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Meta-analysis: Serum vitamin D and breast cancer risk

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ABSTRACT

We reviewed and summarised observational epidemiological studies regarding the association between serum vitamin D (measured as 25(OH)D levels) and the risk of breast cancer (BC). Relevant studies published until September 2009 were identified by systematically electronic searching Ovid Medline, EMBASE and ISI Web of Knowledge databases and by cross-referencing. The following data were extracted in a standardised manner from eligible studies: first author, publication year, country, study design, characteristics of the study population, duration of follow-up, BC incidence/BC mortality according to serum 25-hydroxyvitamin D (25(OH)D) and the respective ratios, and covariates adjusted for in the analysis. All existing observational epidemiological studies that reported at least one serum 25(OH)D level in subjects in any time period before or after a diagnosis of breast cancer were included in our review. Individual and summary risk ratios (RRs) for an increase of serum 25(OH)D by 20 ng/ml were calculated using meta-analysis methods. Only 25(OH)D was considered. Overall, 10 articles were included. Specific results for BC incidence were reported in nine articles and for BC mortality in one article. In meta-analyses, summary RRs (95% confidence interval (CI)) for an increase of 25(OH)D by 20 ng/ml were 0.59 (0.48–0.73), 0.92 (0.82–1.04) and 0.73 (0.60–0.88) with *P* values of <0.001, 0.164 and 0.001 for case-control studies, nested case-control studies and both study designs combined, respectively. No indication for publication bias was found, but there was large heterogeneity between studies. In conclusion, while case-control studies with measurement of 25(OH)D after diagnosis suggest an inverse association, a statistically significant inverse association remained unconfirmed in prospective studies with measurement of 25(OH)D years before diagnosis. Further studies are needed to clarify the potential role and the relevant exposure time regarding vitamin D and breast cancer risk.

1. Introduction

Although vitamin D is obtained from diet and dietary supplements, the main source for vitamin D is its production in the skin under the influence of solar ultraviolet B (UV-B) radiation. In 1980, Garland and Garland[1] hypothesised that lower levels of vitamin D resulting from much weaker UV-B radiation at higher latitudes may account for the striking geographical pattern of cancer mortality. Partly stimulated by this article, further research in this area has been conducted in observational studies over the past 20 years.[2–4]

A number of ecological studies found vitamin D status to increase with decreasing latitude and to parallel the south to north gradient in the incidence of female breast cancer (BC),[5–9] however, results were not consistent, and even inverse associations have being reported from Europe.[10,11] Most epidemiologic studies addressing the association between vitamin D and BC have assessed dietary vitamin D intake,

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and results have also been inconsistent.[12–20] In recent years, several studies have addressed the association of BC risk and serum 25(OH)D levels representing an integrated measure for vitamin D from diet, dietary supplements and skin production, which has a relatively long half-life in the circulatory system of about 2–3 weeks. By contrast, serum levels of $1,25(OH)_2$, the active metabolite of vitamin D has only a short half-life and its physiological control depends on many factors other than UV exposure or diet, such as calcium balance and the parathyroid hormone. Hence, only serum 25(OH)D is considered to be a useful marker reflecting the 'vitamin D status'.[21]

Combining two studies identified by searching the Medline database for 1966–2006, Garland and colleagues[22] performed a pooled analysis regarding the association between serum 25(OH)D and BC risk. They found a 50% lower risk of BC associated with a serum 25(OH)D level $\geqslant$52 ng/ml, compared to $\leqslant$13 ng/ml. Since then, a rapidly increasing number of studies have addressed the association of 25(OH)D with BC risk. Therefore, we aimed to provide an up-to-date systematic review and meta-analyses of observational epidemiological studies investigating the association between serum 25(OH)D levels and BC risk by using methods for comprehensive trend estimation from summarised dose–response data.[23]

