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Association of pre-diagnostic vitamin D level with postmenopausal breast cancer risk: A systematic review

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ABSTRACT

Introduction: Breast cancer is a disease in which there is a rapid multiplying of cells in the breast. It has been a serious concern as it is the most commonly diagnosed cancer among women, especially in the old-age group. Vitamin D is a fat-soluble vitamin that is consumed via diet or produced when the ultraviolet (UV) rays of the sun make contact with the skin. Its putative anticarcinogenic property might play a role to minimize the increasing burden of breast cancer. Thus, this study focuses on vitamin D level as a risk factor for postmenopausal breast cancer.

Methodology: A systematic review of prospective cohort studies was conducted. The search was performed in MEDLINE (Ovid) using the mesh terms and keywords of the modified PICOS diagram. The free-text search was done in Google Scholar. The reference lists of relevant systematic reviews were screened manually. The population for the review was healthy women, the exposure was vitamin D level, and the outcome was postmenopausal breast cancer.

The information from the eligible studies was extracted and presented in the table. The Risk of bias (RoB) assessment was done using a CASP tool.

Results: Eight studies met the inclusion criteria. All the studies were prospective cohorts. The included studies were conducted in high-resource settings. The study population was diverse. Vitamin D was measured in various forms and the data was collected using a questionnaire. Breast cancer occurrence was self-reported but was confirmed through reports.

The effect estimates of the fully adjusted models in the included studies ranged from 0.87 to 1.30. The result showed that there was no association between pre-diagnostic vitamin D level and postmenopausal breast cancer risk.

Conclusion: The review does not have enough evidence to conclude the association between pre-diagnostic vitamin D level and postmenopausal breast cancer risk. Further research is necessary to assess the relationship.

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LIST OF ABBREVIATIONS

ASIR: Age-specific Incidence Rate

ASMR: Age-specific Mortality Rate

HDI: Human Development Index

DALYs: Disability Adjusted Life Years

CVD: Cardiovascular disease

RoB: Risk of Bias

CASP: Critical Appraisal Skills Programme

EPIC: European Prospective Investigation into Cancer and nutrition

NHS: Nurses' Health Study

CPS: Cancer Prevention Study

SUN: Seguimiento Universidad de Navarra

MHT: Menopausal Hormone Therapy

RCT: Randomized Controlled Trial

RQ: Research Question

1 INTRODUCTION

1.1 Breast cancer

Breast cancer is a condition in which there is an uncontrolled growth of cells in the breast (1). There are modifiable and non-modifiable risk factors that influence breast cancer. The well-known non-modifiable risk factors are race, ethnicity, family history, and gene whereas the modifiable risk factors are alcohol consumption, sedentary lifestyle, female reproductive behaviours, and use of exogenous hormones (2, 3). Additionally, the factors related to sex hormones like early menarche, parity, and late first full-term pregnancy contribute to a higher risk of breast cancer. Especially among postmenopausal women, the circulation of endogenous sex steroid hormones like oestradiol might escalate the risk (3, 4).

Age is the predominant risk factor for breast cancer. The young population is at high risk with the risk increasing by two-fold every 10 years (5). Approximately 95% of breast cancer cases are diagnosed in women aged 40 years and above (3). More than three-quarters of breast cancer incidence is among women 50 years and older and most of the cases are in high-resource settings (6). However, cases among women aged 15-49 years are twice as much in low-resource settings comparatively (7). Irrespective of the age group, exposure to radiation and Hormone Replacement Therapy (HRT) accelerates the risk (5).

Breast cancer cases rose by 30% in two decades from 1980 to the late 1990s. However, the condition was stable, and the cases decreased after 2000 in several countries (3). This might be because of the enhancement in the screening facilities. After 1990, due to the affordable provision of mammography services and routine screening, mortality declined in North America and Europe (3).

Breast cancer is a severe issue for women, with a significant increase in new cases and deaths in several countries (3, 8). It is the second most common cancer with 1.7 million cases reported in 2012. Due to its relatively better prognosis, it is the fifth leading cause of cancer death with 522,000 in the same year (5). Globally, among females, 22% of all cancer cases are breast cancer , and around 42% of the total cases are from developing countries (9, 10).

In 2018, approximately 2.1 million breast cancer cases were diagnosed in women globally. Among them, the premenopausal and postmenopausal breast cancer cases per 100 000 population were 19.7 and 152.6 respectively, when analysed as per ASIR (Age-specific Incidence Rate). In terms of mortality, there were 630 000 deaths reported in the same year. The ASMR (Age-specific Mortality Rate) equated for premenopausal and postmenopausal breast cancer was 4.1 and 48.9 cases per 100 000 population. The postmenopausal breast cancer death in low HDI (Human Development Index) was 49.8% of the total breast cancer deaths whereas this number was higher in medium, high, and very high HDI countries i.e., 72.9%,81.4%, and 90.1% respectively (11).

However, it is expected that in two decades breast cancer rate shall increase in developing countries with the incidence rising by 55% and the mortality by 58% (12). On the other hand, the low resource settings countries tend to suffer more in terms of survival as compared to the high resource settings countries. The data presented on five-year survival rates showed that the survival rates were lower in poor countries in 2009. The survival rates were more than 80% in the high-income countries whereas it was below 80% or even lower in the low-income countries (13).

In 2019, the total burden of breast cancer was 247.63 DALYs (Disability Adjusted Life Years) per 100,000 individuals and was in the fourth position among all the cancer types. Similarly, breast cancer was the fourth leading cause, among cancer mortality, with 700,660 deaths in the same year. The prevalence of breast cancer was 0.24% in 2019 making it the highest of all cancer types (13).

