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Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis

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Background: Experimental studies suggest potential anti-carcinogenic properties of vitamin D against breast cancer risk, but the epidemiological evidence to date is inconsistent.

Methods: We searched MEDLINE and EMBASE databases along with a hand search for eligible studies to examine the association between vitamin D status (based on diet and blood 25-hydroxyvitamin D (25(OH)D)) and breast cancer risk or mortality in a meta-analysis. A random-effect model was used to calculate a pooled adjusted relative risk (RR).

Results: A total of 30 prospective studies (nested case-control or cohort) were included for breast cancer incidence ($n=24$ studies; 31 867 cases) or mortality ($n=6$ studies; 870 deaths) among 6092 breast cancer patients. The pooled RRs of breast cancer incidence for the highest *vs* the lowest vitamin D intake and blood 25(OH)D levels were 0.95 (95% CI: 0.88–1.01) and 0.92 (95% CI: 0.83–1.02), respectively. Among breast cancer patients, high blood 25(OH)D levels were significantly associated with lower breast cancer mortality (pooled RR = 0.58, 95% CI: 0.40–0.85) and overall mortality (pooled RR = 0.61, 95% CI: 0.48–0.79). There was no evidence of heterogeneity and publication bias.

Conclusions: Our findings suggest that high vitamin D status is weakly associated with low breast cancer risk but strongly associated with better breast cancer survival.

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related mortality among women worldwide, amounting to 23% and 14% of the total new cancer cases and deaths in 2008, respectively (Jemal *et al*, 2011). The most updated report from the World Cancer Research Fund (WCRF) indicated that lifestyle factors, including physical activity and alcohol drinking habit, may modify the risk of breast cancer (World Cancer Research Fund, 2010). Some dietary factors may increase or decrease the risk of breast cancer (Tirona *et al*, 2010), but most of the foods and nutrients, including vitamin D, listed in the report were classified as 'Limited—no conclusion'.

Vitamin D is generally known for its major role in bone metabolism (Bouillon *et al*, 2008; Holick and Chen, 2008), but accumulating studies also suggest that vitamin D has anti-cancer benefits against several cancers, including breast, colorectal, and prostate cancers (Giovannucci, 2005). Ecological studies reported an inverse association between sunlight exposure and breast cancer risk (Anderson *et al*, 2011; Fuhrman *et al*, 2013). Moreover, experimental studies have found that 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the biologically active form of vitamin D, can prevent breast cancer development and progression by inhibiting cell proliferation and angiogenesis (Krishnan *et al*, 2012; Lopes *et al*, 2012; Mohr *et al*, 2012). In addition, one large study conducted in Norway suggested that vitamin D from sunlight may improve the prognosis of breast, colon, and prostate cancers (Robsahm *et al*, 2004). Several epidemiological studies have been conducted to demonstrate the association between dietary vitamin D intake, blood 25-hydroxyvitamin D (25(OH)D) levels, and the risk of breast cancer (Gissel *et al*, 2008; Chen *et al*, 2010; Yin *et al*, 2010; Gandini *et al*, 2011; Mohr *et al*, 2011; Amir *et al*, 2012;

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Bauer *et al*, 2013; Chen *et al*, 2013; Wang *et al*, 2013) or mortality (Rose *et al*, 2013). There was, however, no comprehensive review and meta-analysis of observational studies examining the association between vitamin D status and breast cancer incidence as well as survival among breast cancer patients in a prospective manner. Thus, we systematically reviewed and performed a meta-analysis to quantitatively assess the association between vitamin D intake, blood 25(OH)D levels, and breast cancer incidence, along with the investigation of breast cancer mortality according to blood 25(OH)D levels among breast cancer patients.

MATERIALS AND METHODS

Literature search and study identification. We conducted a literature search through the MEDLINE and EMBASE databases to identify eligible studies published in English up to November 2013. The following keywords were used in our searching: '(vitamin D, cholecalciferol, ergocalciferol, or 25-hydroxyvitamin D) combined with (breast cancer risk or incidence)', and '(25-hydroxyvitamin D) combined with (breast cancer mortality, death, or survival).' We also reviewed the references in the retrieved articles to search for additional relevant studies. Studies were included in the meta-analysis if they met the following criteria: (1) Studies that presented original data from cohort or nested case-control studies; (2) The outcome of interest was definitely defined as breast cancer incidence or mortality from breast cancer or all-cause mortality among breast cancer patients; (3) The exposure of interest was vitamin D intake or blood 25(OH)D levels; and (4) Studies that provided relative risks (RRs) and their confidence intervals (CIs).

Data extraction. Data were extracted using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines independently by two investigators (YK and YJ) (Stroup *et al*, 2000). Discrepancies were resolved by discussion and repeated examination of the studies to reach a consensus. The following information was extracted from each study: first author's last name, publication year, study design, country where the study was conducted, follow-up period or study period, number of cases and controls/subjects or person-time, adjustment for potential confounders, and RRs with corresponding 95% CIs for vitamin D intake or blood 25(OH)D levels. If studies provided several RRs, we extracted the RRs with the greatest degree of control for potential confounders.

Statistical analysis. Study-specific RRs were combined using the DerSimonian and Laird (1986) random-effects models, which considers both within- and between-study variations. If results were reported for both dietary and total vitamin D intake in one study, we used the results for total vitamin D intake in the main analysis. If original studies did not use the lowest category as a reference, the RR and its 95% CI were recalculated (Chlebowski *et al*, 2008; Goodwin *et al*, 2009; Jacobs *et al*, 2011; Amir *et al*, 2012; Neuhouser *et al*, 2012; Mohr *et al*, 2013; Ordonez-Mena *et al*, 2013; Vrieling *et al*, 2013). The summary measures were presented as forest plots where the size of data markers (squares) corresponds to the inverse of the variance of the natural logarithm of RR from each study, and the diamond indicates pooled RR. Statistical heterogeneity among studies was evaluated by using the Q statistic, and inconsistency was quantified by I^2 statistic (Cochran, 1954; Higgins *et al*, 2003).

We conducted stratified analyses by geographic regions, menopausal status, and source of vitamin D intake (diet or supplements). To test for variations in risk estimates by the stratification factors, we carried out a meta-regression analysis. As a way to assess the quality of the prospective studies included in the meta-analysis, we calculated pooled RRs of studies with adjustment for potential confounders, such as BMI and physical activity. In addition, we performed sensitivity analyses in which one study at a time was eliminated and the rest were analysed to assess whether the results could have been influenced substantially by a single study.

To assess dose-response relationships among different categories of vitamin D intake and blood 25(OH)D, we used generalised least-squares trend (GLST) estimation analysis based on the method developed by Greenland and Longnecker (1992) (Berlin *et al*, 1993; Orsini *et al*, 2006); study-specific slopes from the correlated natural logarithm of the RRs across categories of vitamin D intake or blood 25(OH)D levels were estimated (Shin *et al*, 2002; McCullough *et al*, 2005; Lin *et al*, 2007; Robien *et al*, 2007; Chlebowski *et al*, 2008; Freedman *et al*, 2008; Rejnmark *et al*, 2009; Almquist *et al*, 2010; Engel *et al*, 2010, 2011; Edvardsen *et al*, 2011; Eliassen *et al*, 2011; Neuhouser *et al*, 2012; Kuhn *et al*, 2013; Mohr *et al*, 2013; Ordonez-Mena *et al*, 2013; Scarmo *et al*, 2013), and then we combined the GLST-estimated study-specific slopes with studies that reported slope estimates (Bertone-Johnson *et al*, 2005; McCullough *et al*, 2009) to derive an overall average slope. The highest, open-ended category was assumed to have the same amplitude of dietary intake or blood levels as the previous category. For a study which used units other than $ng\,ml^{-1}$, we converted these into $ng\,ml^{-1}$ ($10\,nmol\,l^{-1} = 4\,ng\,ml^{-1}$) (Chlebowski *et al*, 2008; McCullough *et al*, 2009; Rejnmark *et al*, 2009; Almquist *et al*, 2010; Neuhouser *et al*, 2012; Kuhn *et al*, 2013). We did not include five studies that provided no information on cutoff or median of vitamin D intake in each intake category (Kuper *et al*, 2009), person-times in each intake category (John *et al*, 1999; Frazier *et al*, 2004; Abbas *et al*, 2013), or provided a risk estimate only for two categories of blood 25(OH)D levels (Amir *et al*, 2012) for dose-response meta-analysis.