2. Materials and methods

2.1. Identification of studies and study selection

A literature search was conducted to identify longitudinal studies, nested case-control studies or case-control studies assessing the association between serum levels of 25(OH)D and BC incidence or mortality. We searched Ovid (Ovid Technologies Inc., New York, 1950 – 18th September 2009), EMBASE (Elsevier, Amsterdam, the Netherlands, 1980 – 24th September 2009) and ISI Web of Knowledge (Thomson Scientific Technical Support, New York, 1945 – 24th September 2009) databases for relevant articles by various combinations of relevant terms in the article including 25-OH-D, cholecalciferol, calcidiol, calcitriol, 25-hydroxyvitamin D, hydroxycholecalciferols, 25-hydroxyvitamin D3 1-alpha-hydroxylase, 1,25-dihydroxyvitamin D, vitamin D, breast, mammary glands, mamma, mastocarcinoma, cancer, tumour, neoplasm. Duplicate publications were deleted. Each title and abstract was checked for relevance. The full text was reviewed if the abstract indicated that the article reported associations between serum vitamin D and BC risk. Only original studies conducted among humans with at least one serum 25(OH)D measurement at any time point before or after a diagnosis of BC were considered for the review. Cross-referencing was employed to complement the study identification process.

2.2. Data extraction

From eligible studies, the first author (Yin L.) and the second author (Grandi N.) extracted the following data independently from each study in a standardised manner: author(s), publication year, country, study design, characteristics of the study population, duration of follow-up, BC incidence or mortality according to serum vitamin D status and the respective measures of relative risk (see below), as well as covariates adjusted for in the analysis. Any initial disagreement was resolved by consensus after additional review of the articles.

2.3. Meta-analyses

Meta-analyses were restricted to serum 25(OH)D levels. Main outcome variables were measures of relative risks for the association between serum 25(OH)D levels and BC. When such data were not explicitly reported, they were derived from data provided in the articles or requested from the authors through personal contacts, wherever possible. For consistency, serum levels of 25(OH)D given in nmol/L were converted to ng/ml, using the pertinent conversion factor (1 ng/ml = 2.5 nmol/L). In most studies, BC incidence or mortality was reported stratified by various categories of 25(OH)D. Depending on available information, median, midpoints or means of the categories were used for meta-analysis. Due to the different categorisation of 25(OH)D levels across studies, all results were recalculated for an increase of serum 25(OH)D by 20 ng/ml, both within studies (taking possible correlations resulting from a common reference category into account),[23] as well as across studies. A 20 ng/ml difference was chosen as this difference approximately reflects the range of difference between categories compared in original articles. Summary ORs from fixed and random effects models were calculated using standard meta-analysis methods.[24]

In a conservative approach, the random effects estimates, which allow for variation of true effects across studies, were taken as 'main results'.[25] Random effects estimates were derived using the DerSimonian–Laird method.[26,27] Heterogeneity was assessed by the I^2 statistic, and standardised deleted residuals analysis was done to identify outliers. Nested case-control studies are far more robust against potential biases than case-control studies with measurements of 25(OH)D after diagnosis. Therefore, meta-regression and subgroup analyses were carried out to investigate associations by study design and the effect sizes observed in the studies.[28] The funnel plot, Begg and Mazumdar rank correlation test and Egger's test of the intercept were employed to assess indications of publication bias.[29] The R/S plus software, version 2.8.1, and the statistics software SAS©, version 9.1 (SAS Institute Inc., Cary, NC, USA), were used for the analysis.

3. Results

3.1. Identification of studies

A flow diagram of the search process is given in Fig. 1. Total searches yielded 4264 entries. Following removal of 1208 duplicates, 3056 titles and abstracts were assessed and 122 articles appeared to be potentially relevant for inclusion into the review. One hundred and ten articles were excluded for the following reasons: no original articles but editorials, comments, reviews ($N = 84$), only vitamin D intake reported ($N = 13$), associations of 25(OH)D with BC not reported/not derivable from reported data ($N = 4$), no BC data ($N = 4$), only 25(OH)D among BC patients assessed ($N = 4$), only

