Representation inequities in research related to vitamin D and breast cancer survival: a rapid scoping review

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Abstract

Background: Black women face disproportionate mortality rates from breast cancer because they are more likely to experience aggressive breast cancer prognosis and metastasis. Previous research findings have indicated that low serum vitamin D levels contribute to the risk of certain breast cancer molecular subtypes such as triple negative breast cancer (TNBC). Vitamin D deficiency is particularly prevalent among African American (AA) individuals, and AA women, in particular, experience higher mortality rates from breast cancer. However, there is a significant gap in research focusing on AA women that examines the association between vitamin D levels in breast cancer patients and mortality, specifically considering molecular subtype characteristics. This scoping review aimed to provide a narrative description of the available research that investigates the relationship between vitamin D and breast cancer mortality in AA women. The review sought to depict the nature, quantity, and scope of existing studies in this area in the U.S.

Methods: A rapid scoping review was conducted, and a total of 388 articles were identified after completing a structured search across 5 databases. This scoping review followed the framework outlined by the PRISMA extension for scoping reviews and the JBI manual. One reviewer conducted both abstract/title screening and full-text screening. Articles were included if they were published in English and contained primary research investigating the relationship between vitamin D and breast cancer mortality in American women, accounting for molecular subtype characteristics.

Results: Five studies were identified as relevant and included in this rapid scoping review. None of the studies included populations with a sample size of AA women equal to or greater than 50%. Out of these five studies, only two reported a significant result. Furthermore, four out of

the five studies were conducted in states with high UV indexes which impacts serum vitamin D levels.

Conclusion: Four significant gaps in research on vitamin D and breast cancer prognosis in studies of predominantly AA women was identified. Future research should prioritize this demographic, as they are the most affected by adverse breast cancer outcomes.

Keywords: Breast cancer; molecular subtype; vitamin D; mortality, African American, women

Introduction

Breast cancer is the most diagnosed cancer and the second leading cause of cancer mortality in the United States [3]. African American women face disproportionate mortality rates from breast cancer due to their higher likelihood of experiencing aggressive breast cancer molecular subtypes [11]. Understanding the risk factors associated with these unequal mortality rates is crucial for identifying potential treatment and intervention strategies.

Breast cancer comprises a diverse array of diseases, encompassing various subtypes with distinct biological characteristics. These variations contribute to differences in patient responses to treatment, ultimately resulting in varying outcomes [23]. Breast cancer prognosis is categorized based on molecular subtype characteristics, including the presence of hormone receptors (estrogen and progesterone), and the expression patterns of HER2 and Ki-67 [1].

Low or deficient serum vitamin D levels have been shown to contribute to poor breast cancer prognosis and increased mortality [2]. African Americans have a reduced ability to synthesize vitamin D in the skin due to higher melanin concentrations [8]. Research indicates that approximately 60% of Black women in the US have vitamin D concentrations below the clinical threshold (20 ng/mL) for sufficiency, indicating deficiency [13].

Vitamin D deficiency is particularly prevalent among AA individuals, and AA women are more likely to experience metastasis and aggressive breast cancer prognosis [13, 21]. Furthermore, studies reveal that AA women with lower serum vitamin D levels are at a higher risk for aggressive molecular subtypes [21]. However, there is a dearth of research focusing on AA female breast cancer patients that examines the connection between serum vitamin D levels and mortality, stratified by molecular subtype characteristics.

The following research questions have been formulated:

1. Is there a literature gap regarding the impact of vitamin D on mortality in AA women with breast cancer, considering molecular subtype characteristics?
2. How does the existing literature on this topic for AA women compare to literature available for American women representing other ethnic groups?

This rapid scoping review aimed to provide a narrative description of the nature, quantity, and scope of published evidence in the literature that analyzes the association between vitamin D and mortality in AA breast cancer patients, accounting for molecular subtype characteristics. The review's findings are valuable in guiding suggestions for future research, with the overarching goal of reducing mortality rates for AA breast cancer patients.

Materials and Methods

Rapid Scoping Review

This rapid scoping review was designed to narratively describe the nature, number, and scope of primary research available that investigates the relationship between vitamin D and breast cancer mortality in American women. Articles included must have adjustments for molecular subtype characteristics during analyses.

To swiftly provide information, rapid reviews are a type of knowledge synthesis that omits or streamlines several elements of the systematic review process [5]. This rapid scoping review adhered to the framework of PRISMA-ScR and JBI [14,17]. To ensure the completion of the rapid scoping review, some suggested steps for scoping reviews were modified or omitted (see Additional File 1 for details). These adjustments included the elimination of protocol registration, and the screening process was conducted by only one individual.