We also examined a potential nonlinear dose-response relationship between vitamin D intake, blood 25(OH)D levels, and breast cancer by adding a quadratic term of vitamin D intake and blood 25(OH)D levels in the model. A P-value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the quadratic term is equal to 0.

Finally, publication bias was evaluated with the use of the Begg's (Begg and Mazumdar, 1994) and Egger's tests (Egger *et al*, 1997) and through visual inspection of a funnel plot. A two-tailed P value of < 0.05 was considered statistically significant. All statistical analyses were performed with the Stata/SE version 12.0 software (Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics. The detailed steps of our literature search are shown in Figure 1. In brief, a total of 30 prospective studies (nested case-control or cohort) were included for breast cancer incidence or mortality among breast cancer patients. The characteristics of the included studies are summarised in Tables 1–3. For breast cancer risk in relation to vitamin D intake, we included 10 prospective cohort studies, including 22 341 incident cases (John *et al*, 1999; Shin *et al*, 2002; Frazier *et al*, 2004; McCullough *et al*, 2005; Lin *et al*, 2007; Robien *et al*, 2007; Kuper *et al*, 2009; Edvardsen *et al*, 2011; Engel *et al*, 2011; Abbas *et al*, 2013; Table 1). Six studies were performed in the United States (John *et al*, 1999; Shin *et al*, 2002; Frazier *et al*, 2004; McCullough *et al*, 2005; Lin *et al*, 2007; Robien *et al*, 2007), whereas four studies were conducted in Europe (Kuper *et al*, 2009; Edvardsen *et al*, 2011; Engel *et al*, 2011; Abbas *et al*, 2013). Five out of the 10 studies presented risk estimates stratified by menopausal status of the study subjects (Shin *et al*, 2002; Lin *et al*, 2007; Robien *et al*, 2007; Engel *et al*, 2011; Abbas *et al*, 2013). Most of the studies provided risk estimates that were adjusted for potential confounders, including BMI (John *et al*, 1999; Shin *et al*, 2002; Frazier *et al*, 2004; Lin *et al*, 2007; Robien *et al*, 2007; Kuper *et al*,

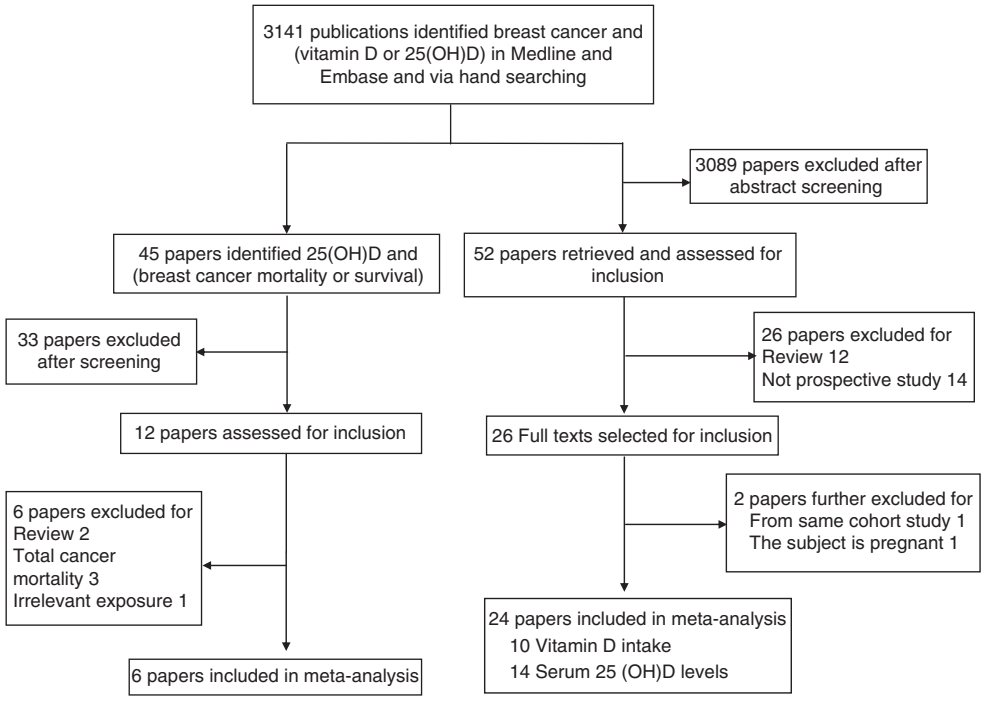

Figure 1. Flowchart of selection of the studies for inclusion in meta-analysis.

2009; Edvardsen *et al*, 2011; Engel *et al*, 2011) and physical activity (John *et al*, 1999; Shin *et al*, 2002; Lin *et al*, 2007; Robien *et al*, 2007; Kuper *et al*, 2009; Engel *et al*, 2011; Abbas *et al*, 2013). One study did not adjust for BMI, but they did adjust for weight and height, which may be considered a proxy for BMI (Abbas *et al*, 2013).

For breast cancer risk in relation to blood 25(OH)D levels, 14 prospective studies (13 nested case-control and 1 cohort), including 9526 incident cases, were included (Bertone-Johnson *et al*, 2005; Chlebowski *et al*, 2008; Freedman *et al*, 2008; McCullough *et al*, 2009; Rejnmark *et al*, 2009; Almquist *et al*, 2010; Engel *et al*, 2010; Eliassen *et al*, 2011; Amir *et al*, 2012; Neuhouser *et al*, 2012; Kuhn *et al*, 2013; Mohr *et al*, 2013; Ordonez-Mena *et al*, 2013; Scarmo *et al*, 2013; Table 2). Eight studies were conducted in the North America (USA/Canada) (Bertone-Johnson *et al*, 2005; Chlebowski *et al*, 2008; Freedman *et al*, 2008; McCullough *et al*, 2009; Eliassen *et al*, 2011; Amir *et al*, 2012; Neuhouser *et al*, 2012; Mohr *et al*, 2013), five in Europe (Rejnmark *et al*, 2009; Almquist *et al*, 2010; Engel *et al*, 2010; Kuhn *et al*, 2013; Ordonez-Mena *et al*, 2013), and one study provided overall results from USA and Sweden (Scarmo *et al*, 2013). Ten out of the 14 studies presented risk estimates stratified by menopausal status of the study subjects (Chlebowski *et al*, 2008; Freedman *et al*, 2008; McCullough *et al*, 2009; Rejnmark *et al*, 2009; Almquist *et al*, 2010; Engel *et al*, 2010; Eliassen *et al*, 2011; Neuhouser *et al*, 2012; Ordonez-Mena *et al*, 2013; Scarmo *et al*, 2013), and the majority of studies adjusted for BMI (Bertone-Johnson *et al*, 2005; Chlebowski *et al*, 2008; Freedman *et al*, 2008; McCullough *et al*, 2009; Almquist *et al*, 2010; Engel *et al*, 2010; Eliassen *et al*, 2011; Amir *et al*, 2012; Neuhouser *et al*, 2012; Kuhn *et al*, 2013; Ordonez-Mena *et al*, 2013; Scarmo *et al*, 2013), and 6 studies were adjusted for physical activity (Chlebowski *et al*, 2008; Engel *et al*, 2010; Neuhouser *et al*, 2012; Kuhn *et al*, 2013; Ordonez-Mena *et al*, 2013; Scarmo *et al*, 2013).