Breast cancer incidence was 2.3 million and mortality was 0.6 million in 2020. Breast cancer incidence and mortality among females are in increasing trend. The incidence and mortality from breast cancer are projected to reach 3.2 million and 1 million respectively by 2040 (14). Despite the issues, the identification of breast cancer risk has not gained the required attention (15, 16).

1.2 Vitamin D

Vitamin D has two physiologically active types, known as cholecalciferol (D_3) and ergocalciferol (D_2). D_3 is produced, from 7-dehydrocholesterol, when the ultraviolet (UV) rays of the sun contact the skin (17, 18). In addition, animal foods contain vitamin D in the form of vitamin D_3 (19). D_2 is plant-based and is formed externally from the irradiation of UV rays (17, 18). The good dietary sources of vitamin D are fish, offal such as liver, egg yolk, and mushroom (19).

Vitamin D is a fat-soluble vitamin which metabolizes in the liver and further in the kidney from 25-hydroxyvitamin D (25(OH)D) to 1,25-dihydroxyvitamin D (1,25(OH)2D) (18, 20). The majority of these metabolites circulate by binding to a protein whereas a small amount is free (21). The measurement of free metabolites of vitamin D is not recommended in the clinical setting. The half-life of 25(OH)D is three weeks, vitamin D is twenty-four hours and 1,25(OH)2D is four hours (21). Therefore, serum 25(OH)D measurement is most suitable to know the status of vitamin D in the body (22).

Classical biological pathways for vitamin D include calcium and phosphate metabolism. vitamin D has also been shown to have the ability to hinder cell proliferation, metastasis, angiogenesis, and invasion, and stimulate differentiation and apoptosis due to which it is capable to alter various aspects of cancer (9, 23).

The quantity of vitamin D required depends on the age and health condition. However, on average the recommended doses of vitamin D for children and adults up to 50 years, adults 51-70 years, and adults aged 71 and above are 200 IU, 400 IU, and 600 IU respectively. If the body does not have an appropriate amount of vitamin D to stay healthy, then it is considered as a deficiency. Vitamin D deficiency can be treated either by supplementation, vitamin D fortified food consumption, or with solar exposure (20, 24-26).

The factors that influence the level of vitamin D are obesity, physical inactivity, race, age, unhealthy diet, age, and high latitude residence (27). There is a vitamin D deficiency problem globally, irrespective of the country's situation or latitude. One of the reasons might be addressing this issue inadequately in the policy (28). Comparatively, Africa, Asia, and the

Middle East region have the highest prevalence of vitamin D deficiency (29). Vitamin D is lower than the recommended level among most young infants residing in Asia. This accounts for approximately 51%, 86%, 61%, and 61% of infants in Turkey, Iran, India, and Pakistan respectively (28). In addition, the concentration of vitamin D level is low in pregnant or lactating women in Asia and Middle East regions i.e. 50%, 45% and 60% of the women residing in Turkey, Pakistan and India respectively (30), The concentration of vitamin D level is low in pregnant or lactating women in Asia and Middle East regions i.e. 50%, 45%, and 60% of the women residing in Turkey, Pakistan, and India respectively (29), On the other hand, low calcium intake is observed in these regions which might act as a catalyst for various health outcomes (31-33).

1.3 Vitamin D and Breast Cancer

As vitamin D is the steroid hormone, it is known to affect various functions of the organs in the human body (34). It plays a vital role in maintaining strong muscles, and bones, and preventing cancer, CVD, and autoimmunity (18, 20). The effect on the development of the breast gland is controlled by the action of vitamin D receptors (VDR) (34). In some studies, breast cancer fatality was approximately half in patients with high serum vitamin D levels compared to those with a lower concentration (35). Substantial linear dose-response relation can be observed between vitamin D concentration and the survival of the breast cancer patient (36). In addition, the nutrition supplement along with the therapy is beneficial to improve the overall survival of the patient (36). Thus, adequate intake of vitamin D plays a vital role (37).

A study reported that Chinese women with breast cancer born in East Asia survived less than those born in the US (38). Another study in British Columbia (BC) also found that Chinese women, compared to South Asians and the predominantly white population had a high breast cancer survival rate (39). According to Grant’s analysis, living with low solar exposure triggered numerous preventable cancers, among which 42% was breast cancer (40). The research done in the US stated that the areas with high solar UVB irradiance had a much lower death rate from breast cancer than those with lower irradiance. The situation is similar globally as well (35, 41). These patterns of survival rates provide information on the burden and

seriousness of breast cancer. It might assist in making policies, programs, and planning to reduce the risk (39).

1.4 Importance of the review

Since the last few decades, vitamin D deficiency has become a pandemic. The majority of the population older than 65 years has vitamin D deficiency (42). There is a link between the deficiency of vitamin D and adverse health consequences like cancer and cardiovascular-related disease and death (34). An inverse relation has been observed between 25 hydroxyvitamin D and the risk of CVD and cancer (43). Hence, vitamin D level might play a role to prevent or add-on therapy, considering its putative anticarcinogenic properties, for decreasing the incidence of various diseases including breast cancer (44).

To study the vitamin D level, the assessment of dietary vitamin D is not regarded as a final analysis of the vitamin D nutritional value, even though its study is essential to understand the initial relationship with breast cancer (45). Additionally, research on vitamin D supplementation is necessary as it plays a vital role in reducing the function of estrogen receptors and control the production of these hormones, thus might reduce the postmenopausal breast cancer risk (27).

The previous systematic review assessed the relationship between vitamin D and the risk of breast cancer and was published in 2018 (46). The review incorporated case control as well as cohort studies. However, this systematic review updated the research as it has been a long time since the previous review was published. Moreover, only prospective cohort studies are included in this paper as it was mentioned previously that the inclusion of case-control studies might have resulted in biases reducing the value of the outcome data (46). In the prior reviews, there was an unclear conclusion about the role of vitamin D in breast cancer risk according to the menopausal status (47) and the evaluation was done for overall breast cancer risk (46) whereas this study has focused solely on the postmenopausal breast cancer risk.