Eligibility criteria

Studies were included if all study participants were women who were diagnosed with breast cancer in the United States. Studies were excluded if they were not peer-reviewed, did not have primary data, and did not report the following variables: vitamin D measurements (serum, dietary, sunlight, or supplement), breast cancer, molecular subtype characteristics, and mortality outcomes. Additionally, studies were excluded if they were not published in English. These criteria were implemented to enhance the feasibility of the rapid scoping review.

Search Strategy

An initial search of MEDLINE (OVID) and CINAHL was conducted in May 2023 to identify key words for the search strategy. A comprehensive search technique for MEDLINE was devised using the text words present in the titles, abstracts, and index terms of relevant articles. The databases that were searched included CINAHL, MEDLINE (OVID), PubMed, Scopus, and Web of Science. Each database was searched using a customized version of the search strategy, which can be found in Additional File 2. The keywords used for the database searches were "female," "breast cancer," "vitamin D," "mortality," and "molecular subtype." Boolean operators were applied to these keywords in all the database searches. Table 1, below, illustrates the search strategy employed for this scoping review.

Table 1: Search Strategy.

Item	**Details**
Databases	Medline (Ovid), Pubmed, Scopus, Web of Science, CINAHL
Key words	(women) AND (breast cancer) AND (vitamin D) AND (mortality) AND (molecular subtype)
Language	English
Location	United States of America

Type of Publication	Primary data research articles
Excluded	Review articles, book chapters, and letters to the editors

Selection of Sources

A search in the five databases was conducted on June 21, 2023. These searches yielded a total of 388 potential articles for this rapid scoping review. Studies were screened according to the eligibility criteria by one reviewer. After the screening process, five articles were included in the rapid scoping review. A more detailed description of the article exclusion and inclusion process is provided in the results section of this article.

Data Charting

A predefined template was designed for assessment to streamline the extraction of pertinent data. To minimize bias, a rigorous procedure was applied to each selected article to ensure its alignment with the goals of this scoping review. The author reviewed each chosen article twice to confirm its relevance to the review's focus before initiating the actual data extraction process. Once the article's relevance was established, data extraction was systematically conducted using the predefined template. Essential details were gathered from eligible articles, including authors, publication year, sample size, demographic characteristics of the population, information on vitamin D measurements, mortality outcomes, key findings, and the significance of results.