In addition, we found six prospective studies that examined mortality in relation to blood 25(OH)D levels among breast cancer patients (Table 3; Goodwin *et al*, 2009; Jacobs *et al*, 2011; Hatse *et al*, 2012; Tretli *et al*, 2012; Villasenor *et al*, 2013; Vrieling *et al*, 2013). The studies included 870 overall deaths among 6092 patients and 301 deaths from breast cancer among 4556 patients. According to geographic region, three studies were performed in North America (Goodwin *et al*, 2009; Jacobs *et al*, 2011; Villasenor *et al*, 2013) and three in Europe (Hatse *et al*, 2012; Tretli *et al*, 2012; Vrieling *et al*, 2013). Three out of the six studies provided multivariable risk estimates adjusted for BMI (Jacobs *et al*, 2011; Hatse *et al*, 2012; Villasenor *et al*, 2013). One study did try adjustment for BMI initially, but the BMI was left out as an adjustment factor in the final model as the result was not changed materially after the adjustment (Vrieling *et al*, 2013).

High *vs* low vitamin D intake or 25(OH)D levels for breast cancer risk. The multivariable-adjusted RRs of breast cancer risk for each study and the pooled RR from all studies combined for the highest *vs* lowest categories of vitamin D intake or blood 25(OH)D levels are shown in Figures 2 and 3. The pooled RR of breast cancer for the highest ($>500\,\text{IU day}^{-1}$, mean) *vs* lowest categories of vitamin D intake ($<148\,\text{IU day}^{-1}$, mean) was 0.95 (95% CI: 0.88–1.01), with no significant heterogeneity among the studies ($P=0.09$, $I^2=38.3\%$) (Figure 2). No significant differences were found by geographic region ($P=0.31$), menopausal status ($P=0.37$), or source of vitamin D intake ($P=0.33$) (Supplementary Table). When limited to studies that had adjusted for BMI (or weight and height) or physical activity, the pooled RRs were similar (pooled RR adjusted for BMI = 0.94, 95% CI: 0.88–1.02; pooled RR adjusted for PA = 0.92, 95% CI: 0.85–0.99) (data not shown). The pooled RR of breast cancer for the highest ($>31\,\text{ng ml}^{-1}$, mean) *vs* lowest categories of 25(OH)D levels ($<18\,\text{ng ml}^{-1}$, mean) was 0.92 (95% CI: 0.83–1.02), with no significant heterogeneity among the studies ($P=0.16$, $I^2=27.3\%$) (Figure 3). When we excluded studies that did not adjust for BMI or physical activity, the results of meta-analyses were similar. In the subgroup analyses, we found no significant variations in pooled RRs by geographic region ($P=0.73$) or menopausal status ($P=0.37$) (Supplementary Table).

High *vs* low 25(OH)D levels for mortality among breast cancer patients. The multivariable-adjusted RRs of mortality for each study and the pooled RR from all studies combined for the

Table 1. Characteristics of prospective studies included in the meta-analysis of vitamin D intake and breast cancer risk

Source	Country	Follow-up period[a]	Age at baseline	Study subjects	No. of BC cases	Vitamin D Intake (IU day^{-1})[b] highest vs lowest	Relative risk (95% CI)	Adjustment factors
John *et al*, 1999	USA	1971–1992 (17.3 years)	25–74 years	4747	179	Dietary vitamin D ⩾200 *vs* <100	0.85 (0.59–1.24)	Age, education, age at menarche, BMI, alcohol, physical activity, calcium intake
Shin *et al*, 2002	USA	1980–1996 (16 years)	46.7 years	88 691	827 PRE 2345 POST	Total vitamin D >500 *vs* ⩽150 Dietary vitamin D >300 *vs* ⩽75 Vitamin D Supplement ⩾400 *vs* none	PRE 0.72 (0.55–0.94) 0.66 (0.43–1.00) 0.88 (0.71–1.10) POST 0.94 (0.80–1.10) 1.06 (0.85–1.34) 0.96 (0.85–1.08)	Age in 5-year categories, time period, physical activity in METs, history of benign breast disease, family history of breast cancer, height, weight change since age 18 years, BMI at age 18 years, age at menarche, parity, age at first birth, alcohol intake, total energy intake, total fat intake, glycemic index, *β*-carotene intake, total active vitamin E intake
Frazier *et al*, 2004	USA	1989–1998	25–42 years	47 355	361	Total vitamin D Q5(591.0) *vs* Q1(159.6)	0.92 (0.66–1.27)	Age, time period, height, parity and age at first birth, BMI at age 18 years, age at menarche, family history of breast cancer, history of benign breast disease, menopausal status, alcohol intake, energy, oral contraceptive use, weight gain since age 18 years
McCullough *et al*, 2005	USA	1992–2001	50–74 years	68 567	2855	Total vitamin D >700 *vs* ⩽100 Dietary vitamin D >300 *vs* ⩽100	0.95 (0.81–1.13) 0.89 (0.76–1.03	Age, energy, history of breast cyst, family history of breast cancer, height, weight gain since age 18 years, alcohol use, race, age at menopause, age at first birth and number of live births, education, mammography history, and hormone replacement therapy
Lin *et al*, 2007	USA	1995–2004 (10 years)	⩾45 years	10 578 PRE 20909 POST	276 PRE 743 POST	Total vitamin D ⩾548 *vs* <162 Dietary vitamin D ⩾319 *vs* <142 Vitamin D supplement ⩾400 *vs* none	PRE 0.65 (0.42–1.00) 1.02 (0.69–1.53) 0.76 (0.50–1.17) POST 1.30 (0.97–1.73) 1.22 (0.95–1.55) 0.87 (0.68–1.12)	Age, randomised treatment assignment (aspirin *vs* placebo or vitamin E *vs* placebo), BMI, 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; additionally adjusted for age at menopause, and baseline postmenopausal hormone therapy for postmenopausal women only
Robien *et al*, 2007	USA	1986–2004	55–69 years	34 321 POST	2440	Total vitamin D ⩾800 *vs* <400 Dietary vitamin D ⩾800 *vs* <400 Vitamin D supplement ⩾800 *vs* none	0.89 (0.77–1.03) 0.55 (0.24–1.22) 0.89 (0.74–1.08)	Age, smoking status, age at menarche, age at menopause, first-degree relative with breast cancer, oestrogen use, age at first live births, number of live births, education category, BMI category, activity level, live on a farm, mammogram history, daily energy, fat, alcohol intake
Kuper *et al*, 2009	Sweden	1991–2004 (12.9 years)	30–49 years	41 889	840	Dietary vitamin D Q4 *vs* Q1	0.9 (0.8–1.1)	Age, parity, age at first birth, BMI, age at menarche, use of hormonal contraceptives, consumption of alcohol, breast-feeding, education, family history of breast cancer, physical activity, smoking
Engel *et al*, 2011	France	1993–2005 (10 years)	41.8–72 years	67 721	2871 ALL 618 PRE 2253 POST	Dietary vitamin D >113 *vs* <80	All 0.94 (0.86–1.03) PRE 1.03 (0.85–1.25) POST 0.92 (0.83–1.02)	Age at menopause, age at menarche menopausal status, BMI, physical activity in 1993, parity, previous use of oral contraceptives, use of menopausal hormone therapy, daily calcium intake, current use of calcium supplement, alcohol intake, total energy intake without alcohol, university degree, previous family history of breast cancer, previous personal history of benign breast disease, previous history of mammographic exam, sun burn resistance, skin complexion