1.5 Review question

Is pre-diagnostic vitamin D level associated with post-menopausal breast cancer risk?

2 METHODOLOGY

To minimize the risk of bias (RoB) for this systematic review three reviewers, the main author, the supervisor, and the co-supervisor were involved in the search process, study selection, data extraction, and risk of bias assessment (48). Nevertheless, the main author is solely responsible for the overall content as this is an individual thesis work under supervision.

2.1 Search strategy

The search was carried out in MEDLINE (Ovid) and Google Scholar databases. Additionally, the reference lists of the relevant systematic reviews were checked thoroughly in case any studies were missed from the database searches. The main author prepared the search strategy and conducted the searches. A rigorous search was done to include the most up-dated relevant articles; hence, the final search was conducted on 8/10/2022. The supervisor and the co-supervisor reviewed them.

A modified PICOS diagram was used to identify search terms of the following categories: Population, Exposure, Outcome, and Study design. Medical Subject Headings (MeSH) terms and keywords of the PICOS were used to conduct the systematic search in MEDLINE (Ovid), accessed via the UiT University library. The following operators were used to retrieve the required records: 'ADJ n' was used to conduct the searches with the terms within a stated number (n-1) of words from each other in any order, '#' was used to obtain plural forms of the words in the results and '*' was used to acquire the searches with all the likely suffix of the specific root word. The mesh terms and keywords within the category were combined by 'OR' whereas the search between the categories was combined with 'AND'. The mesh terms and the keywords used in the search process are presented in the table below. The full search strategy is in appendix 1. A free-text search was carried out in Google Scholar. The search terms used were vitamin D, postmenopausal breast cancer, and healthy women. The results were sorted based on the relevancy of the searched words, and the finding was limited to the papers published after 2000.

Table 1: Mesh terms and keywords of the modified PICO

	Population	**Exposure**	**Outcome**	**Study Design**
RQ	Healthy women	Vitamin D	Post-menopausal breast cancer	Prospective Cohort Study Design
Mesh terms	Female	Vitamin D	Breast neoplasm	Prospective studies
				Cohort studies
Keywords	Female	Cholecalciferol	Postmenopausal breast cancer	Population based study
	Women	Ergocalciferols	Breast neoplasm	Prospective Cohort Study
	Healthy women	Hydroxycholecalciferols	Breast cancer	Prospective studies
		25- hydroxyvitamin D_2		Cohort studies
		Dihydrotachysterol		
		Vitamin D_2		
		Vitamin D_3		
		Vitamin D		

2.2 Selection of literature

The results from each database search were screened separately. The main author assessed the titles and abstracts of the search results. The process was guided by the supervisors. After the exclusion of the duplicates and the irrelevant papers, others were eligible for full-text reading. The main author and the supervisors independently reviewed the papers in full text. Based on the inclusion criteria the final papers were selected. Any confusion regarding the selection of the paper was cleared out by reading it multiple times and discussing it with the supervisors.

2.3 Inclusion and exclusion criteria

2.3.1 Study design

The studies with a prospective cohort study design were eligible for inclusion in the review. Those studies having retrospective study designs were excluded manually.

2.3.2 Population

Healthy women who did not have breast cancer were included. The paper considering breast cancer cases as study participants were excluded. Only the researchers conducted on humans were selected using a filtering criterion via the ‘Limits’function in ‘Advanced Search’.

2.3.3 Exposure

The measurement of vitamin D levels in any form was accepted. This included studies consisting of information about solar exposure, plasma 25-hydroxyvitamin D, dietary vitamin D, supplementary vitamin D, and the combination of these. The research containing multiple exposures along with vitamin D was also selected.

2.3.4 Outcome

Postmenopausal Breast cancer cases were eligible for inclusion in the review. The paper analysing only the data for premenopausal breast cancer patients was excluded. Moreover, the papers containing the outcome data for both the premenopausal and the postmenopausal breast cancer cases were also included if there was a separate effect estimate for the postmenopausal breast cancer cases.

2.3.5 Others

The included papers were written in the English language. Papers written in other languages were excluded. Only the research published after the year 2000 was included in this review. These papers were filtered using a 'Limits' function in 'Advanced Search' in MEDLINE (Ovid) and using a 'Custom range 'function in Google Scholar.

The information from the books, chapters, commentary, unpublished papers, and papers containing only the qualitative data were ineligible and this was sorted manually.

2.4 Extraction of data

The main author was responsible for the extraction of the information from the paper. The obtained information was filled in an excel sheet. The excel sheet was pre-designed by the main author with the help of the supervisors to find relevant data.

The data was filled in the table accordingly and checked rigorously. The supervisors assisted the main author to insure the precision and comprehensiveness of the extracted data from the relevant studies. The discrepancies were solved by discussion.

The information obtained from the included studies are:

- Title and author
- Study design, study cohort, and location

- Cohort information (total number of postmenopausal breast cancer cases, total number of participants, age at baseline, and follow-up period)
- Exposure data (exposition, measurement, and cut-off levels)
- Outcome evidence (effect estimate, age-adjusted effect estimate, confounder, outcome assessment method)

2.5 Methodological quality assessment

CASP (Critical Appraisal Skills Programme) checklist for Cohort Study was used to assess the Risk of Bias (RoB) for the included studies (49). Moreover, for papers with multiple exposure and outcome, only the portion of the study that consists of the exposure and outcome of interest (i.e., any forms of Vitamin D and postmenopausal breast cancer) were assessed.

To assess the research papers, CASP checklist focuses on three major domains: the main result of the study, its validity, and the significance of the outcome in a particular setting. Each question has three options to choose from Yes, Can't tell, and No (49, 50).