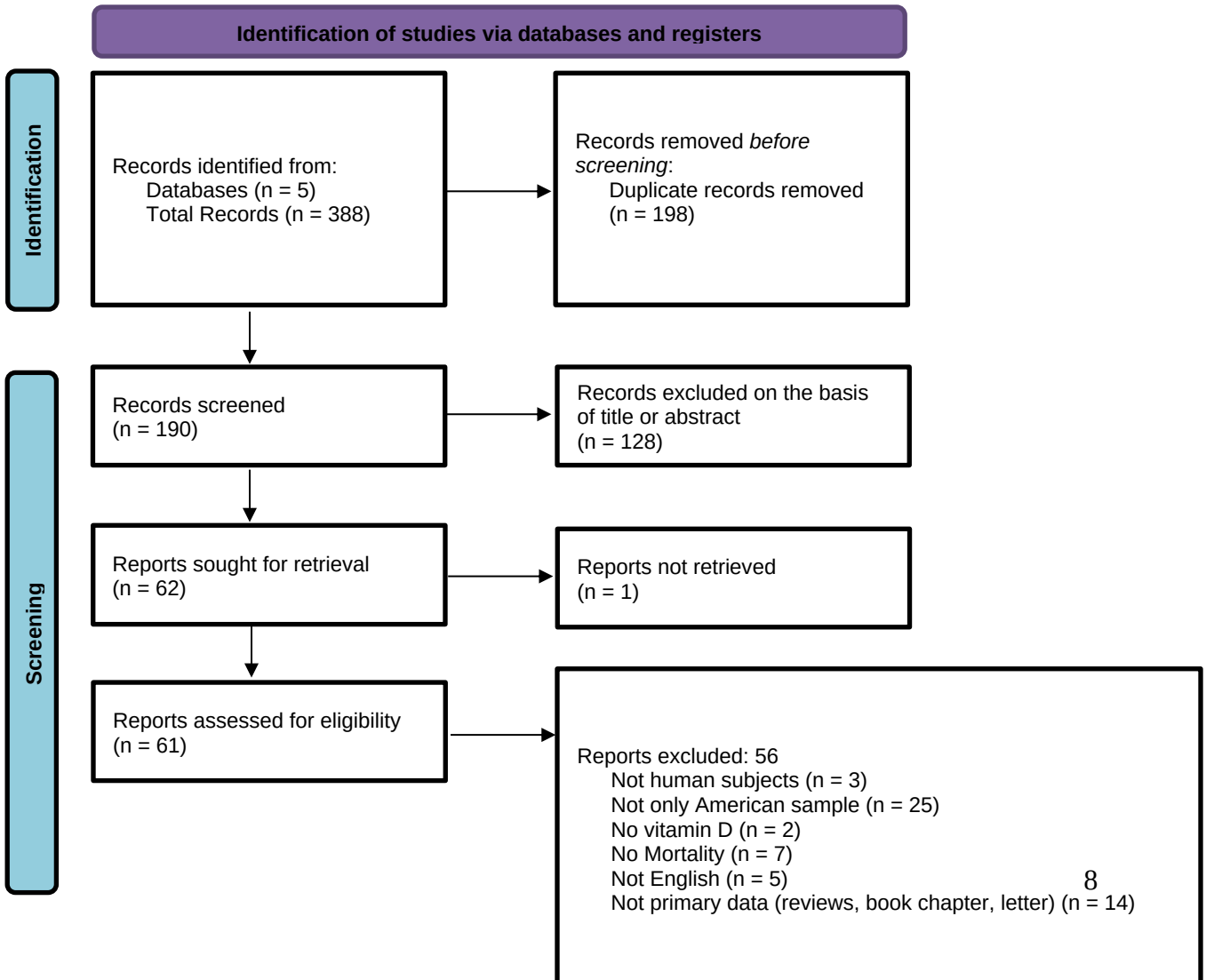
Synthesis of results

The relevant information was condensed and inserted into the appropriate sections of the charting table. To ensure accuracy, the data in the table were cross-referenced with the original articles. In line with the focus of the scoping review, the collected data was then aggregated, summarized, and reviewed for any noticeable research gaps.

Results

Literature Search

A total of 388 articles were initially identified through the database searches. Deduplication reduced this number by 198 articles. After deduplication, the remaining 190 underwent a title/abstract screening process. During the title/abstract screening, 128 articles were excluded based on a clear indication that they did not meet the inclusion criteria. The remaining 62 articles were retrieved, and only one article was not successfully retrieved, resulting in 61 articles available for full-text assessment. Out of these 61 articles, 56 were excluded during the full-text assessment process because their contents did not align with the focus of the scoping review. This left a total of five articles as the final selections for this scoping review. The process of source selection is illustrated in Figure 1 below.



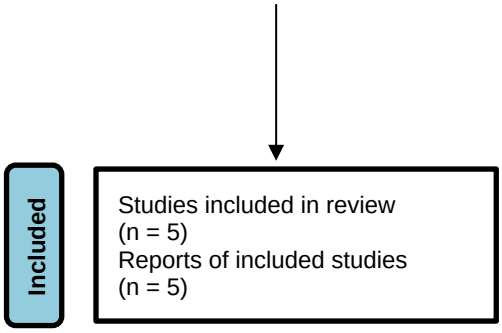


Figure 1. PRISMA-ScR process of selection of sources of evidence

Literature Characteristics

As indicated on Table 2, three out of five of the studies were conducted on the West Coast [18,20,22], one study was conducted across ten sites [4], and another study was carried out in Florida [24]. Four of these studies were conducted in areas with high UV indexes [18,20,22,24]. There was considerable variation in the designs of studies conducted on this topic. There was one prospective cohort studies [18], one retrospective chart-review [24], one retrospective cohort [4], one prospective case-control [20], and one prospective case-cohort [22]. Overall, the objectives of each study were very similar and revolved around determining the relationship between vitamin D (either through supplementation [24] or serum levels [4,18,20,22] and breast cancer outcomes. Lastly, only one study had a population size exceeding 1,000 [22]. The remaining population sizes ranged from 82 to 660 [4,18,20,24].

Gaps in Representation

As indicated in Table 3, a disparity in research on AA women is evident. Among the five studies included in this scoping review, none of them featured a sample in which AA women constituted most of the population [4,18,20,22,24]. Out of the five studies, three had samples that comprised predominantly white women [4,18,22], while the remaining two studies included predominantly Hispanic [20,24]. Furthermore, only one study encompassed all types of breast cancer in its investigation [20]. The other studies specified their sample/case compositions as

follows: invasive breast cancer [18], non-metastatic HER2+ [24], no-distant metastases and only HER2- [4], and invasive breast cancer [22]. Lastly, the age distribution in each article varied.

Vitamin D measurements

As shown in Table 4, all the studies recruited individuals diagnosed with breast cancer between the years 1995 and 2013 [4,18,20,22,24]. Among these studies, four out of five had recruitment periods lasting under seven years [4,18,20,24], while one of the studies conducted recruitment over a 12-year period [22]. Two studies explicitly indicated that they collected serum vitamin D levels pre-treatment [4,20], one collected supplementation data during treatment [24], another collected serum vitamin D levels post-treatment [18], and the final study did not specify the timing of serum vitamin D collection [22].