Table 1. (Continued)

Source	Country	Follow-up period[a]	Age at baseline	Study subjects	No. of BC cases	Vitamin D Intake (IU day^{-1})[b] highest vs lowest	Relative risk (95% CI)	Adjustment factors
Edvardsen *et al*, 2011	Norway	1997–2007 (8.5 years)	40–70 years	41 758	844	Dietary vitamin D Q4 (832) *vs* Q1(108)	1.07 (0.87–1.32)	Age, age at entry, BMI, height, menopausal status, hormone therapy use, use of oral contraceptives, mothers' history of breast cancer, frequency of mammography, combined parity, age at first birth, daily intake of alcohol, vitamin D dose, sun-seeking holidays, use of solarium, frequency of sun burn
Abbas *et al*, 2013	Europe	8.8 years	50.2 years	319 985	7760	Dietary vitamin D ⩾218.4 *vs* <74	All 1.04 (0.94–1.14) PRE 1.07 (0.87–1.32) POST 1.02 (0.90–1.16)	Age, center, adjusted for nonfat, nonalcohol energy, fat, alcohol consumption, weight, height, smoking status, education level, menopausal status, current use of contraceptives or hormones, physical activity, age at menarche

Abbreviations: BC = breast cancer; BMI = body mass index (kg m^{-2}); CI = confidence interval; POST = postmenopausal; PRE = premenopausal.
[a]Mean or median duration of follow-up in parenthesis.
[b]Vitamin D intake (μl day^{-1}) were converted to IU day^{-1} using the conversion factor, 1 μl day^{-1} = 40 IU day^{-1}.

Table 2. Characteristics of prospective studies included in the meta-analysis of blood 25-hydroxyvitamin D and breast cancer risk

Source	Country	Study type	Follow-up period[a]	Age at baseline	No. of cases/ controls	25(OH)D level (ng ml^{-1})[b]	Relative risk (95% CI)	Adjustment factors
Bertone-Johnson *et al*, 2005	USA	Nested case–control	1989–1996 (6.5–7.5 years)	43–69 years	701/701	Q5 *vs* Q1[c]	0.73 (0.49–1.07)	Age, menopausal status, month of blood collection, time of day of blood collection, fasting status, BMI at age 18 years, parity/age at first birth, family history, history of benign breast disease, postmenopausal hormone use, age at menarche, age at menopause, alcohol intake, plasma α-carotene
Chlebowski *et al*, 2008	USA	Nested case–control	7 years	50–79 years	895/898 POST	<12.96 *vs* ⩾27.04	1.22 (0.89–1.67)[d]	Age, race/ethnicity, latitude of clinical center, venipuncture date, randomisation in the hormone therapy, dietary modification trials, BMI, physical activity, family history of breast cancer, history of breast biopsy, current oestrogen plus progestin use, current oestrogen-only use
Freedman *et al*, 2008	USA	Nested case–control	4–8.5 years	55–74 years	1005/1005 POST (99%)	⩾ 33.7 *vs* <18.3	1.04 (0.75–1.45)	Age, period of blood draw, season of serum collection, BMI, 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, daily dietary calcium intake
McCullough *et al*, 2009	USA	Nested case-control	1999–2005 (6.9 years)	47–85 years	516/516 POST	⩾ 29.28 *vs* <14.68	1.09 (0.70–1.68)	Birth year, year of blood draw, race, season, parity and age at first birth, BMI at blood collection, weight change from age 18 years to blood collection
Rejnmark *et al*, 2009	Denmark	Nested case–control	2003–2007	58 years	142/420	>33.6 *vs* <24	All 0.52(0.32–0.85) PRE 0.38(0.15–0.97) POST 0.71(0.38–1.30)	Unadjusted
Engel *et al*, 2010	France	Nested case–control	1995–2005 (10.5 years)	56.9 years	636/1272 54/90 PRE 472/948 POST	>27 *vs* <19.8	All 0.73(0.55–0.96) PRE 0.37(0.12–1.15) POST 0.80(0.60–1.07)	Age, menopausal status at blood collection, age at menopause, study center, date of blood collection, BMI at the time of blood collection, physical activity, age at menarche, number of children, tobacco status, previous use of oral contraceptives, MHT use (among postmenopausal women only), personal history of mammography, benign breast disease, and previous family history of breast cancer, alcohol consumption, total energy intake without alcohol, calcium and vitamin D dietary and supplement intakes, serum

Table 2. (Continued)

Source	Country	Study type	Follow-up period[a]	Age at baseline	No. of cases/ controls	25(OH)D level (ng ml^{-1})[b]	Relative risk (95% CI)	Adjustment factors
								calcium, PTH, estradiol, progesterone concentrations
Almquist *et al*, 2010	Sweden	Nested case–control	1991–2006 (10–15 years)	57 years	764/764 196/196 PRE 568 POST	⩾42.8 *vs* ⩽28.4	All 0.96 (0.68–1.37) PRE 1.74 (0.84–3.60) POST 0.88 (0.60–1.29)	BMI, educational level, socioeconomic index, alcohol consumption, smoking status, marital status, country of birth, age at menarche, use of oral contraception, number of children, HRT use, quartiles of 25OHD, PTH and calcium, and continuous values of albumin, creatinine and phosphate
Eliassen *et al*, 2011	USA	Nested case–control	1996–2007 (8.5–11.5 years)	32–54 years	613/1218	⩾30.6 *vs* <18.4	1.20 (0.88–1.63)	Age at menarche, BMI at age 18, parity, age at first birth, BMI at blood collection, family history of breast cancer, history of benign breast disease
Amir *et al*, 2012	Canada	Nested case–control	1992–1997 (4.6 years)	⩾35 years	231/856	<12.4 ⩾34.4	1.00 0.86 (0.62–1.21)[d]	Tamoxifen treatment, BMI
Neuhouser *et al*, 2012	USA	Nested case–control	1994–2005 (7–11 years)	50–79 years	310/310 POST	<14.68 *vs* ⩾25.96	1.06 (0.78–1.43)[d]	WHI intervention arm, BMI, physical activity, smoking, mammography within the past 2 years, Gail 5-year risk score, HRT use, alcohol intake
Ordonez-Mena *et al*, 2013	Germany	Cohort	2002–2009 (8 years)	50–74 years	137/5124 POST	Q4 *vs* Q2,3[e] Q1 *vs* Q2,3	1.08(0.72–1.60)[d] 1.39(0.89–2.18)	Age, sex, multivitamin use, Fish consumption less than once a week, red meat consumption less than once a week, daily fruit intake, daily vegetables intake, BMI, scholarly education, physical activity, smoking, family history of cancer
Mohr *et al*, 2013	USA	Nested case–control	1994–2009	39.6 years	600/600 Mostly PRE	⩽14.9 *vs* ⩾35.2	1.19(0.8–1.8)[d]	Unadjusted
Scarmo *et al*, 2013	USA, Sweden (NYUWHS, NSMSC)	Nested case–control	1991–2010	34–65 years (NYUWHS) 40–69 years (NSMSC)	1585/2940 (both cohort) 893/1642 (NYUWHS) 692/1298 (NSMSC) 637/1134 PRE 968/1806 POST	Q5 *vs* Q1	0.94 (0.76, 1.16) NYUWHS 0.90 (0.68, 1.19) NSMSC 1.04 (0.75, 1.45) PRE 0.67 (0.48, 0.92) POST 1.21 (0.92, 1.58)	Age at sampling, age at menarche, age at first birth/parity, family history of breast cancer, BMI, hormone replacement therapy use, alcohol consumption, physical activity, multivitamin use
Kuhn *et al*, 2013	Europe	Nested case–control	1992–2006	35–70 years	1391/1391	>25.2 *vs* ⩽15.72	1.07 (0.85–1.36)	BMI, age at first period, age at first full-term pregnancy, number of full-term pregnancies, breastfeeding, alcohol consumption, smoking status, education level and physical activity