If there was a strong reason to select the 'Yes' and 'No' options, it was recorded with a reason else 'can't tell' was chosen when the conclusion could not be made. The CASP checklist was completed by the main author then it was reviewed by the supervisor and co-supervisor. The critical appraisal of the included studies using the CASP tool is attached as a supplementary document with the thesis.

3 RESULT

3.1 Search Results

The database search in MEDLINE (Ovid) displayed 157 results (details in Appendix 1). Among these, 93 studies were excluded after reading the title and the abstract. The remaining 64 studies were selected for detailed screening. After removing the 57 ineligible studies, 7 studies were selected to include in this review. The search in Google Scholar displayed 9,840 results. Only the first 200 relevant articles were selected for the review. Due to the time constraint, all the searches were not possible to incorporate into this study. Out of 200 studies, 169 papers were discarded after reading the titles and the abstracts. The full text of 31 articles was screened in detail. Of these documents, 30 documents were rejected, and a remaining study was selected to include in this review. The major common reasons for the exclusion of the studies were: the study population and the study design were not according to the inclusion criteria, the exposure was not as per the interest, the outcomes were not appropriate, unavailability of the full-text document, and the required effect estimates were not obtainable. Additionally, the reference lists of the related systematic reviews were checked manually. However, additional studies that met all the eligibility criteria for this study were not identified. After screening and finalizing all the inclusion criteria, eight studies were selected for the review (51-58).

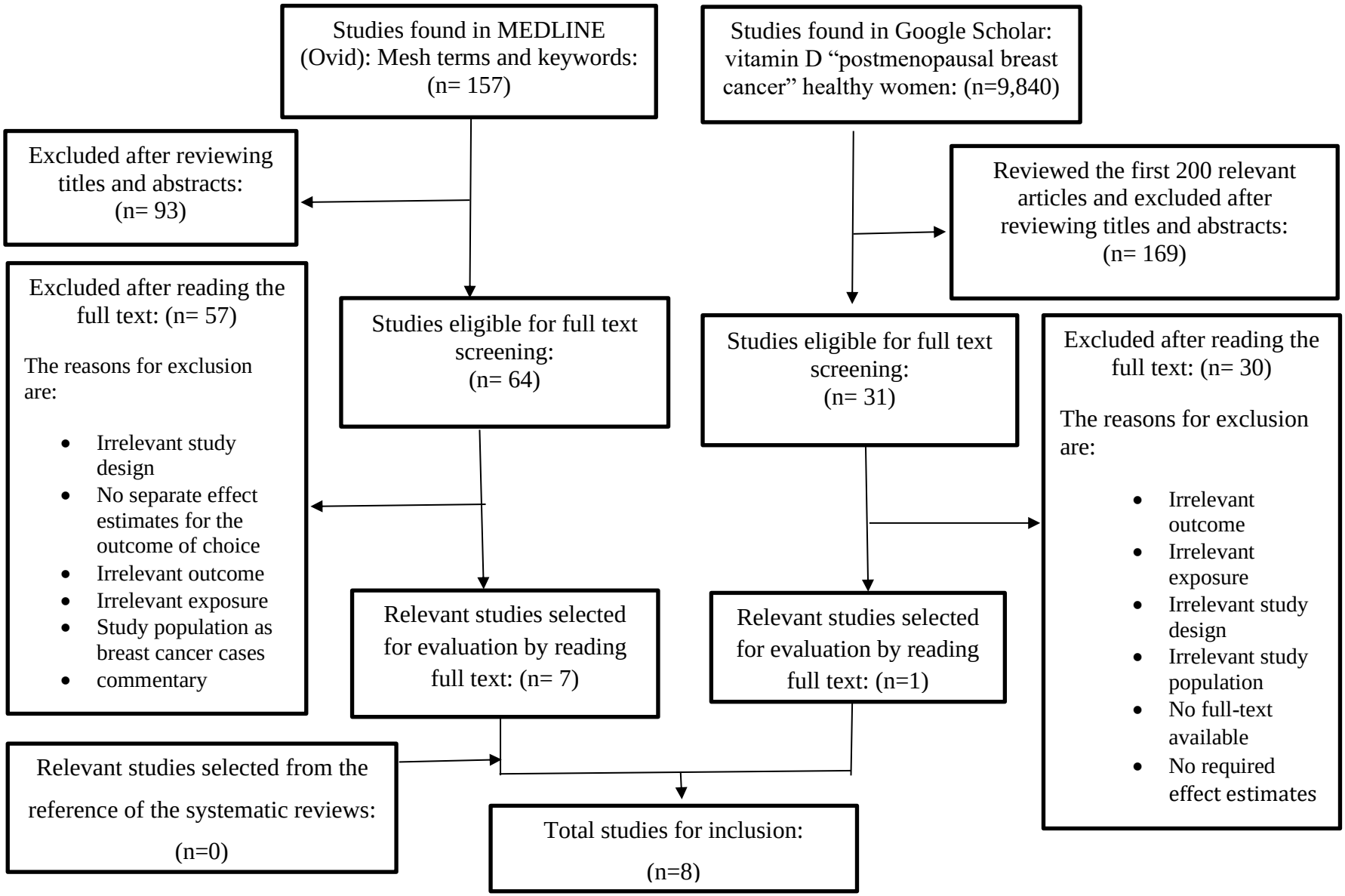

Figure 1: Flowchart for articles selection

3.2 Description of the included studies

The included studies were conducted between 1980-2018. The studies included in the review were published in the peer-reviewed scientific journals: JAMA Internal Medicine (51), University of Zurich (52), Journal of the National Cancer Institute (53), The American Journal of Clinical Nutrition (54), AACR journal (55, 56) and Cancer Causes & Control (57) and European Journal of Nutrition (58).