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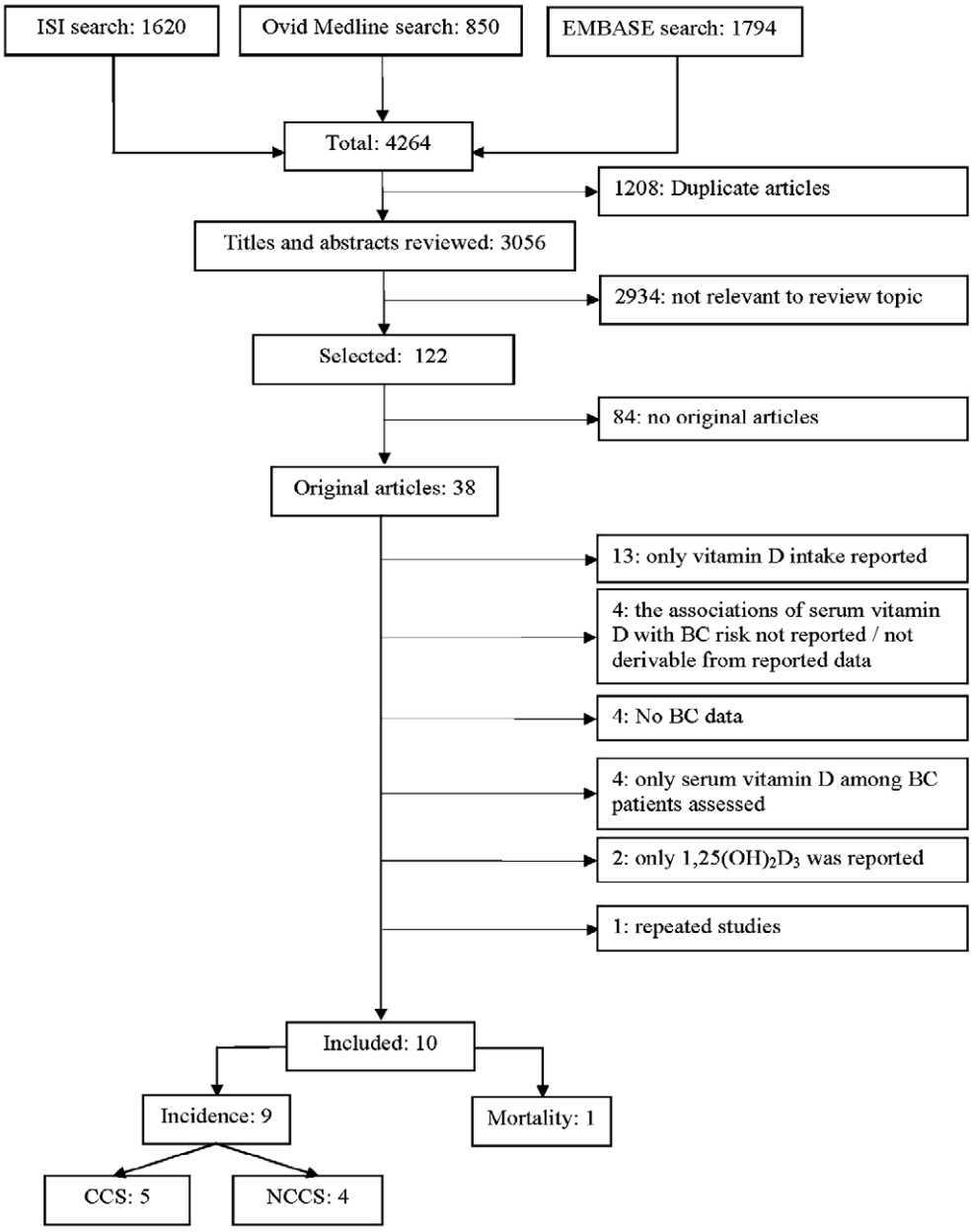

Fig. 1 – Flow diagram of the literature search process. NCCS, nested case-control study; CCS, case-control study.

$1,25(OH)_2D_3$ were reported ($N = 2$), repeated studies from the same study population ($N = 1$). The references of excluded studies are provided in Appendix 1.

Articles from Colston and colleagues[30] and Lowe and colleagues[31] reported the results among the same Caucasian women. Only Lowe and colleagues[31] reported sufficient data for calculating and transforming measures of association as needed, which were included in our meta-analysis, and the article by Colston and colleagues[30] was excluded.

In total, 10 studies were included in our review. Associations of 25(OH)D with BC incidence and mortality were reported in nine studies and one study,[32] respectively, including four nested case-control studies[33–36] and five case-control studies.[31,37–40] Details on the respective study design, the study populations, the study results and covariates adjusted for are shown in Tables 1–3, and the results of single studies are further illustrated in Fig. 2.

3.2. *Results of meta-analyses*

The results of meta-analyses on the association between serum 25(OH)D levels and BC incidence are shown in Fig. 3. All ORs refer to an increase of 25(OH)D by 20 ng/ml. Seven of nine studies showed an inverse association for an increase in 25(OH)D levels, and this association was significant in five studies. A significant inverse association was observed in pooled analyses using either a fixed effects model (OR, 0.74; 95% confidence interval (CI), 0.69–0.80; $P < 0.001$) or a random effects model (OR, 0.73; 95% CI, 0.60–0.88; $P = 0.001$). Large statistical heterogeneity among these nine included studies was

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Table 1 – Nested case-control studies reporting on the association of serum 25(OH)D concentration with incidence of breast cancer.