In terms of vitamin D exposure characterization for descriptive analysis, two studies [18,22] employed three categories based on clinical cutpoints: deficiency (<20 ng/mL), insufficiency (20-30 ng/mL), and sufficiency (>=30 ng/mL) [7]. Among these two studies, one had a study population with relatively even distribution of individuals in each category [18]. In contrast, the other study population showed a larger proportion of individuals who were deficient (48%), and a significantly smaller proportion of individuals who were sufficient (11%) [22].

Additionally, two studies that collected serum vitamin D levels categorized their samples into two groups [4,20]. One of which utilized the categories of <20 ng/mL or >= 20 ng/mL and further divided these categories by race (AA and Hispanic) [20]. Among the AA sample, 69.2% had serum vitamin D <20 ng/mL, whereas only 37.8% of Hispanic women serum vitamin D <20 ng/mL. The second study [4] that categorized their sample into two groups did so by dichotomizing vitamin D based on Institute of Medicine (IoM) definitions where vitamin D deficiency and insufficiency are <20 vs. ≥20 ng/mL and <30 vs. ≥30 ng/mL, respectively (IoM,

2011). This study found that 41% were classified as deficient and 72% were insufficient. Lastly, the Zeichner study [24], which analyzed vitamin D supplementation during treatment, categorized the sample into two categories: individuals who took supplements during treatment (yes) and individuals who did not (no). This study showed a relatively even distribution in both categories, with the "yes" category being slightly more numerous (54.5%).

Outcomes

As shown in Table 5, two of the studies had median follow-up times exceeding five years [18,22]. One study had a median follow-up of approximately 3 years for both disease-free survival (DFS) and overall survival (OS) [24]. Lastly, while two studies did not specify the median follow-up time, they indicated follow-up periods of 3 years [4] and 5 years [20].

The method of analysis for outcomes were as follows. All studies conducted Cox proportional hazards regression analyses, but the method of conducting this analysis varied. In terms of adjusting for molecular subtype characteristics (ER, PR, and HER2 status), Villaseñor [18] only examined hormone receptor which was defined as ER+/- for inclusion, but they were not retained as covariates in the final models. The Yao study [22] adjusted for HR (defined as ER and PR) and HER2 status and denoted four molecular subtypes (HR+, HER2-; luminal A) (HR+, HER2+; luminal B) (HR-, HER2+; HER2 enriched) (HR-, HER2-; TNBC) in the analysis. Wu [20] adjusted for ER, PR, and HER2 status without grouping by molecular subtype. Clark [4] stratified and adjusted based on hormone receptor presence or absence (HR+/-) but did not specific if HR is defined as both ER and PR. Lastly, Zeichner….

Only two of the five studies included in this review found significant protective associations between vitamin D and breast cancer outcomes [22,24]. The Zeichner study [24] discovered significant results for the difference in DFS among patients who were receiving

vitamin D supplementation during chemotherapy compared to those who were not. Additionally, the Yao study [22] discovered significant results for the trend in OS among patients.

Discussion

Main Findings and Implications

The purpose of this rapid scoping review was to describe the available primary research that investigates the association between vitamin D and mortality in AA breast cancer patients, categorized by their molecular subtype. Molecular subtype was included as an eligibility criterion because it contributes to making breast cancer a heterogeneous disease that is characterized by the expression levels of ER, PR, and HER2 [23]. The overexpression, presence, or absence of these genes in an individual with breast cancer contributes to the aggressiveness of their cancer and may cause them to respond differently to vitamin D [23]. For example, TNBC is the most aggressive form of breast cancer due to its difficulty to treat. Five studies, meeting the criteria for primary data analysis, were included in this scoping review [4,18,20,22,24]. Upon reviewing these five studies, four significant research gaps became apparent.

Firstly, a notable disparity exists in research exploring the impact of vitamin D on breast cancer survival within the AA population. Among these five studies, none of them encompassed a population of AA women that accounted for 50% or more of the sample [4,18,20,22,24]. This research gap pertaining to AA women necessitates more observational studies focusing on the relationship between serum vitamin D levels and mortality, while considering molecular subtype characteristics.

Secondly, apart from the insufficient representation of AA women, it is vital to emphasize that out of the five studies, four were conducted in regions with high UV exposure [18,20,22,24]. Despite this, a higher proportion of AA women had vitamin D deficiency

compared to either white or Hispanic breast cancer patients. Future studies should encompass geographic locations with low UV exposure as well since UV exposure significantly influences serum vitamin D levels [12,15].

Thirdly, although we specifically targeted studies with available data on tumor molecular subtype, many of the studies excluded specific types of breast cancer from the study or the analysis [4,18,22,24]. It is important for future studies to encompass all types of breast cancer, considering that breast cancer constitutes a complex spectrum of diseases with distinct biological features leading to variations in response patterns to treatments and clinical outcomes [23]. Limiting the study population to certain breast cancer types could hinder the ability to determine the impact of vitamin D on breast cancer outcomes. Given that some molecular subtypes are less common, this calls for larger study populations.