The mean follow-up time in the studies was between 8.8 years to 19 years. The age at baseline in the studies ranged from 34.7 years to 61 years. The study design of all the studies was a prospective cohort. The participants were randomly drawn from different study cohorts: Women's health study (51), European Prospective Investigation into Cancer and Nutrition (EPIC) (52), Nurses' Health Cohort (53), E3N cohort (54), French E3N cohort (55), Cancer Prevention Study Cohort (CPS) II Nutrition Cohort (56), Lowa Women's Health Study and Seguimiento Universidad de Navarra (SUN) cohort (58). The breast cancer cases in the studies were identified from the questionnaire and were confirmed from the medical reports and registries. As observed from table 2, all the studies were conducted in high-resource settings. Among the studies four were performed in the US (51, 53, 56, 57), two in France (54, 55), one in Europe (52) and one in Spain (58).

Vitamin D was measured in various forms: Dietary Vitamin D, Supplementary Vitamin D, Total Vitamin D intake, and UV solar exposure. All the studies used the questionnaire to collect data on exposure. Among the included studies, four (51, 52, 55, 58) measured vitamin D only once at the baseline whereas four studies (53, 54, 57, 58) measured it repeatedly. Within the studies that conducted multiple measurements two of them (53, 54) gathered the information four times, one study (56) collected the data three times whereas one (57) of the study gathered the exposure information twice during the study duration.

Different forms of vitamin D were measured on a different scale and their cut-off levels varied. The number of included confounders in the statistical models of the studies ranged from ten to twenty-one. The extracted information is presented in the table below (additional information in Appendix 2).

Table 2: Extraction of the data from the included studies

Article	Author	Exposition/ Measurement of Vitmain D	Study Cohort, Location	Study design	Number of measurement	Age adjusted RR (95%CI)	RR (95%CI)	Cases/ Total	Age at baseline	follow-up period	Mean follow-up time	Cut off levels (Upper vs Lower)
Intakes of Calcium and Vitamin D and Breast Cancer Risk in Women	Lin et al. (51)	total vitamin D intake, dietary vitamin D, supplementary vitamin D/ Questionnaire	Women's health study, USA	prospective cohort	once at baseline	1.21(0.95-1.55), 1.18(0.93-1.49) and 0.87(0.72-1.05)	1.30(0.97-1.73), 1.22(0.95-1.55) and 0.87(0.68-1.12)	743/ 20909	≥45	1993-2003	10 years	>548 vs < 162 IU/day
Dietary intake of Vitamin D and calcium and breast cancer risk in the European Prospective	Abbas et al. (52)	dietary vitamin D/ Questionnaire	European Prospective Investigation into Cancer and Nutrition	prospective cohort	no repeated measurements	NA	1.02(0.9-1.16)	4259 / 319985	50.2	1992-2005	8.8 years	≥5.46 vs <1.85 µg/day

Investigation into Cancer and nutrition			(EPIC), Europe									
Intake of Dairy Products, Calcium and Vitamin D and Risk of Breast Cancer	Shin et al. (53)	total vitamin D intake and dietary vitamin D/ Questionnaire	Nurses' Health Study Cohort (NHS), USA	prospective cohort	repeated measurements (1984, 1986, 1990, and 1994)	NA	0.94 (0.80-1.10) and 1.06 (0.85-1.34)	2345 /88691	46.7	1980-1996	16 years	>500 vs ≤150 IU/day
Interaction between current Vitamin D supplementation and menopausal hormone therapy use on breast cancer	Cadeau et al. (54)	vitamin D supplement/ Questionnaire	E3N cohort, France	prospective cohort	multiple measurements (1995, 2000, 2002, and 2005)	1.12 (0.94-1.33)	1.10 (0.92–1.31)	2482/ 57403	40-65	1995-2008	13 years	Current vs never

risk: evidence form the E3N cohort												
Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort	Engel et al. (55)	overall vitamin D intakes from diet and supplementary vitamin D, UV solar exposure / dietary vitamin D (questionnaire) and UVRd (interpolation in a validated look-up table (LUT))	French E3N cohort, France	prospective cohort	single assessment	NA	0.92 (0.83–1.02) , 0.91(0.73-1.14) and 0.92 (0.82-0.98)	2253 /67721	52.8	1993-2005	10.4 years	>113 vs <80 IU/day and supplemented , >2.7 vs <2.4 kJ/m

Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort	McCullough et al. (56)	total vitamin D intake and dietary vitamin D / Questionnaire	Cancer Prevention Study (CPS) II Nutrition Cohort, USA	prospective cohort	repeted mearements (1997,1999, and 2001)	0.94 (0.8–1.1) and 0.87 (0.75–1)	0.95(0.81-1.13) and 0.94(0.80-1.10)	2855/ 68567	50–74	1992–2001	9 years	>700 vs ≤100 IU/ day and >300 vs ≤100 IU/ day
Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study	Robien et al. (57)	total vitamin D intake, dietary vitamin D and supplementary vitamin D / Questionnaire	Lowa Women's Health Study , USA	prospective cohort	twice (at baseline and 2004)	0.90 (0.78-1.04), 0.55 (0.25-1.22) and	0.89 (0.74–1.08) , 0.55 (0.24–1.22) and	2440/ 34321	61 (55–69)	1986–2004	18 years	≥800 vs <400 IU/day

						0.91(0.75 -1.09)	0.89 (0.77– 1.03)					
Dietary calcium, vitamin D, and breast cancer risk in women: findings from the SUN cohort	Fernandez-Lazaro (58)	total vitamin D and dietary vitamin D/ Questionnaire	Seguimiento Universidad de Navarra (SUN), Spain	prospective cohort	once at baseline	0.91 (0.38-2.15) and 0.92 (0.39-2.17)	1.02(0.42 -2.48) and 1.04 (0.43-2.52)	34/ 3089	34.7	1999-2018	19 years	>6.45 vs <4.05 µg/day and >6.45 vs <3.96 µg/day