Ref.	Author(s), (year)	Study population					RR (95% CI) of BC incidence according to 25(OH)D (range or median) (ng/ml)[a,b]	Matched/adjusted for
		Country (baseline; follow-up)	No. of participants		Age range at baseline (mean)	Setting		
			Cases	Controls				
[33]	Bertone-Johnson et al. (2005)	USA (1976–1990; 1990–1996)	701	701	43–69 (57)	Female nurses	Batch 1/batch 2/batch 3:[c] ⩽20/⩽28/⩽18: 1.00 21–28/29–34/19–24: 0.95 (0.66, 1.36) 29–33/35–39/25–29: 0.74 (0.51, 1.06) 34–39/40–47/30–36: 0.77 (0.54, 1.11) ⩾40/⩾48/⩾37: 0.73 (0.49, 1.07)	Age, fasting status at blood collection, month of blood collection, time of day of blood collection, menopausal status, and current use of post-menopausal hormones, BMI[4] at age 18, parity /age at first birth, family history of breast cancer, history of benign breast disease, age at menarche, age at menopause, alcohol intake and plasma α-carotene
[35]	Freedman et al. (2008)	USA (1993–2001; 1993–2005)	1005	1005	55–74 (62)	Population based	<18.3: 1.00 18.3–23.4: 1.02 (0.75, 1.41) 23.5–28.2: 1.36 (0.99, 1.87) 28.3–33.6: 1.13 (0.82, 1.55) ⩾33.7: 1.04 (0.75, 1.45)	Period of blood collection, age, and season of serum collection, BMI[4] (ages 18–20), age at menarche, age at menopause, hormone replacement therapy use, benign breast disease family history of breast cancer, combination of parity and age at first birth, smoking status, daily alcohol intake and daily dietary calcium intake
[34]	Chlebowski et al. (2008)	USA (1995–2000; 1995–2005)	895	898	50–79 N/A[d]	Post-menopausal population based	9.44: 1.22 (0.89, 1.67) 15.40: 1.17 (0.86, 1.60) 19.68: 1.35 (0.99, 1.82) 24.36: 1.15 (0.86, 1.55) 32.76: 1.00	Age, race/ethnicity, latitude of clinical centre, venipuncture date, randomisation in the hormone therapy and dietary modification trials, BMI[d], physical activity, family history of breast cancer, history of breast biopsy, current oestrogen plus progestin use and current oestrogen-only use
[36]	McCullough et al. (2009)	USA (1998–2001; 1998–2005)	516	516	47–85 (69)	Post-menopausal population based	<14.68: 1.00 14.68–19.91: 1.29 (0.86, 1.94) 19.92–24.31: 1.14 (0.75, 1.72) 24.32–29.27: 1.44 (0.96, 2.18) ⩾29.28: 1.09 (0.70, 1.68)	Birth year, year of blood collection, race, season, parity and age at first birth, body mass index at blood collection and weight change from age 18 years to blood collection

[a] For consistency, serum concentrations of 25(OH)D in nmol/L were converted to ng/ml using the conversion factor, 1 ng/ml = 2.5 nmol/L.

[b] RR, risk ratio; CI, confidence interval; BC, breast cancer.

[c] Samples were analysed in three batches: batch 1, 178 cases and 184 controls were analysed between November 1993 and July 1994; batch 2, 279 cases and 286 controls were analysed between October 1999 and June 2000; batch 3, 244 cases and 254 controls were analysed between June and September 2003.

[d] N/A, not available; BMI, body mass index.

Table 2 – Case-control studies reporting on the association of serum 25(OH)D concentration with incidence of breast cancer.