Abbreviations: BC = breast cancer; BMI = body mass index (kg m^{-2}); CI = confidence interval; HRT = hormone replacement therapy; MHT = menopausal hormone therapy; POST = postmenopausal; PRE = premenopausal; PTH = parathyroid hormone; WHI = Women's Health Initiative.

[a]Mean or median duration of follow-up in parenthesis.

[b]Blood levels of 25(OH)D in nmol l^{-1} were converted to ng ml^{-1} using the conversion factor, 1 ng ml^{-1} = 2.5 nmol l^{-1}.

[c]Samples were analysed in three batches: batch 1 (178 cases and 184 controls) between November 1993 and July 1994, batch 2 (279 cases and 286 controls) between October 1999 and June 2000, and batch 3 samples (244 cases and 254 controls) between June and September 2003; quintile cut points for batch 1 were ⩽20, 21–28, 29–33, 34–39, and ⩾40 ng ml^{-1}; for batch 2, ⩽28, 29–34, 35–39,40–47, and ⩾48 ng ml^{-1}; and for batch 3, ⩽18, 19–24, 25–29, 30–36, and ⩾37 ng ml^{-1}.

[d]RRs that used the highest or middle category of 25(OH)D levels as a reference were recalculated using the lowest category as a reference to be included in the meta-analysis.

[e]Cutoff points for season-standardised 25(OH)D quartiles were for winter, spring, summer, and autumn: 30, 35, 45, and 36 nmol l^{-1} 25(OH)D for Q1; and 55, 60, 70, and 61 nmol l^{-1} 25(OH)D for Q3, respectively.

highest *vs* lowest categories of blood 25(OH)D levels are shown in Figures 4 and 5. Among breast cancer patients, women with high blood 25(OH)D levels (>29.1 ng ml^{-1}, mean) were significantly associated with lower mortality from breast cancer ($n = 4$ studies) compared with those who had low blood 25(OH)D levels (<21 ng ml^{-1}, mean) (pooled RR = 0.58, 95% CI: 0.40–0.85; Figure 4). Similarly, for overall mortality, ($n = 6$ studies), the pooled RR for the highest (>27.5 ng ml^{-1}, mean) *vs* lowest (<20.7 ng ml^{-1}, mean) categories of blood 25(OH)D levels was 0.61 (95% CI: 0.48–0.79; Figure 5). No significant heterogeneity among the studies was found in the meta-analyses (breast cancer mortality: $P = 0.25$, $I^2 = 26.7\%$; overall mortality: $P = 0.17$, $I^2 = 35.9\%$). When we excluded one study that did not adjust for BMI (Tretli *et al*, 2012), the pooled RR of overall mortality was 0.67 (95% CI: 0.51–0.90). For the risk of breast cancer recurrence ($n = 3$ studies), we also found a significant inverse association (for >26.9 *vs* <14.7 ng ml^{-1}, mean: pooled RR = 0.61, 95% CI: 0.47–0.80) (data not shown).

Dose-response meta-analysis. For the dose-response analysis of breast cancer risk, 6 and 13 studies were included for the analysis of vitamin D intake and 25(OH)D levels, respectively. The pooled RRs of breast cancer risk for a 100-IU day^{-1} increment in vitamin D intake and 10 ng ml^{-1} increment in blood 25(OH)D levels were 0.99 (95% CI: 0.98–1.00) and 0.98(95% CI: 0.96–1.00), with no significant heterogeneity among the studies. For mortality among breast cancer patients, the pooled RRs for a 10-ng ml^{-1} increment in blood 25(OH) D levels were 0.88 (95% CI: 0.79-0.98) for breast cancer mortality ($n = 3$ studies) and 0.84 (95% CI: 0.78–0.91) for overall mortality ($n = 3$ studies), respectively. No significant

Table 3. Characteristics of prospective studies reporting on the association of circulating 25-hydroxyvitamin D concentrations with mortality from breast cancer or all-cause mortality among breast cancer patients

						Relative risk (95% CI)		
Source	**Country**	**Median follow-up years**	**Age at baseline**	**No. of patients**	**25(OH)D level (ng ml^{-1})[a]**	**BC death (no. of events)**	**Overall death (no. of events)**	**Adjustment factors**
Goodwin *et al*, 2009	Canada	11.6 years	50.4 years	512 early BC	<20 *vs* >28.8	—	1.60 (0.96–2.64)[b] 106	Age, tumour stage, nodal stage, oestrogen receptor, grade
Jacobs *et al*, 2011	USA	7.3 years	51.6 years	1024 stage I-IIIa BC	<10 *vs* $\geqslant 30 < 20$ *vs* $\geqslant 20$	—	1.13 (0.72–1.79)[b] 250	BMI (continuous), ethnicity, intervention group, calcium intake, tumour grade
Tretli *et al*, 2012	Norway	—	35–49 years	251 stage I-IV BC	>34.4 *vs* <20.0	0.42 (0.21–0.82) 82	0.37 (0.21–0.67) 98	Sex, age at diagnosis, season of blood sampling
Hatse *et al*, 2012	Belgium	4.7 years	57.7 years	1800 stage I-III BC	$\geqslant 30$ *vs* <30	0.49 (0.27–0.89) 64	0.53 (0.33–0.86) 134	Age, tumour size, nodal status, tumour grade, ER status, BMI
Villasenor *et al*, 2013	USA	—	9.2 years	585 stage I-IIIa BC	>30 *vs* <20	1.21 (0.52–2.80) 48	0.90 (0.50–1.61) 110	Age at diagnosis, tumour stage, BMI, race–ethnicity/study site, Tamoxifen use, season of blood draw, treatment, physical activity, smoking status
Vrieling *et al*, 2013	Germany	5.3	50–74 years	1920 stage I-IIIa BC (POST)	<14 *vs* $\geqslant 22$	1.72 (1.00–2.96)[b] 107	1.86 (1.22–2.82)[b] 172	Age, study center, season, tumour size, nodal status, metastases, tumour grade, ER/PR receptor, diabetes, cardiovascular disease, mode of detection, smoking status, HRT use at diagnosis

Abbreviations: BC = breast cancer; BMI = body mass index (kg m^{-2}); CI = confidence interval; ER = oestrogen receptor; ER/PR = oestrogen/progesterone; HRT = hormone replacement therapy; POST = postmenopausal.
[a]Blood 25(OH)D levels in nmol l^{-1} were converted to ng ml^{-1} using the conversion factor, 1 ng ml^{-1} = 2.5 nmol^{-1}l.
[b]The RRs of three studies that used the highest category of 25(OH)D levels as a reference were recalculated using the lowest category as a reference to be included in the meta-analysis.