3.3 Summary of included studies

In a study, Lin et al. (51) analyzed the relationship between calcium and vitamin D, and breast cancer. There were 20909 post-menopausal participants in the US. Vitamin intake from the diet and supplement was the exposure along with the calcium intake and supplement. However, both nutrients were concurrently adjusted to evaluate the difference in the outcome. After 10 years of follow-up, some women were diagnosed with invasive breast cancer. The study concluded that there was no association between a higher intake of calcium and vitamin D and a low risk of postmenopausal breast cancer. However, calcium and vitamin D might play a role to lower the risk of developing premenopausal breast cancer and the prevention might be evident for aggressive breast tumors as well (51).

Abbas et al. (52) assessed the interaction between vitamin D and calcium intake and breast cancer risk. The study location was in Europe in which there were 319985 sample populations. The exposure was dietary calcium and vitamin D. However, to observe the difference in the result the two nutrients were adjusted, i.e, vitamin D and calcium for the calcium and Vitamin D model respectively. In 8.8 years several breast cancer cases were identified among the cohort. The research concluded no significant association between the intake of calcium and vitamin D and preand postmenopausal breast cancer risk (52).

Shin et al. (53) researched the association between high intake of dairy products, calcium, or vitamin D and the risk of breast cancer. There were 88691 participants, and the study was conducted in the USA. Dietary calcium, vitamin D, and dairy products were the exposure in the study. Vitamin D and calcium supplements were also taken into consideration. Moreover, separate measurement of the impacts of calcium and vitamin D from dairy products was considered. After 16 years of follow-up, the study identified the premenopausal and postmenopausal women with breast cancer. The association was not significant in postmenopausal women but in premenopausal women high intake of low-fat dairy products was associated with reduced breast cancer risk. The inverse association was evident with vitamin D and calcium from dairy products. However, the study could not conclude their independent role in reducing the risk of breast cancer (53).

The research conducted by McCullough et al. (56) has evaluated the association of calcium, vitamin D, and dairy products with postmenopausal breast cancer. The study was conducted in the US and 34321 postmenopausal women were the sample population. The exposure in the study was dairy intake, vitamin D, and calcium. After almost 11 years of follow-up, it was concluded that calcium and some ingredients in dairy products play a role in moderately reducing the risk of postmenopausal breast cancer. However, there was no association between calcium supplementation and vitamin D intake with risk reduction (56).

Engel et al. (55) researched the relationship between pre-and postmenopausal breast cancer and the overall intake of vitamin D from solar exposure, diet, and supplements. For the study, the sample population was 67721 women, and the study area was France. Vitamin D was the sole exposure. With 10 years of follow-up, breast cancer cases were diagnosed. The cancer was not associated with diet and supplements. However, sun exposure played a role to reduce the risk of postmenopausal breast cancer when backed up with a high dose of supplementary and dietary vitamin D (55).

The study conducted by Robien et al. (57) assessed the association between intake of vitamin D and post-menopausal breast cancer risk. The sample was followed from 1986 to 2004 and breast cancer cases were identified. The study area was the US, and the sample participants were 34321 post-menopausal women. Vitamin D was the only exposure considered for the research. There was the strongest relationship between the high dose of vitamin D intake and postmenopausal breast cancer risk reduction only in the first five years after the dietary information evaluation. However, the association disappeared over time which might be due to the inconsistent doses of vitamin D intake (57).

The study conducted by Cadeau et al.(54) aimed to evaluate the relationship between breast cancer in postmenopausal women and the intake of vitamin D supplements either in the present or in the past with its relation to MHT (Menopausal Hormone Therapy) usage. The paper included 57403 post-menopausal women and the study area was France. Vitamin D supplementation and MHT use was the exposure for the research. After the follow-up from 1995 to 2008, breast cancer cases were identified. The study concluded the reduction in risk of breast cancer among the current user of vitamin D supplements but not among past users. Also,

the result was different among MHT users. Hence, the risk of postmenopausal breast cancer among the MHT users decreased with the intake of vitamin D supplements regularly (54).

Fernandez-Lazaro et al. (58) investigated the association between calcium and vitamin D intake with the overall breast cancer risk and also among premenopausal and postmenopausal women. The study location was in Spain. It included 3089 postmenopausal women in the research. Dietary, as well as supplementary vitamin D along with calcium, was the exposure for this study. After a follow-up of 10.7 years, breast cancer cases were identified. The curve for the relationship between overall calcium intake and breast cancer incidence was L-shaped. This implies that only a sufficient amount of calcium might help in the overall and postmenopausal breast cancer risk reduction. However, there was no statistically significant association between vitamin D intake and premenopausal and postmenopausal breast cancer risk (58).

3.4 Main result of the study

The overall adjusted effect estimates among the studies varied from 0.87 to 1.30. This means that the studies portray a weak association between pre-diagnostic vitamin D levels and postmenopausal breast cancer. Moreover, the age-adjusted estimates ranged from 0.87 to 1.21. There was no major difference between the effect size in the fully adjusted model compared to the age-adjusted model. The results of the fully adjusted and age-adjusted models were found not to be statistically significant as the confidence interval consisted of 1.

4 DISCUSSION

4.1 Comparison to other metanalysis

There are reviews aimed at the association of vitamin D and the overall breast cancer risk, while some have stratified breast cancer in terms of menopausal status. While comparing the association of vitamin D and postmenopausal breast cancer risk, previously conducted metanalysis of observational studies by Estebanez et.al (59) (which included 68 cohort and case-control studies) showed a consistent result with this study. In the study when the outcome was classified based on menopausal status, no significant association or much weaker protection of vitamin D on postmenopausal breast cancer was observed.