Ref.	Author(s), (year)	Study population					RR (95% CI) of BC incidence according to 25(OH)D (range or median) (ng/ml)[a,b]	Matched/adjusted for
		Country (time of recruitment)	No. of participants		Age range at recruitment (mean)	Setting		
			Cases	Controls				
[31]	Lowe et al. (2005)	UK (1998–2003)	179	179	34–84 (58)	Pre- and post-menopausal population based	<20: 5.83 (2.31, 14.7) 20–40: 1.83 (0.83, 4.03) 40–60: 1.61 (0.71, 3.64) >60: 1.00	Time of year the blood collection was taken, age at sampling and menopausal status
[37]	Abbas et al. (2008)	Germany (2002–2005)	1394	1365	50–74 (63)	Post-menopausal population based	<12: 1.00 12–18: 0.57 (0.45, 0.73) 18–24: 0.49 (0.38, 0.64) 24–30: 0.43 (0.32, 0.57) ⩾30: 0.31 (0.24, 0.42)	Year of birth, time of blood collection, age at menopause, first-degree family history of breast cancer, history of benign breast disease, number of pregnancies, age at menarche, breastfeeding history, total number of mammograms, use of HT[c], BMI[c], education level and smoking status
[38]	Abbas et al. (2009)	Germany (1992–1995)	289	595	30–50 (42)	Pre-menopausal population based	<12: 1.00 12–18: 0.68 (0.43, 1.07) 18–24: 0.59 (0.37, 0.94) ⩾24: 0.45 (0.29, 0.70)	Age, time of blood collection, number of births, first-degree family history, age at menarche, duration of breast-feeding, BMI[c], alcohol consumption
[39]	Crew et al. (2009)	USA (1996–1997)	1026	1075	20–90 (57)	Pre- and post-menopausal population based	<20: 1.00 20–29: 0.80 (0.62, 1.04) 30–39: 0.83 (0.64, 1.07) ⩾40: 0.56 (0.41, 0.78)	Age, race, age of menarche, age of first birth, parity, breastfeeding history, menopausal status, use of hormone replacement therapy, first-degree family history of breast cancer, history of benign breast disease, BMI[c], physical activity and season of blood collection
[40]	Rejnmark et al. (2009)	Denmark (2003–2008)	142	420	29–87 (58)	Pre- and post-menopausal population based	Overall: <24: 1.00 24–33.6: 0.94 (0.59, 1.47) >33.7: 0.52 (0.32, 0.85) Pre-menopausal: <24: 1.00 24–33.6: 0.59 (0.26, 1.33) >33.7: 0.38 (0.15, 0.97) Post-menopausal: <24: 1.00 24–33.6: 1.20 (0.67, 2.16) >33.7: 0.71 (0.38, 1.30)	None

[a] For consistency, serum concentrations of 25(OH)D in nmol/L were converted to ng/ml using the conversion factor, 1 ng/ml = 2.5 nmol/L.
[b] RR, risk ratio; CI, confidence interval; BC, breast cancer.
[c] BMI, body mass index; HT, hormone therapy.

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observed (I^2 = 83.9%; $P < 0.01$). The funnel plot did not show evidence of publication bias (Kendall's tau = –0.22; $P = 0.48$; Egger's t value = –0.88, $P = 0.38$).

In meta-regression, study design (case-control study versus nested case-control study) was indentified as a moderator of BC risk ($P < 0.01$). Estimates from subgroup analysis presented in Fig. 3 showed that the association between 25(OH)D and BC in case-control studies was statistically significant in both the fixed effects model (OR, 0.60; 95% CI, 0.54–0.67; $P < 0.001$) and the random effects model (OR, 0.59; 95%CI, 0.48–0.73; $P < 0.001$). By contrast, a much weaker and non-significant association was found in nested case-control studies (the fixed effects model: OR, 0.92; 95% CI, 0.82–1.02; $P = 0.104$; the random effects model: OR, 0.92; 95% CI, 0.82–1.04; $P = 0.164$).

In standardised deleted residuals analysis, the study conducted by Abbas and colleagues[37] in 2008 was identified as an outlier (standardised deleted residual = –2.82). After excluding this study, strong inverse associations between serum 25(OH)D and BC incidence were still found in case-control studies (OR, 0.67; 95% CI, 0.59–0.76; $P < 0.001$) and in both study design combined (OR, 0.79; 95% CI, 0.68–0.91; $P = 0.001$).

Table 3 – Prospective cohort study reporting on the association of serum 25(OH)D concentration with breast cancer mortality.

Ref.	Author (s) (year)	Study population					RR (95% CI) of BC mortality according to median 25(OH)D (ng/ml) [a,b]	Matched/adjusted for
		Country (baseline; follow-up)	No. participants		Age range at baseline (mean)	Setting		
			Deaths	Total				
[32]	Freedman et al. (2007)	USA (1988–1994, 1988–2000)	28	9185	N/A[c] (44)	Population based	15.3: 1.00 31.9: 0.28 (0.08, 0.93)	Age, race/ethnicity, and smoking history

[a] For consistency, serum concentrations of 25(OH)D in nmol/L were converted to ng/ml using the conversion factor, 1 ng/ml = 2.5 nmol/L.
[b] RR: risk ratio; CI: confidence interval; BC: breast cancer.
[c] N/A: not available.