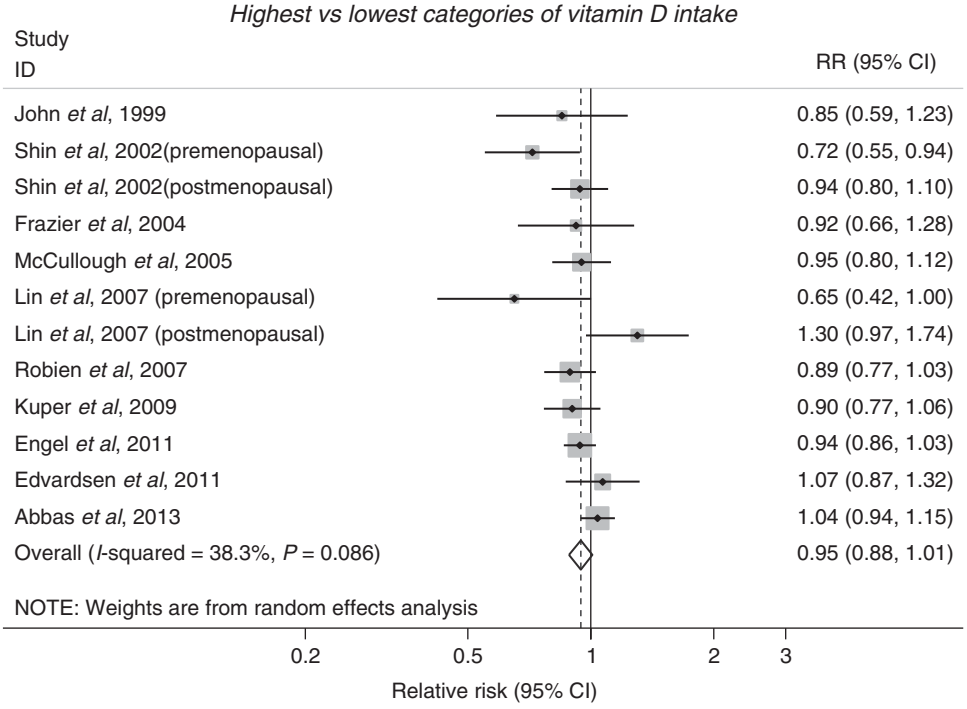

Figure 2. Forest plot of meta-analysis of breast cancer risk in relation to vitamin D intake. Individual studies represented by relative risk (RR) and 95% confidence interval (CI).

heterogeneity among the studies were found (breast cancer mortality: $P = 0.27$, $I^2 = 23.2\%$; overall mortality: $P = 0.31$, $I^2 = 15.0\%$).

Publication bias. There was no indication of publication bias in the literature on breast cancer risk and vitamin D intake (Begg's $P = 0.68$, Egger's $P = 0.33$) or blood 25(OH)D levels (Begg's $P = 0.74$, Egger's $P = 0.46$). For mortality from breast cancer or all-cause mortality among patients, we found no evidence of publication bias either (breast cancer mortality: Begg's $P > 0.99$, Egger's $P = 0.38$; overall mortality: Begg's $P = 0.85$, Egger's $P = 0.90$).

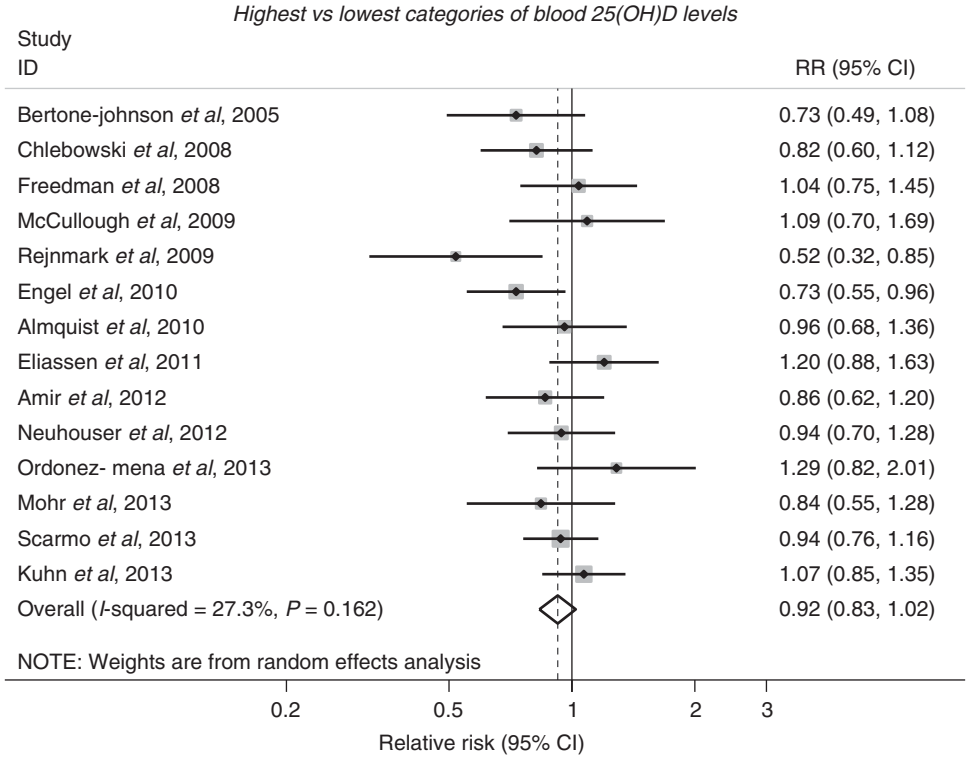

Figure 3. Forest plot of meta-analysis of breast cancer risk in relation to blood 25(OH)D levels. Individual studies represented by relative risk (RR) and 95% confidence interval (CI).

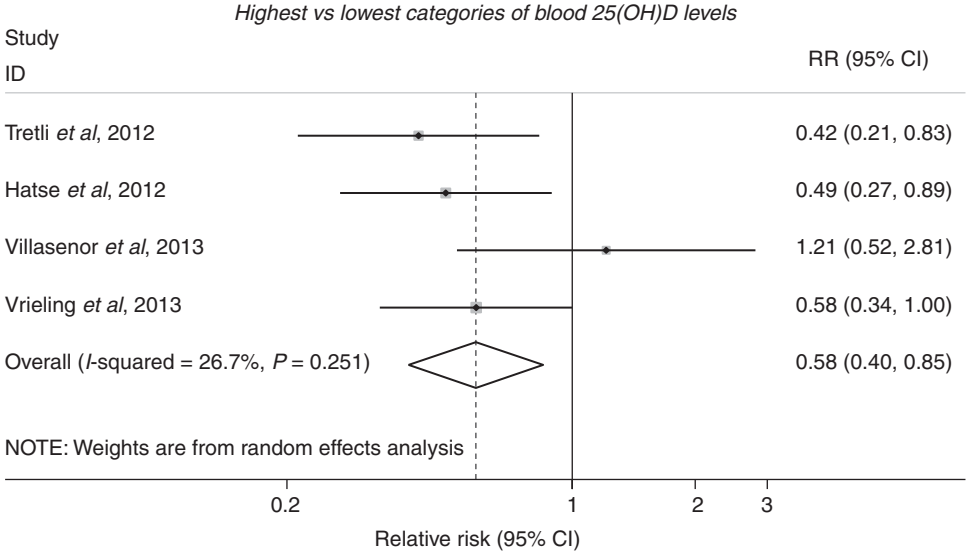

Figure 4. Forest plot of meta-analysis of breast cancer mortality in relation to blood 25(OH)D levels among breast cancer patients. Individual studies represented by relative risk (RR) and 95% confidence interval (CI).

