and PMD (MRI)	Null	Age at randomization, race, education, BMI-Z score, percentage body fat, age at visit, smoking status, clinic, number of full-term gestations, hormonal contraceptives, PA at age 14-17 years and during the past year
Haars et al,[96] 2010	CSS	DOM-project; n = 356 (Holland)	10-18/53 years	Short-term energy restriction	Exposure to hunger, cold, and weight loss (retrospective recalls of 1944-1945 Dutch famine)	PMD, NDT, DT, BS (visual mammographic assessment)	Null	Menopausal status, parity, BMI, and age at mammography

Abbreviations: BD, breast density; CSS, cross-sectional study; VD, vitamin D; PMD, percentage mammographic density; PA, physical activity; OC, oral contraceptive; BMI, body mass index; FH, family history; BC, breast cancer; EPIC, European Prospective Investigation Into Cancer; MBCFSC, Minnesota Breast Cancer Family Study cohort; NH-Whites, Non-Hispanic Whites; HRT, hormone replacement therapy; ER, estrogen receptor; MDAS WHI, Mammogram Density Ancillary Study of the Women's Health Initiative; MV, multivitamins; TDA, total dense area; NBSS, National Breast Screening Study; RCT, randomized controlled trial; TBA, total breast area; AD, absolute density; Hx, history; ADT, area of dense tissue; NDA, nondense area; NHSBSP, National Health Service Breast Screening Programme; DPBCSP, Dutch Population-Based Breast Cancer Screening Programme; OPUS, osteoporosis prevention using soy; LS, longitudinal study; MRI, magnetic resonance imaging; M-M, multivitamin-multimineral; BI-RADS, Breast Imaging Reporting and Data System; PCS, prospective cohort study; SES, socioeconomic status; CHO, carbohydrates; NBCSP, Norwegian Breast Cancer Screening Program DISC, dietary intervention study in children; DBV, dense breast volume; ADBV, absolute dense breast volume; MRC NSHD; Medical Research Council National Survey of Health and Development; ADT, area of dense tissue; ANDT, area of non-dense tissue; VDT, volume of dense tissue NDT, non-dense tissue; DT, dense tissue; BS, breast size.

postmenopausal women alone ($P < .05$)[92] and the other demonstrating higher BD in premenopausal women but not in postmenopausal women (Table 4).[24]

Discussion

One encouraging attribute of BD is that it can be altered.[8] Because most determinants of BD and BC are interrelated and interdependent,[5] it is logical that parameters that lower BD may lower BC risk. Many parameters are thought to alter BD; however, this review focuses on SERMs, AIs, PA, and diet.

Estrogen plays a critical role in BD and increased BC risk[5]; therefore, it is intuitive that interventions that decrease estrogen bioavailability may lower BD. A few substances with strong binding affinity for estrogen receptors such as SERMs have been identified to antagonize the action of estrogen on breast tissue through inhibition of 17β-estradiol activity.[97] SERMs also decrease insulin-like growth factor (IGF)-1 levels and increase IGF binding protein (IGFBP) and sex hormone binding-globulin.[8,9,15] Other substances (AIs) inhibit the production of estrogen by aromatase.[15,56] Evidence shows that TAM mediates BD reduction in both premenopausal and postmenopausal women, but no concrete evidence exists for BD reduction with RLX, tibolone, letrozole, anastrozole, or exemestane (Table 2). The BD reduction in TAM studies might be explained by the prevalence of premenopausal women as shown by the stronger BD decreases in premenopausal women. Most of the AIs, tibolone, and RLX studies were performed in postmenopausal women. Because menopause is associated with tissue involution,[98] postmenopausal breast tissue may not be responsive to AIs and RLX therapies.

A few limitations are noted in studies on antiestrogen agents. About 80% of the studies on TAM and tibolone did not adjust for BD confounders. Two of the studies on estrogen modulators had very small sample sizes,[11,17] and 1 study[99] reported duration of treatment but not dosage administered. There was variability in age, populations, and sample size between studies, thus making comparison of studies difficult. A majority of the studies did not assess the consistency of MBD assessments, and 90% of the studies used area-based approaches for MBD assessment, which may not detect change in BD when the quantity of dense tissue changes but the dense area remains unchanged. Significant changes in BD with 3 different estrogen-receptor modulators were demonstrated where VBD assessment was performed[11,40,49] and emphasize the need for further studies using volumetric methods to assess the effect of RLX, tibolone, and AIs on BD in premenopausal women. Thus, variability in MBD assessment continues to be a confounding factor in studies assessing the impact of interventions on BD, as demonstrated by the heterogeneity in results obtained in the same patients when different MBD measurement approaches were used.[35,40,54]