4. Discussion

Our review and meta-analysis summarising the results of nine studies on the association between serum 25(OH)D and incident BC show ambiguous evidence: while case-control studies with measurement of serum 25(OH)D levels after diagnosis support the hypothesis that serum 25(OH)D levels are inversely associated with BC risk, a statistically significant inverse association remained unconfirmed in nested case-control studies, with measurement of serum 25(OH)D levels from blood taken at baseline of cohort studies typically years before cancer diagnosis.

The strongly divergent results of case-control studies and nested case-control studies along with the lack of an impact on breast cancer incidence seen in a randomised trial with calcium and vitamin D supplementation (WHI trial from which the observational data included in this review were derived[34] raise concern regarding the temporal and causal relationship between vitamin D levels and BC. Case-control studies are more prone to a variety of biases such as selection bias. Furthermore, it is conceivable that the lower vitamin D levels observed after diagnosis among breast cancer patients in case-control studies might be affected by the disease or changes of life habits, such as dietary habits or time spent outdoors. Measurement of serum vitamin D levels prior to diagnosis in longitudinal studies is less prone to this potential source of bias. However, longitudinal approaches are also needed to delineate relevant time windows of exposure for BC risk. So far, serum levels of 25(OH)D were determined at a single point of time only within studies and the time period between measurement and diagnosis of BC varied between studies. Ideally, long-term longitudinal studies with repeated measurements of serum vitamin D levels over time would be desirable to clarify potentially relevant exposure time windows, but such studies might be difficult to realise and are not available to date.

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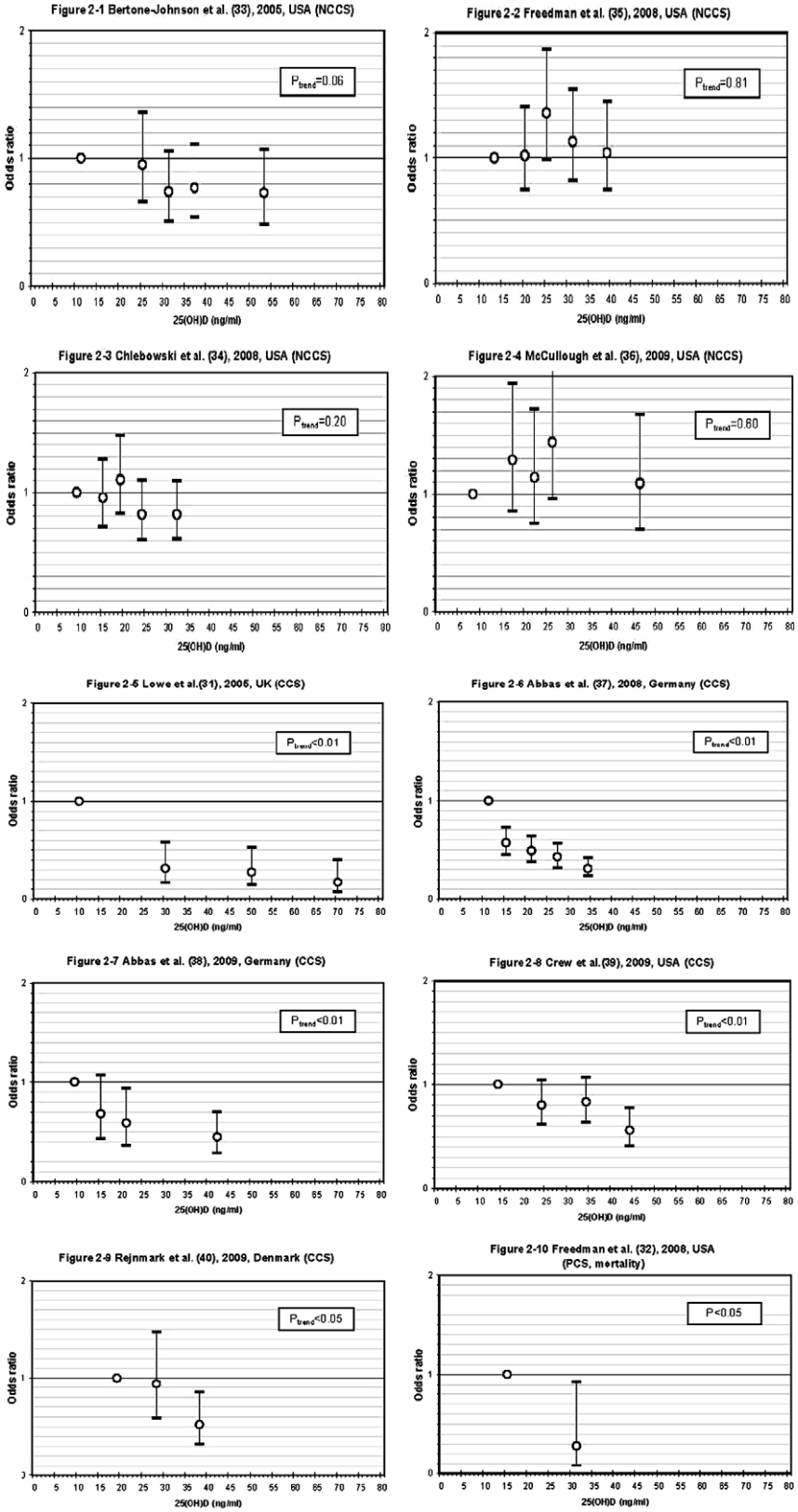