DISCUSSION

The current meta-analysis assessed the association between vitamin D intake/blood 25(OH)D levels and breast cancer risk or mortality based on 30 prospective studies. We found an overall nonsignificant, weak inverse association between vitamin D intake or 25(OH)D levels and breast cancer risk. Among breast cancer patients, however, high blood 25(OH)D levels were significantly associated with low breast cancer mortality. The risk of death from breast cancer decreased by 42% for high ($>29.1\,ng\,ml^{-1}$, mean) *vs* low 25(OH)D levels ($<21\,ng\,ml^{-1}$, mean). Overall, there was no significant heterogeneity among the studies.

Vitamin D can be obtained from foods or supplements, but endogenous production of vitamin D is an important source as well. When our skin is exposed to UV light, Vitamin D_3 is synthesised via the initial conversation of 7-dyhydrocholesterol, and then within 48 h, the liver hydroxylates all vitamin D to 25(OH)D, which has a biological half-life of at least 2 months (Knight *et al*, 2007; Moukayed and Grant, 2013). A biologically active form of vitamin D, $1,25(OH)_2D$, can be produced in many tissues, including the breast as well as the kidney, by 25(OH)D-1α-

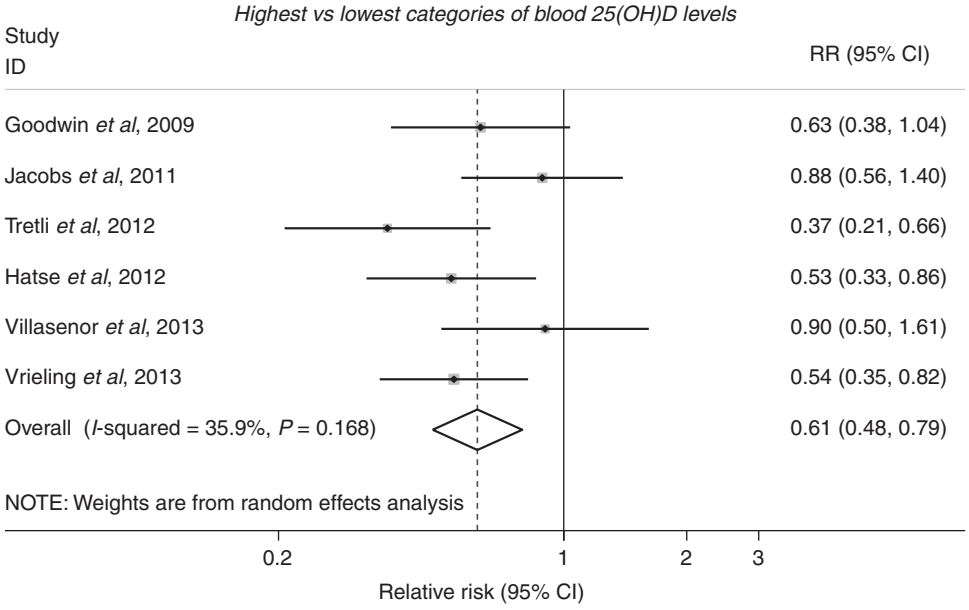

Figure 5. Forest plot of meta-analysis of overall mortality in relation to blood 25(OH)D levels among breast cancer patients. Individual studies represented by relative risk (RR) and 95% confidence interval (CI).

hydroxylase (Zehnder *et al*, 2001). The active hormone has relatively a short half-life (4–6 h) and is tightly regulated by the kidneys to maintain calcium homeostasis. In addition, $1,25(OH)_2D$ levels are often normal or even elevated in vitamin D-deficient patients as a result of secondary hyperparathyroidism (Holick, 2007). Thus, plasma 25(OH)D rather than $1,25(OH)_2D$ is a more appropriate measure to determine vitamin D status for the human body (Holick, 2009). The association of breast cancer risk in relation to high *vs* low vitamin D intake from diet and supplements (pooled RR = 0.95) was slightly weaker than the association with 25(OH)D levels (pooled RR = 0.92) in our meta-analyses, both of which estimates were not statistically significant. As relatively small amounts of vitamin D can be obtained through a limited number of dietary sources such as fatty fish and fortified milk (Knight *et al*, 2007), the effect estimate for disease risk tends to be stronger in studies using blood 25(OH)D than vitamin D intake. A previous meta-analysis of vitamin D intake showed a significant inverse association between high *vs* low vitamin D intake and breast cancer risk (RR = 0.91, 95% CI: 0.85–0.97), but the study included case-control studies that are susceptible to methodological biases (Chen *et al*, 2010), while our results were based on 10 prospective cohort studies. When we conducted stratified meta-analyses according to the source of vitamin D (diet or supplements), the association with supplemental vitamin D intake was slightly stronger (pooled RR = 0.91, 95% CI: 0.84–1.00) than the association with dietary vitamin D intake (pooled RR = 0.96; 95% CI: 0.89–1.03), which was consistent with the previous report (Chen *et al*, 2010). The difference in the risk estimates, however, did not vary by sources of vitamin D substantially (P for difference = 0.33).

The recent meta-analysis of nine prospective studies to examine 25(OH)D levels and breast cancer risk showed a significant inverse association among postmenopausal women (RR per 5 ng ml^{-1} = 0.97, 95% CI: 0.93–1.00) but not among premenopausal women (RR per 5 ng ml^{-1} = 1.01, 95% CI: 0.98–1.04) (P = 0.05 for effect modification) (Bauer *et al*, 2013). In our meta-analysis of 14 prospective studies for 25(OH)D levels and breast cancer risk, additional 6 prospective studies (Neuhouser *et al*, 2012; Amir *et al*, 2012; Kuhn *et al*, 2013; Mohr *et al*, 2013; Ordonez-Mena *et al*, 2013; Scarmo *et al*, 2013) were included, while 1 study conducted on pregnant women was not included (Agborsangaya *et al*, 2010). Our meta-analysis stratified by menopausal status tended to show slightly stronger inverse association among premenopausal women than among postmenopausal women, but the difference did not vary substantially, the tendency of which was similar for the analysis of vitamin D intake as well. The recent pooled analysis of two randomised clinical trials (Lappe *et al*, 2007; Avenell *et al*, 2012) focusing on vitamin D supplementation in breast cancer prevention did not support a role of vitamin D in reducing breast cancer risk in postmenopausal women, which might be due, in part, to dose inadequacy and insufficient study length of the trials to the detection of incident cancer cases (Sperati *et al*, 2013).