Lastly, the current evidence available on vitamin D and breast cancer prognosis in the United States lacks evidence to suggest that vitamin D decreases the risk of survival in breast cancer patients. Although nobody is protected against death, studies from other countries have indicated that vitamin D might improve mortality rates among breast cancer patients [6,16,19]. This absence of significant evidence among American women could be attributed to various factors, such as the relatively short duration of many of these studies, and the small sample size and/or inadequate statistical power. Further research is required to identify the distinguishing factors among international studies that report significant findings. Additionally, future research on this topic should be designed with large sample sizes and sufficient statistical power to effectively conduct survival analyses.

Limitations

This review possesses both strengths and limitations. The review comprehensively explores the spectrum of research existing on the association between vitamin D and survival rates in female breast cancer patients within the United States, offering a comprehensive perspective on the subject matter. This research serves the purpose of pinpointing gaps in research concerning vitamin D and breast cancer while also highlighting avenues for future research. However, it is important to acknowledge limitations of the study. The results are restricted to a narrative synthesis rather than an in-depth critical analysis. Moreover, the review process was carried out by a sole reviewer.

Conclusion

In conclusion, this scoping review has determined that there is currently no available research that investigates the association between vitamin D and mortality outcomes within predominantly AA women with breast cancer. The urgency for research into the association between vitamin D and breast cancer survival in AA women is evident. Previous research has highlighted that low or deficient serum vitamin D levels contribute to unfavorable breast cancer prognosis and an increased risk of mortality [2]. Notably, vitamin D deficiency is highly prevalent among AA individuals, with AA women being more susceptible to aggressive breast cancer prognosis and mortality [11]. Hence, there is a clear demand for further observational studies within the United States to provide clarity regarding the role of vitamin D and breast cancer survival within this high-risk population.

Abbreviations

TNBC: triple negative breast cancer; HER2: human epidermal growth factor receptor 2; MV: multivariate; AA: African American; DFS: disease-free survival; OS: overall survival; Wash/NM: Washington State/ New Mexico; LA: Los Angeles, California; ER/PR: estrogen receptor/progesterone receptor; BMI: body-mass index; BCSM: breast cancer specific mortality; RFS: recurrence-free survival; BCSS: breast cancer specific survival; IDFS: invasive disease-free survival; SPCFS: second primary cancer-free survival; IOM: Institute of Medicine.

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests:

The author declares no competing interests.

Funding:

This research article was funded by the American Cancer Society Master's Scholar Diversity in Cancer Research Program through Howard University. This funding supported the entire process of conducting the scoping review.

Authors' contributions:

AV conceptualized the study, devised the search strategy, conducted the literature search, screened the results, developed the data analysis plan, extracted the data, interpreted the results, and composed the manuscript. MM, PCN, and CW contributed to conceptualizing the scoping review, participated in constructing the search strategy, and reviewed the data extraction plan. All authors reviewed and edited the manuscript and approved the final version for submission.

Acknowledgements:

This work was supported by the Howard University Cancer Center and the American Cancer Society Diversity in Cancer Research Program. We extend our gratitude to Jeremy Gunnoe and Peter Tagtmeyer for their assistance in developing the search strategy, and to Dr. Robert Copeland for his help in obtaining full-text articles.

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Figures

Table 2. Literature characteristics

Author, Year (Location)	Study Type	Objectives	Population Size
Villasenor, 2013 (Washington, New Mexico, Los Angeles) [18]	Prospective cohort	To examine the relationship of serum 25(OH)D with overall and breast cancer-specific mortality.	585
Zeichner, 2015 (Miami) [24]	Retrospective chart-review	To examine if vitamin D supplementation during adjuvant chemotherapy improves survival for patients with HER2+ nonmetastatic breast cancer.	246
Clark, 2014 (10 sites, I-SPY study) [4]	Retrospective cohort	Primary aim: to determine the relationship between vitamin D levels and response to NACT. Secondary aims: to examine the relationship between vitamin D levels and biomarkers of proliferation, cell death, and differentiation as well as breast cancer relapse-free survival (RFS).	82
Wu, 2017 (Los Angeles) [20]	Prospective case-control	To assess the association of circulating vitamin D levels with: (a) breast cancer; (b) clinicopathological breast cancer features; (c) breast cancer disease-outcome in a hospital-based setting within a community comprised mostly of self-identified African-American and Hispanic individuals.	660
Yao, 2017 (California) [22]	Prospective case-cohort	To investigate associations of serum 25OHD with breast cancer prognostic characteristics and outcomes, including recurrence, second primary cancers, and	1,666

		death.	