Fig. 2 – Risk ratios and 95% confidence intervals (CIs) of BC risk according to serum 25(OH)D levels. Depending on available information, median, midpoints or means of the categories were used for definition of study specific levels of serum 25(OH)D categories. NCCS, nested case-control study; CCS, case-control study; PCS, prospective cohort study.

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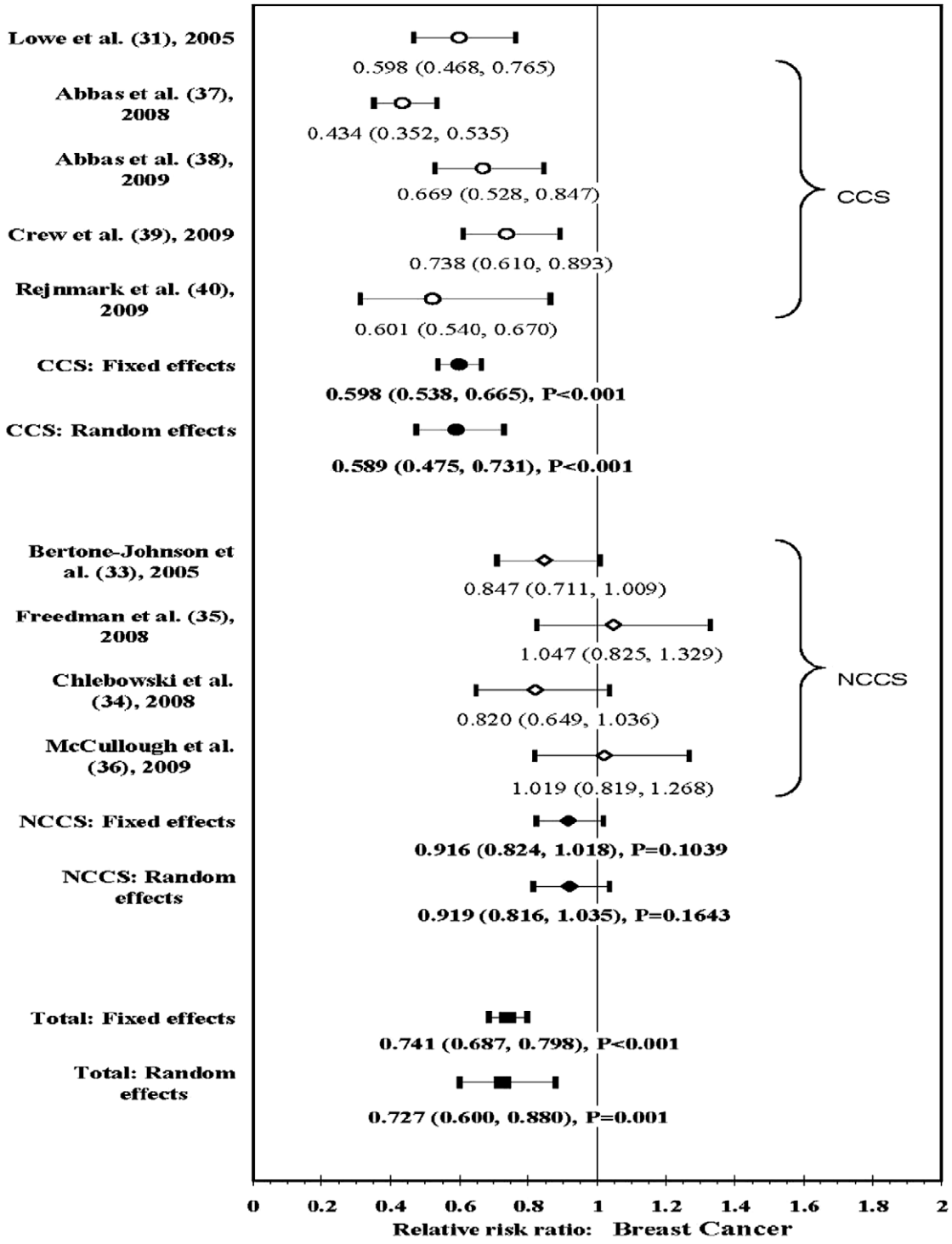