We also conducted a meta-analysis after restricting to studies that had adjusted for BMI or physical inactivity, which are well-known risk factors for breast cancer (Key *et al*, 2003; Renehan *et al*, 2008; Steindorf *et al*, 2013; Wu *et al*, 2013). Higher BMI generally means more body fat, and body fatness directly affects levels of serum concentrations of some hormones such as oestrogens, insulin, and insulin-like growth factors, which may facilitate breast carcinogenesis (Key *et al*, 2003). These hormones contribute to the development of breast cancer by stimulating the body's inflammatory response (Howe *et al*, 2013). Physical activity seems to reduce the risk of breast cancer by directly decreasing the levels of serum oestrogens (McTiernan *et al*, 2004) and serum insulin (Borghouts and Keizer, 2000) or through the reduction of body fat. BMI and physical activity were also associated with vitamin D status. People who exercise regularly are more likely to be exposed to sunlight, which elevates blood 25(OH)D levels. Higher BMI has been found to be associated with lower concentrations of blood 25(OH)D levels (Muscogiuri *et al*, 2010; Vaidya *et al*, 2012), which is probably due to decreased bioavailability of vitamin D resulting from deposition in adipose tissue (Wortsman *et al*, 2000; Earthman *et al*, 2012). As BMI and physical activity are potential confounders for the association between vitamin D and breast cancer risk, studies that adjusted for BMI or physical activity can provide more accurate risk estimates to determine the association. The nonsignificant, weak inverse association of vitamin D intake and breast cancer risk that we found in the main analysis tended to be stronger in the secondary analyses of studies that adjusted for BMI or physical activity.

In terms of mortality from breast cancer or all-cause mortality, we found significant inverse associations between vitamin D status and cancer prognosis, which was consistent with the previous report (Rose *et al*, 2013). There are some potential mechanisms through which high blood levels of 25(OH)D may improve survival among breast cancer patients. Vitamin D receptors, which are activated by $1,25(OH)_2D$, control a variety of cellular mechanisms with respect to cancer development such as differentiation, cell proliferation, apoptosis, angiogenesis, and metastatic potential (Welsh, 2004; Mohr *et al*, 2012). Some experimental studies reported that vitamin D analogs suppressed tumour growth in mouse model with breast cancer (Sundaram *et al*, 2003; Lee *et al*, 2008; Ooi *et al*, 2010; So *et al*, 2011). In addition, $1,25(OH)_2D$ inhibited breast cancer cell growth by reducing oestrogen levels (Swami *et al*, 2012), which is achieved through repressing the expression of genes related to oestrogen synthesis (Stoica *et al*, 1999; Swami *et al*, 2000, 2012; Krishnan *et al*, 2010). Another potential anti-cancer activity of vitamin D is related to prostaglandin, which stimulates tumour progression by increasing proliferation and angiogenesis (Wang and Dubois, 2004; Cordes *et al*, 2012). $1,25(OH)_2D$ repressed the expression of cyclooxygenase-2, which has an important role in prostaglandin synthesis (Moreno *et al*, 2005; Krishnan *et al*, 2010). In addition, vitamin D sufficiency seems to suppress down-regulation of E-cadherin, a glycoprotein that helps to keep cells in close contact and thus a well-differentiated state, which occurs in vitamin D deficiency, thereby improving breast cancer prognosis (Berx and Van Roy, 2001; Mohr *et al*, 2012).

Our study has some strengths. This quantitative assessment was based on prospective studies. The design of case-control studies are more prone to methodological biases such as recall bias and selection bias, which limits the strength and quality of the evidence, and our meta-analysis of prospective studies can overcome the shortcoming of the retrospective studies. The included studies in the meta-analysis of breast cancer risk measured vitamin D intake or blood 25(OH)D levels before breast cancer is diagnosed, so that the possibility that cancer status affects vitamin D status can be minimised. Furthermore, we performed a comprehensive meta-analysis of vitamin D related to breast cancer survival as well as breast cancer incidence. In the breast cancer risk analysis, both measurements of vitamin D intake (from food and/or supplements) and circulating 25(OH)D levels were used. We also reported the results of 25(OH)D levels for the risk of breast cancer mortality or overall mortality among breast cancer patients, which has been less thoroughly investigated compared with the analyses of breast cancer risk in healthy women. We found no evidence of either significant heterogeneity among the studies or any publication bias in our meta-analyses, which may suggest that our results are robust.

Despite these strengths, our study also has several limitations. First, some misclassification of vitamin D status may exist, which influences the results of individual studies and thus pooled estimates in this meta-analyses. For the measurements of vitamin D intake or blood 25(OH)D levels, most of the studies included in the meta-analyses used a single measurement at baseline, which could lead to an underestimation of risk estimates. Three studies updated the information about diet during study periods (Shin *et al*, 2002; McCullough *et al*, 2005; Robien *et al*, 2007), which can reduce the possibility of exposure misclassification. There is one study showing that risk estimates tend to be weaker as follow-up period increases (Grant, 2011). It is possible that our pooled estimates would be likely to be stronger if repeated measurement of vitamin D status were available in each study. There was a strong inverse association with vitamin D levels for breast cancer risk among case-control studies (Yin *et al,* 2010; Amir *et al*, 2012; Chen *et al*, 2013), and this may be due, in part, to less exposure misclassification as there was a relatively short time interval between blood collection and breast cancer diagnosis in the design of case-control studies. Nonetheless, we cannot rule out the possibility that lower vitamin D level for the cancer patients was influenced by breast cancer presence and stage among case-control studies where blood was collected after lower breast cancer diagnosis (Chlebowski, 2013). Second, unmeasured or residual confounding may still affect the risk estimates in each study and thus pooled estimates in the meta-analyses, although the majority of studies tried to adjust for important confounders in the multivariable models. When we conducted meta-analyses of studies that adjusted for BMI or physical activity, the inverse association with vitamin D intake tended to be stronger. Third, a relatively small number of studies were included for the analysis of mortality among breast cancer patients, which was due to limited number of data published. Nevertheless, we found a significant inverse association between vitamin D status and breast cancer mortality outcome. Fourth, the cutoffs for high and low vitamin D categories varied among the studies, which is often considered as a limitation inherent in the meta-analysis. However, we found no significant heterogeneity among the studies for high *vs* low vitamin D analyses, and we also conducted a dose-response meta-analysis. Results of a sensitivity analysis excluding one study at a time (e.g., including the exclusion of Almquist *et al* (2010) that used relatively high levels of 25(OH)D as a cutoff in the lowest category) showed that not one single study affected the pooled RR substantially. Finally, our search was restricted to studies published in English, so language bias remains a possibility.

In conclusion, findings from this meta-analysis of 30 prospective studies suggest that high vitamin D status is weakly associated with low risk of breast cancer but strongly associated with better cancer survival among breast cancer patients. As studies consistently report a high prevalence of relatively low 25(OH)D levels in breast cancer patients (Neuhouser *et al*, 2008; Chlebowski, 2013), we may recommend them to increase their vitamin D levels by considering taking a vitamin D supplementation to achieve optimal levels (30–50 $ng\,ml^{-1}$ as recommended by the Institute of Medicine). For every 100 IU of vitamin D, blood 25(OH) D levels increase by 1 $ng\,ml^{-1}$, and most experts agree that a minimum of 1000 $IU\,day^{-1}$ vitamin D is needed to have a preferred healthy level of $>30\,ng\,ml^{-1}$ of blood 25(OH)D, which is difficult to be achieved without supplementation (Heaney, 2008; Heaney *et al*, 2003). As all of the studies included in the meta-analysis were observational and research evidence from clinical trials was limited, current evidence does not support use of high dose vitamin D regimens to get benefits for breast cancer survival. More large randomised clinical trials with sufficient study length and dose adequacy should be conducted to provide definitive evidence and have implications for clinical practice.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final version submitted for publication. YJ developed study concept and design and contributed to critical revision of the manuscript for important intellectual content; YK wrote the manuscript; YK and YJ researched data, conducted the statistical analysis, contributed to discussion and reviewed/edited the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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