Table 3. Gaps in representation

Author	Population Characteristics	Population Age		Demographics	
		Category	**% or median**	**Race**	**%**
Villasenor [18]	Women from the HEAL study who were diagnosed with invasive breast cancer, who had successfully measured serum 25(OH)D, and who were alive but had not experienced either a disease recurrence or new primary cancer before the 2nd assessment blood draw were used in the final analysis.	< age 50	25.6	White/ Wash & NM	59.9
		>= age 50	74.4	AA/ LA	26.2
				Hispanic/NM	11.1
				Other/ Wash & NM	2.9
Zeichner [24]	Women, who had sufficient records to clarify vitamin D supplement use, patients without secondary cancer, with non-metastatic HER2+ breast cancer, weren't just one-time consults, or lost to follow-up, and received adjuvant chemotherapy. Case: Used vitamin D supplementation during chemotherapy. Control: Did not use vitamin D supplementation during chemotherapy.	< age 50	43.8	Hispanic	54.5
		>= age 50	56.2	Non-Hispanic	45.5
Clark [4]	Women had histologically confirmed breast cancer that was 3.0 cm or greater without evidence of distant metastatic disease. Available pre- treatment serum. All patients received NACT with an anthracycline, 90% also received a taxane, and 98% ultimately underwent	mean age, 48.3 (SD, 8.9)		Caucasian	75
				Non-caucasian	25

	definitive surgery. Women with HER2-overexpressing tumors were excluded from this study because serum samples were not available.		
Wu [20]	Cases: Self-identifying Black and Hispanic women with breast cancer with disease follow-up information. Controls: Self-identifying Black and Hispanic women with no breast cancer for 2-years.	AA- case median 52 AA- control median 55 Hispanic- case median 49 Hispanic- control median 46	Hispanic 64.1 AA 35.9
Yao [22]	Women diagnosed with incident invasive breast cancer who consented and enrolled within 2 months of diagnosis.	< age 50 75 >= age 50 25	White 55 Hispanic 17 Asian 16 Black 11 Other 1

Abbreviations: *AA* African American, *Wash/NM* Washington State/ New Mexico, *LA* Los Angeles, California.

Table 4. Vitamin D Data

Author	Date of Diagnosis	Time of Blood Draw/Supplementation	Assay	Categorization of Vitamin D Serum or Dosage		Number of Patients	
				Category	**[ng/mL]**	**#**	**%**
Villasenor [18]	1996-1999 (3 years)	Blood drawn on avg 36 months after diagnosis; post treatment.	Radioimmunosorbent assay (DiaSorin Inc., Sillwater, MN)	Deficient	<20	211	31.6%
				Insufficient	20–30	189	32.2%
				Sufficient	>30	185	36.2%
Zeichner [24]	2006-2012 (6 yrs)	Case: Those who used vit D supplementation during adjuvant chemotherapy. Control: Those who did not use vit D supplementation during adjuvant chemotherapy.	N/A	Yes	N/A	134	54.5%
				No	N/A	112	45.5%
Clark [4]	2002-2006 (4 years)	Blood drawn pre-treatment (didn't specify how long after diagnosis).	Vit D levels were measured via DiaSorin radioimmunoassay.	Deficiency	<20 vs. ≥20		41%
				Insufficiency	<30 vs. ≥30		71%[1]
Wu [20]	1995-2007 (12 years)	Blood drawn pre-treatment (avg 4-weeks prior to treatment).	The serum 25(OH)D2, 25(OH)D3 and total level of 25(OH)D were measured using a Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) method	AA, Deficiency	<20		69.2%
				AA, Not Deficient	≥20		30.8%
				Hispanic, Deficiency	<20		37.8%
				Hispanic, Not Deficient	≥20		62.2%

Yao [22]	2006-2013 (follow-up is ongoing) (7 years)	Blood drawn with a median time of 69 days after diagnosis (31-455 days).	Serum samples were analyzed for 25OHD concentration by an immunochemiluminometric assay performed at Heartland Assays	Deficient Insufficient Sufficient	<20 20–29.9 ≥30	48% 35% 17%

Abbreviations: *AA* African American. [1]Data was measured as a dichotomous variable based on IOM definition of deficiency and insufficiency.

Table 5. Effect of Vitamin D on Breast Cancer Survival

Author	**Median Length of Follow Up**	**Covariates Included**	**Method of Analysis for Vitamin D Serum**		**Outcomes**
			Category	**[ng/mL]**	
Villasenor[1] [18]	9.2 years	OS - age, tumor stage, BMI, race/study site, tamoxifen use, season of blood draw and treatment used, physical activity, and smoking status. BCSM - age, tumor stage, BMI, race/study site, adjuvant hormone therapy, season of blood draw, and treatment used.	MV, Continuous MV, Vitamin D status (deficient as referent) Deficient Insufficient	per 10 ng/mL increments <20 20–30	OS (HR, 0.85; 95% CI, 0.68-1.09; P f 0.20) BCSM (HR, 1.08; 95% CI, 0.75-1.54 0.68) OS (HR, 1.00) BCSM (HR, 1.00) OS (HR, 1.07; 95% CI, 0.66-1.75) BCSM (HR, 1.12; 95% CI, 0.54-2.33