Fig. 3 – Meta-analyses: relative risk ratios of breast cancer risk per 20 ng/ml increase in serum 25(OH)D. NCCS, nested case-control study; CCS, case-control study.

Most studies reported to date included both pre- and post-menopausal women and did not differentiate by menopausal status in the analyses. An exception is the recent study by Crew and colleagues[39] in which the inverse association between serum 25(OH)D levels and BC risk was confined to post-menopausal women. However, in the case-control studies from Germany, Abbas and colleagues found inverse association for both pre-menopausal women[38] and post-menopausal women.[37] More studies are needed to clarify association of 25(OH)D with breast cancer among pre-menopausal and post-menopausal women, especially longitudinal studies.

From the existing literature, we identified factors that are known to influence circulating 25(OH)D concentrations,

including region as a surrogate of UV-B radiation exposure, behaviours related to sun exposure, skin pigmentation, body mass index (BMI), intake, season and age. All studies included in our meta-analysis provided risk estimates adjusted for potentially influential confounders, except one.[40] In particular, potential confounding by physical activity was controlled for in only two studies.[34,39] Physical activity has been shown to be associated with increased vitamin D status.[41–43] The mechanism by which physical activity increases serum 25(OH)D levels remains unclear, and it is also possible that physical activity is just a surrogate parameter for factors such as sun exposure, a healthier lifestyle or a diet rich in vitamin D.

Our analysis has specific strengths and limitations. A major strength of our study is the application of advanced techniques of statistical analysis that allowed to summarise adjusted associations across studies and over the entire range of serum 25(OH)D values, despite the very heterogeneous categorisation of 25(OH)D levels in the individual studies. Our study also has important limitations. Analyses are limited by the data provided by the individual studies. Depending on the results reported, median, midpoints and mean 25(OH)D levels of the group had to be used for pooling. As a result, estimates of risk may be less accurate than if individual-level data had been available. Also, different studies used different methods of measuring serum vitamin D, which might affect comparability of studies and introduce heterogeneity between studies. Furthermore, despite the lack of indication of major publication bias in the formal evaluations employed, potential publication bias is impossible to be excluded completely, especially in the light of the low number of studies. Finally, although our review searched three databases, i.e. Ovid Medline, EMBASE and ISI Web of Knowledge, and extensive checks for completeness by cross-referencing were employed, we cannot exclude having missed a relevant study.

5. Conclusions

Despite its limitations, our review and meta-analysis provide the most comprehensive and updated summary of epidemiological evidence to date on the association between serum 25(OH)D and BC risk. While case-control studies with measurement of serum 25(OH)D levels after diagnosis seem to support the hypothesis that serum 25(OH)D levels are inversely associated with BC risk, a statistically significant inverse association remained unconfirmed in nested case-control studies, with measurement of serum 25(OH)D levels from blood taken at baseline of cohort studies typically years before cancer diagnosis. Available data are still sparse and in-depth analyses of the assessed associations in the context of additional human studies, especially measuring repeatedly 25(OH)D at different time points before diagnosis, are highly desirable to enable more precise estimates and a better understanding of the role of vitamin D in breast cancer development and prevention.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.03.037.

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