The result of this study was similar to the outcome from the meta-analysis of RCTs (8 studies included) conducted by Zhou et.al. (60) where there was a weak association between vitamin D supplementation and breast cancer risk. However, the analysis did not segregate women in terms of menopausal status, but it was mentioned in the study that there was less inclusion of premenopausal women in the trials included.

Another meta-analysis (which included 10 RCTs) researched by Li Z et.al. (61) showed no relation between the intake of vitamin D supplements and breast cancer occurrence. Though the study observed overall breast cancer risk, the mean age group in the included studies was 43 to 77 years. The result was consistent with the outcome of this review.

The study (which consisted of 22 case-control and cohort studies) conducted by Hossain S et.al (34) where the mean age of the participants was 53.6, observed no association between serum 25 (OH) D and breast cancer risk and a negligible inverse association with intake of vitamin D and overall breast cancer occurrence. Even though the previous study was conducted in different strata with the inclusion of both postmenopausal and premenopausal women and this review only focused on postmenopausal breast cancer, the results were similar.

However, the study (which included 9 prospective studies) conducted by Bauer SR et.al (62) found that serum 25(OH)D has an inverse association with postmenopausal breast cancer risk.

This result contradicts the outcome of this review. This might be because the exposure measurement in the previous study was done from a blood sample whereas in this review it is through the questionnaire. Also, a notable dose-response relationship was observed in the review by Bauer et al.

Moreover, another metanalysis of RCTs (two studies included) conducted by Sperati F et.al. (63) observed a less chance of occurrence of postmenopausal breast cancer among the population group that administered vitamin D as well as calcium as compared to the group that consumed calcium and placebo. Hence, this result contradicted the outcome of this review. This is possibly because the previous review was conducted with RCTs whereas this review is based on prospective cohort studies.

4.2 CASP results

All the studies had a properly addressed research question. The studies were conducted in varieties of cohorts including nurses, teachers, people having a driving license, university graduates, people covered by the insurance plan as well as the general population. Hence, the inclusion of a diverse group of participants might enable the generalisability of the outcome of the study. However, the included studies were carried out only in the high-resource settings countries. This may compromise the implication of findings in the low resource settings countries. The exposure measurement in all the included papers was done using a questionnaire. This might lead to overestimation or underestimation of the dietary habit, which will result in misclassification bias. The outcome occurrence was self-reported, and it was confirmed through medical reports, which reduced the chances of bias.

Confounders are the variables that might alter the outcome of the study as they are related to both the independent and dependent variables (64). Multiple parameters are taken into consideration in the analysis of most of the studies. Hence, it is likely that in many of the included studies the models were over adjusted. Unnecessary adjustment might have resulted in biased estimates. (65)

The latency period of breast cancer is approximately 16.3 years (58). Among the included papers three studies had a satisfactory follow-up period of 16 years (53),18 years (57), and 19 years (58) for the disease development from initiation. However, in other included research the follow-up time is less than 16 years, which may not be sufficient to reveal a protective effect of vitamin D that interrupts the breast cancer onset.

4.3 Methodological discussion related to literature review

4.3.1 Search

There are some limitations in this research. The systematic search was confined to Medline (Ovid) search and did not include other potential databases. However, Medline is one of the largest databases that contains global literature on medicine and health-related sector (66). Moreover, google scholar was used to further confirm the inclusion of all the eligible research. Also, the reference list of relevant studies was manually checked. Therefore, it is highly unlikely that a search in other databases would alter the outcome of this study.

To reduce the risk of bias, the main author as well as the supervisor and co-supervisor were involved to review and finalize the search strategy. Due to resource constraints for translation, papers written in other languages except English could not be incorporated into the review. However, there were no eligible studies identified in other languages.

4.3.2 CASP as a tool

CASP (Critical Appraisal Skills Programme) is a tool that enables the evaluation of the reliability and significance of the context and the outcome of the research thoroughly and scientifically. It is the process to analyse the quality of the research. Research on medicine and

health care must be concluded based on a well-informed decision. Hence the study should be conducted with an accurate methodology to generate a strong result (67).

It is vital to assess the strengths and weaknesses of the paper which decides its worth. Along with this, another element the checklist considers is the suitability of the research question and the research procedure. It is also concerned with the statistical analysis, its result, and the interpretation. It also considers the consistency of the study with other research and the potential application (68).

On the other hand, various studies are susceptible to various biases. There is a specific CASP tool based on the study design. When the cohort studies evaluate the beneficial effect of intervention then the research might encounter the problem of confounding and selection bias. Hence critical appraisal is important (68).

CASP tool least considers the evaluative, theoretical, and interpretative validity of the study. However, it is a frequently used tool to assess the quality of the health care related research (69).

5 CONCLUSION

This review finds no association between pre-diagnostic vitamin D level and postmenopausal breast cancer risk. Hence, the included studies do not support using vitamin D for postmenopausal breast cancer prevention. However, this review highlights the importance of well conducted RCTs to assess the potential protective effect of vitamin D. Moreover, repeated measurement of vitamin D levels in different seasons is beneficial due to the frequent fluctuation of the level in the human body in different environments. Additionally, the study should be of a longer duration to reveal an actual protective effect of vitamin D to reduce breast cancer occurrence. Future studies should prioritize low-resource settings while doing the research.