			Sufficient	>30	OS (HR, 0.90; 95% CI, 0.50-1.61) BCSM (HR, 1.21; 95% CI, 0.52-2.80
Zeichner[1] [24]	DFS 29.5 months OS 40.2 months	Vitamin D use during chemotherapy, age at diagnosis, ethnicity only in overall survival, tumor size, no. of metastatic lymph nodes, lymphovascular invasion, and statin use during chemotherapy (ethnicity was not included in analysis of OS).	VD use during chemo (yes vs no) ER status (positive vs negative)	N/A N/A	DFS (HR, 0.36; 95% CI, 0.15-0.88; P OS (HR, 0.30; 95% CI, 0.07-1.37; P = DFS (HR, 0.70; 95% CI, 0.17-2.82; P OS (HR, 0.62; 95% CI, 0.05-7.43; P
Clark [4]	N/A; Specifies follow-up was conducted for 3 years	Individual adjustment: hormone receptor status (- or +) and continuous vitamin D. Stratified adjustment: hormone receptor status (- or +) and continuous vitamin D.	MV with individual adjustment, Continuous MV with stratified analysis, Continuous	not specified not specified	RFS: Hormone receptor status (HR, 0.99; 9 1.03; P = 0.571) Hormone receptor+ status (HR, 1.00; 1.05; P = 0.908) Hormone receptor- status (HR, 0.98; 1.03; P = 0.468)
Wu [20]	N/A; Specifies follow-up was conducted for 5 years	ER/PR/HER2 status, ethnicity, tumor size, node stage, BMI, the seasons of blood draw and the age at the time of diagnosis.	MV, Vitamin D status by quartile (Q1 as referent) Q1 Q2	 >24 18-23	 DFS: Q1, (RR, 1.00) Q2, (RR, 1.60; 95% CI, 0.80-4.80; P

			Q3 13 -17 Q4 <=12ng/mL	Q3, (RR, 2.20; 95% CI 0.90-5.00; P = Q4, (RR, 1.90; 95% CI, 0.70-3.80; P OS: Q1, (RR, 1.00) Q2, (RR, 2.40; 95% CI, 0.50-11.6; P Q3, (RR, 3.40; 95% CI, 0.70-16.1; P Q4, (RR, 4.40; 95% CI, 0.9-22.7; P=
Yao [22]	7 years	Tumor stage, grade, and Immunohistochemistry clinical subtype (luminal A, luminal B, HER2 enriched, TNBC), age at diagnosis, BMI, race/ethnicity, and season of blood collection.	MV, Vitamin D status by tertile (T1 as referent) T1 <16.75 T2 16.75–25.09 T3 ≥25.10	RFS: T1, (HR, 1.00) T2, (HR, 0 .87; 95% CI, 0.62-1.21) T3, (HR, 1.13; 95% CI, 0.82-1.58) P for trend = 0.47 OS: T1, (HR, 1.00) T2, (HR, 0.78; 95% CI, 0.59-1.04) T3, (HR, 0.72; 95% CI, 0.54-0.98) P for trend = 0.03 BCSS:

				T1, (HR, 1.00) T2, (HR, 1.12; 95% CI, 0.76-1.67) T3, (HR, 0.85; 95% CI, 0.55-1.33) P for trend = 0.53 IDFS: T1, (HR, 1.00) T2, (HR, 0.81; 95% CI, 0.57-1.14) T3, (HR, 0.85; 95% CI, 0.60-1.20) P for trend = 0.36 SPCFS: T1, (HR, 1.00) T2, (HR, 0.98; 95% CI, 0.61-1.60) T3, (HR, 0.84; 95% CI, 0.51-1.39) P for trend = 0.49

Abbreviations: *ER/PR* estrogen receptor/progesterone receptor**,** *BMI* body-mass index**,** *OS* Overall Survival, *BCSM* Breast cancer specific mortality, *MV* multivariate analysis, *DFS* disease-free survival, *RFS* recurrence-free survival, *BCSS* Breast cancer specific survival, *IDFS* Invasive disease-free survival, and *SPCFS* second primary cancer-free survival. [1]Villasenor and Zeichner examined

hormone receptor (Er+/-, yes or no) and ER status (respectively) for inclusion, but they were not retained as covariates in the final models.