PA alters BMI by reducing adiposity and increasing muscle mass, and the association between BMI, BD, and cancer is well established.[100] However, the evidence for the association between PA and BD is conflicting. Of the 21 studies, 81%, including a RCT of aerobic exercise on BD,[23] found no association between PA and BD. It is well established that BMI and postmenopausal status are negative confounders for BD.[100] BMI was found to attenuate the association between PA and BD, but only 9 studies adjusted for menopausal status; 95% of the studies did not report whether participants were premenopausal or postmenopausal at the time of PA, and 1 study[70] did not specify the timing of PA. There was heterogeneity in the type, duration, and intensity of PA, making comparison of results difficult. The only RCT that assessed change in BD with aerobic exercise was in postmenopausal women. Involution of the breast and depletion of sex hormones and growth factors is common in postmenopausal women.[5,98] Because exercise acts through these hormonal agents, it is unsurprising that no change was noted in BD with aerobic exercise in postmenopausal women. About 90% of the studies assessed Caucasian women, limiting the generalization of results to other ethnic populations. As yet, there is no evidence to suggest that PA is associated with lower BD. Nonetheless, because PA is inversely related to serum IGF-1, estrogen, and progesterone bioavailability and reduction in their serum concentration reduces cell proliferation and exposure to carcinogens, PA is a controllable, important BC risk mitigation agent.

Although evidence for the association between diet and BD is also contradictory,[27,64,68,93-96] intake of vitamin D and calcium; a low-fat, high-carbohydrate diet; and vegetables appears to be associated with lower BD, mostly in premenopausal women (Table 4). Calcium and vitamin D play an important role in the modulation of epithelial cell growth, proliferation, and differentiation.[101] The inverse association between these food sources and BD in premenopausal women is stronger at higher threshold consumption and among women with high concentrations of IGF-I or IGFBP-3.[77] Lower BD from calcium and vitamin D intake has been attributed to antioxidant activity[101] and inhibition of IGFs.[77] Premenopausal, compared with postmenopausal, women have more proliferating cells and mitogens implicated in BD increases,[5,8,77] which is perhaps the reason for the inverse association between calcium and vitamin D with BD in premenopausal women only. Isoflavone consumption has been shown to be associated with lower cancer incidence[102] but not BD.[31,86-89] A recent LS shows that soy-product consumers who metabolize daidzein manufactured by intestinal bacteria to equol (a nonsteroidal estrogen) demonstrate slightly lower BD than non–equol producers.[91] This suggests that the metabolism of a specific diet may influence its association with BD and needs to be explored. Isoflavones reduce the effects of mitogens and mutagens

through increases in antioxidant activity and sex hormone–binding globulin serum bioactivity,[102] and these 2 properties reduce cell proliferation associated with BD increases. Isoflavone studies are limited by the area-based assessment of MBD and inadequate adjustment for BD confounders.

The literature on the association between carbohydrates and proteins with BD also presents conflicting outcomes: direct association,[82] inverse association,[80] and no association.[81] However, RCTs on low-fat, high-carbohydrate diet have shown an inverse association with BD in premenopausal and postmenopausal women.[25,29] There is evidence that the fiber make-up of carbohydrates influences the IGF/IGFBP sequence and oxidative stress.[103] Therefore, varying fiber content in the different sources of carbohydrates may differentially influence growth factors responsible for BD variations, and this may be the reason for the inconsistent relationship between carbohydrate intake and BD.

Vegetables and carotene inhibit cell proliferation and IGF-1,[104] and these may be the reasons for their association with lower BD in premenopausal and postmenopausal women.[26,73] Although regular use of M-M supplements has generated different outcomes, these supplements contain antioxidants that reduce the activity of mitogens responsible for BD increases[24] and, therefore, need to be further investigated.

Generally, the reliance of CSSs on questionnaires whose reliability can be diminished by memory deficiency makes it difficult to measure the extent of exposure to dietary factors.[105] The association between a specific diet and BD may also be attenuated if such food is consumed in combination with other counteracting food substances and if intake occurred before mammogenesis. Therefore, RCTs using VBD measurement approaches may provide more accurate evidence for the impact of interventions on BD. The literature demonstrates that antidiabetes agents such as metformin inhibit IGF-1 and insulin/IGF chain and alter metabolic processes.[106] These processes are associated with reduction in cell proliferation,[106] which may lower BD. Thus, it may be important to assess the effect of antidiabetes agents and changes in glucose homeostasis on BD. Finally and encouragingly, change in BD over time is consistent with change in BC risk,[107,108] and reduced BD is associated with a reduced risk of BC[108,109] and death from the disease.[110] Therefore, BD may have potential utility as a biomarker for the efficacy of chemopreventive interventions.

Conclusion

There is substantial evidence that BD is potentially reducible. Tamoxifen reduces BD; however, the effect of RLX, tibolone, and AIs on BD is still unclear. There is no evidence for association of PA and childhood or adolescent diet with BD. Although data on the association between dietary factors and BD are conflicting, intake of vegetables, vitamin D, and calcium in adulthood is associated with lower BD in premenopausal women. It is hoped that lowering BD with interventions may lower BC risk and improve early detection of BC with mammography. However, these benefits can only be amassed if women are adequately informed about BD and BC risk mitigation strategies. Implementation of these strategies may hold the key to reducing the risk of BC.

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