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APPENDICES

Appendix 1: Databases Search

1. **MEDLINE (Ovid)**

Date: 6/10/2022

Search Strategy:

# ▲	Searches	Results
1	exp Female/	9510143
2	female*.ti,ab,kw.	1129360
3	wom#n.ti,ab,kw.	1327342
4	healthy wom#n.ti,ab,kw.	20093
5	1 or 2 or 3 or 4	9898947
6	exp Vitamin D/	67054
7	cholecalciferol*.ti,ab,kw.	3256
8	ergocalciferol*.ti,ab,kw.	832
9	hydroxycholecalciferol*.ab,kw,ti.	1449
10	25-hydroxyvitamin D 2.ti,ab,kw.	50
11	dihydrotachysterol*.ti,ab,kw.	473
12	Vitamin D*.ab,kw,ti.	83504

13	6 or 7 or 8 or 9 or 10 or 11 or 12	101904
14	exp Breast Neoplasms/	333629
15	(postmenopaus* adj3 breast cancer).ti,ab,kw.	4200
16	breast neoplasm*.ti,ab,kw.	11692
17	breast cancer.ti,ab,kw.	322332
18	14 or 15 or 16 or 17	426883
19	exp Prospective Studies/	643955
20	(population adj3 stud*).ti,ab,kw.	223451
21	(prospective adj3 stud*).ti,ab,kw.	422739
22	cohort stud*.ti,ab,kw.	296545
23	19 or 20 or 21 or 22	1178194
24	5 and 13 and 18 and 23	181
25	limit 24 to (english language and humans and yr="2000 -Current")	157

2. **Google Scholar**

Date: 7/10/2022

Search terms: vitamin D “postmenopausal breast cancer”healthy women

Year : 2000 to current

Sort by relevance

Total results: 9,840

Total selected for inclusion: 200

Appendix 2: Additional information on extraction of the data from the included studies

Article	**Confounder**	**Outcome Assessment**
Intakes of Calcium and Vitamin D and Breast Cancer Risk in Women	age, randomized treatment assignment (aspirin vs placebo or vitamin E vs placebo), body mass index , physical activity, family history of breast cancer in a first-degree relative, history of benign breast disease, age at menarche, parity, age at first birth, multivitamin use, smoking status, alcohol consumption , total energy intake, age at menopause and baseline postmenopausal hormone therapy, presence of a mammogram screening test during the first 12-months of follow-up questionnaire (excluded the confirmed cases.)	follow-up questionnaires (participants reported whether they have been diagnosed with breast cancer); obtained medical and pathological report for those who died.
Dietary intake of Vitamin D and calcium and breast cancer risk in the European	total energy excluding energy from fat and alcohol, fat consumption, alcohol consumption, weight, height, smoking status, education level, menopausal status, total physical activity, current use of oral contraceptives or hormones for menopause, age at menarche.	incident cancer were identified though linkage with population registries, active follow-up, health insurance company (France), direct contact with

Prospective Investigation into Cancer and nutrition		the subject, or their kin (France, Germany, and Greece). Mortality data were also obtained from either the cancer or mortality registries at the regional or national level.
Intake of Dairy Products, Calcium and Vitamin D and Risk of Breast Cancer	age, time period, physical activity in METs (metabolic equivalent-hours, history of benign breast disease, family history of breast cancer, height, weight , body mass index , age at menarche, parity, age at first birth, alcohol intake, total energy intake, total fat intake, glycemic index, carotene intake, and total active vitamin E intake, calcium intake, total vitamin D intake.	Self-reported and deaths were identified from their family, postal service, or the National Death Index. (medical reports were also obtained for confirmation).
Interaction between current Vitamin D supplementation and menopausal hormone therapy use on breast	age , BMI , use of oral contraceptives before menopause, use of MHT, parity and age at first full-term pregnancy, age at menarche, age at menopause, total energy intake without alcohol, dietary vitamin D intake, calcium intakes, dietary intake , supplementation with micronutrients other than calcium and vitamin D, skin complexion, ultraviolet radiation dose	Self-reported (physicians address and permission to contact them), insurance files, death certificates and pathology reports.

cancer risk: evidence form the E3N cohort	exposure at place of residence , alcohol consumption , smoking status, physical activity, personal history of benign breast disease, mammography in the previous follow-up period, family history of breast cancer in first-degree relatives, and educational level.	
Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort	body mass index (BMI) before and after menopause , physical activity , menopausal status (time-dependent), age at menopause, age at menarche, number of full-term pregnancies, previous use of oral contraceptives, use of MHT, mean dietary calcium intakes, current use of calcium supplement, alcohol intake, total energy intake without alcohol , university degree, previous family history of breast cancer, previous history of personal benign breast disease , previous mammography, sun burn resistance, and skin complexion.	self-reported, insurance file and information on causes of death (pathology report used to confirm)
Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer	age, energy, history of breast cyst, family history of breast cancer, height, weight gain, alcohol use, race, age at menopause, and number of live births, education, mammography history, and HRT.	Self-reported and deaths were confirmed through National Death Index.

Prevention Study II Nutrition Cohort		
Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study	age, smoking status, age at menarche, age at menopause, first degree relative with breast cancer, estrogen use, age at first live birth, number of live births, education category, BMI category, activity level, live on a farm, mammogram history and daily energy, fat and alcohol intake.	Linkage to state Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology and End Results program (SEER)
Dietary calcium, vitamin D, and breast cancer risk in women: findings from the SUN cohort	age of menarche, age at menopause, alcohol intake, BMI, height, hormone replacement therapy and its duration, months of breast-feeding, obstetric history, age at first pregnancy, physical activity, first degree family history of breast cancer, smoking status, and years at university , total intake of Ca and vitamin D and further controlled for fat intake, Mediterranean diet adherence, sugar-sweetened beverages and total energy intake, global sun radiation exposure and sunscreen use when sunbathing (no sunbathing,	self-reported (A trained oncologist, blinded to dietary exposures, reviewed medical records, and confirmed the diagnosis of breast malignancy)

	sunscreen users tertiles of a propensity score obtained from a multinomial logistic regression.