Additional File 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist**.**

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	27
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6/7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	n/a

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	7
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7/8
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	n/a
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	9-11
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	10
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	11-12
Limitations	20	Discuss the limitations of the scoping review process.	13
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	13
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	14

Additional File 2. Search strategy for all five databases

MEDLINE (OVID)	PUBMED	CINAHL	Web of Science/ Scopus
1. exp Breast Neoplasms/ 2. (breast adj6 cancer$).mp. 3. (breast adj6 neoplasm$).mp. 4. (breast adj6 carcinoma$).mp. 5. (breast adj6 tumour$). mp.	"Breast neoplasms"[mesh] OR "Breast cancer*"[tw] OR "Mammary cancer*"[tw] OR "Breast neoplasm*"[tw] OR "breast carcinoma*"[tw]	MH("breast neoplasms+") OR TX("breast cancer*"OR "Mammary cancer*"OR "Breast neoplasm*"OR "breast carcinoma*"OR "breast tumour*" OR "breast tumor*")	"breast neoplasms" OR "breast cancer*" OR "Mammary cancer*" OR "Breast neoplasm*" OR "breast carcinoma*" OR "breast tumour*" OR "breast tumor*"

6. (breast adj6 tumor$). mp. 7. (mammary cancer).mp.	OR “breast tumour*”[tw] OR “breast tumor*”[tw]		
1. Exp Mortality/ 2. Exp survival/ 3. Exp survival analysis/ 4. Exp death/ 5. (survival adj6 analysis).mp. 6. Mortality.mp. 7. (mortality adj6 rate).mp. 8. (death adj6 rate).mp. 9. Fatality.mp. 10. Survival.mp. 11. Death.mp. 12. Died.mp. 13. Dying.mp.	mortality[mesh] OR survival[mesh] OR “survival analysis”[mesh] OR death[mesh] OR fatality[tw] OR Mortalit*[tw] OR “Death rate*”[tw] OR “Mortality rate*”[tw] OR survival [tw] OR death[tw] OR died[tw] OR dying[tw] OR “survival analysis” [tw]	MH(“mortality+” OR survival OR “survival analysis+”) OR TX(death OR fatality OR Mortalit* OR “Death rate*” OR “Mortality rate*”OR survival OR death OR died OR dying OR “survival analysis”)	“mortality” OR survival OR “survival analysis” OR death OR fatality OR Mortalit* OR “Death rate*” OR “Mortality rate*” OR survival OR death OR died OR dying OR “survival analysis”
1. exp vitamin d/ 2. exp cholecalciferol/ 3. Exp ergocalciferol/ 4. Exp Vitamin d deficiency/ 5. Vitamin d.mp. 6. cholecalciferol$.mp. 7. ergocalciferol$.mp. 8. (25-hydroxyvitamin D).mp.	"Vitamin D"[mesh] OR Ergocalciferols[mesh] OR "Vitamin D Deficiency"[mesh] OR Cholecalciferol[mesh] OR Cholecalciferol[tw] OR Ergocalciferol[tw] OR "Vitamin D"[tw] OR "25-hydroxyvitamin D"[tw]	MH("Vitamin D+" OR Ergocalciferols OR “Vitamin D Deficiency+" OR Cholecalciferol) OR TX(Cholecalciferol OR Ergocalciferol OR "Vitamin D" OR "25-hydroxyvitamin D")	"Vitamin D" OR Ergocalciferols OR "Vitamin D Deficiency" OR Cholecalciferol OR Cholecalciferol OR Ergocalciferol OR "Vitamin D" OR "25-hydroxyvitamin D"
1. Exp women/ 2. Exp female/ 3. Woman.mp. 4. women.mp.	women[mesh] OR female[mesh] OR female*[tw] OR women[tw] OR woman[tw]	MH(women+ OR female+) OR TX(female* OR women OR woman)	women OR female OR female* OR women OR woman

5. female$.mp.			
1. Exp Biomarker/ 2. biomarker$.mp. 3. (Molecular adj6 subtype$).mp. 4. (prognosis adj6 categor*).mp. 5. subtype$.mp. 6. Aggressiv*.mp 7. (Luminal A).mp. 8. (Luminal B).mp. 9. (normal-like).mp. 10. (HER2*).mp. 11. (Triple negative).mp. 12. (ERBB2*).mp. 13. prognosis.mp.	Biomarkers[mesh] OR biomarker*[tw] OR "Molecular subtype*"[tw] OR subtype*[tw] OR prognosis categor*[tw] OR Aggressiv*[tw] OR "luminal a"[tw] OR "luminal b"[tw] OR "normal like"[tw] OR HER2*[tw] OR "triple negative"[tw] or ERBB2*[tw] OR prognosis[tw]	MH("Biological markers+") OR TX(biomarker* OR "Molecular subtype*" OR subtype*OR prognosis categor* OR Aggressiv* OR "luminal a"OR "luminal b"OR "normal like" OR HER2* OR "triple negative" OR ERBB2* OR prognosis)	"Biological markers" OR biomarker* OR "Molecular subtype*" OR subtype*OR prognosis categor* OR Aggressiv* OR "luminal a" OR "luminal b" OR "normal like" OR HER2* OR "triple negative" OR ERBB2* OR prognosis