Breast Cancer Res Treat
DOI 10.1007/s10549-012-2172-8

LETTER TO THE EDITOR

Dietary calcium intake, vitamin D levels, and breast cancer risk: a dose–response analysis of observational studies

Zhiqiang Hong · Changwei Tian · Xingliang Zhang

Received: 25 June 2012 / Accepted: 13 July 2012

Abstract Results from the recent meta-analysis suggested a favorable effect of dietary calcium and vitamin D levels on breast cancer risk. However, the relationship of dietary calcium and vitamin D levels with breast cancer risk is unclear. Thus, the dose–response relationship was assessed by restricted cubic spline model and multivariate random-effect meta-regression. Results suggested that women might suffer from the lowest risk of breast cancer with dietary calcium intake of about 600 mg/day, dietary vitamin D intake of about 400 IU/day, and serum vitamin D levels of about 30 ng/ml.

Keywords Calcium intake · Vitamin D levels · Breast cancer · Dose–response analysis

To the Editor,

Results from the meta-analysis by Chen et al. in 2010 [1] showed an interesting result that an inverse relation was found between dietary calcium, vitamin D intake, and breast cancer risk [compared to the lowest quantile, the relative risk (RR) for the highest quantile of calcium, vitamin D intake, and serum vitamin D (measured as 25(OH)D levels) is 0.81 (95 %CI = 0.72–0.90), 0.91 (95 %CI = 0.85–0.97), and 0.55 (0.38–0.80), respectively]. And, Yin et al. in 2010 [2], assuming a linear relationship without performing a formal test, also found that the RR for an increase of 25(OH)D by 20 ng/ml is 0.73 (0.60–0.88). This investigation has much practical implication regarding the prevention of breast cancer among women. However, we would like to draw attention to the type of dose–response analysis between dietary calcium intake, vitamin D levels, and breast cancer and the possibility that calcium intake and vitamin D levels might have a threshold effect on the risk of breast cancer because a linear association in epidemiologic research can rarely be assumed a priori [3]. Besides, categories of calcium intake and vitamin D levels differed between studies, which might complicate the interpretation of the pooled results across study populations with different categories. In this respect, a dose–response meta-analysis with restricted cubic spline functions provides a solution to the problem [3] from which a summary risk estimate can be derived for a standardized increase and specific exposure values for calcium intake and vitamin D levels. And, many studies were published for the association of calcium intake and vitamin D levels with risk of breast cancer after 2010.

A comprehensive literature search was performed to Jun 2012 using the databases of Pubmed, Web of Knowledge, China Biology Medical literature database (CBM), Database of Chinese Scientific and Technical Periodicals (VIP), China National Knowledge Infrastructure (CNKI), and Google scholar. Medical Subject Headings (MeSH) were used as the search terms without restriction to MeSH Major Topic, and the search strategy was as follows: *((((“1,25-dihydroxyvitamin D” [Mesh]) OR “Calcium”[Mesh]) OR “Vitamin D”[Mesh]) OR “25-hydroxyvitamin D 2”[Mesh]) AND “Breast Neoplasms”[Mesh]*. In addition, we reviewed the reference lists of all identified relevant publications and relevant reviews.

The number of cases and participants (person-years), and RR 95 %CI for each category of calcium intake and vitamin D levels were extracted. We extracted the RR

Z. Hong · C. Tian (✉)
Kunshan Municipal Center for Disease Control and Prevention, Kunshan 215300, Jiangsu, People’s Republic of China
e-mail: tiancwcdc@126.com

X. Zhang
Hangzhou Center for Disease Control and Prevention, Hangzhou 310021, Zhejiang, People’s Republic of China

Published online: 25 July 2012

(95 %CI) which reflected the greatest degree of control for potential confounders. The median or mean calcium intake and vitamin D levels for each category were assigned to each corresponding RR for every study. If the results were reported for both dietary and total intake of calcium and vitamin D intake, we used the results for total intake. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category.

A 2-stage random-effects dose–response meta-analysis was performed taking into account the between-study heterogeneity proposed by Orsini et al. [4] to compute the trend from the correlated log RR estimates across categories of calcium intake and vitamin D levels. Briefly, a restricted cubic spline model, with 4 knots at the 5th, 35th, 65th, and 95th percentiles [5] of the calcium intake and vitamin D levels, was estimated by generalized least square regression taking into account the correlation within each set of published RRs [6]. Then, we combined the study-specific estimates by the restricted maximum likelihood method in a multivariate random-effects meta-analysis [7]. A P value for nonlinearity and overall significance was calculated by the method proposed by Greenland and Longnecker [8]. All statistical analyses were performed by means of STATA version 12 (Stata Corporation, College Station, Texas, USA). All reported probabilities (P values) were two-sided with $P \leq 0.05$ considered statistically significant.

For dietary calcium intake, data from 10 publications [9–18] were used including 14450 breast cancer cases. A linear relationship was found for calcium intake with risk of breast cancer ($P_{\text{for non-linearity}} = 0.23$, $P_{\text{for overall significance}} < 0.00$), and the RRs (95 %CI) of breast cancer were 0.96 (0.93–0.99), 0.95 (0.91–0.99), 0.93 (0.89–0.98), 0.92 (0.87–0.98), 0.91 (0.86–0.97), 0.91 (0.86–0.96), 0.91 (0.86–0.96), 0.91 (0.86–0.96), and 0.91 (0.86–0.96) for 250, 350, 450, 550, 650, 750, 850, 950 and 1100 mg/day, respectively (Fig. 1).

For dietary vitamin D intake, data from 13 publications [9–13, 15, 16, 19–24] were used including 20,343 breast cancer cases. A nonlinear relationship was found for vitamin D intake with risk of breast cancer ($P_{\text{for non-linearity}} < 0.01$, $P_{\text{for overall significance}} < 0.00$), and the RRs (95 %CI) of breast cancer were 0.98 (0.95–1.00), 0.95 (0.92–0.99), 0.93 (0.89–0.98), 0.92 (0.88–0.96), 0.91 (0.87–0.96), 0.91 (0.87–0.85), 0.90 (0.86–0.95), 0.90 (0.85–0.95), and 0.90 (0.85–0.95) for 50, 100, 150, 200, 250, 300, 350, 500, and 600 IU/day, respectively (Fig. 2).

For serum vitamin D levels, data from 4 publications with 1,25-dihydroxyvitamin D [23, 25–27], and 8 publications with 25-hydroxyvitamin D [25, 28–34] were used including 8,716 breast cancer cases. A nonlinear relationship was found of serum vitamin D levels with risk for breast cancer ($P_{\text{for non-linearity}} < 0.01$, $P_{\text{for overall significance}} < 0.00$), and the RRs (95 %CI) of breast cancer were 0.97 (0.93–1.02), 0.95 (0.88–1.03), 0.92 (0.84–1.02), 0.87 (0.79–0.96), 0.82 (0.75–0.89), 0.78 (0.71–0.85), 0.77 (0.71–0.84), 0.80 (0.75–0.85) for 5, 10, 15, 20, 25, 30, 35, and 40 ng/ml, respectively (Fig. 3).

Overall, this dose–response analysis suggested that women might suffer from the lowest risk of breast cancer with dietary calcium intake of about 600 mg/day, dietary vitamin D intake of 400 IU/day, and serum vitamin D levels of 30 ng/ml. Further researches deserve to confirm the findings and to determine the utility of dietary calcium intake and vitamin D levels for the primary prevention of breast cancer.

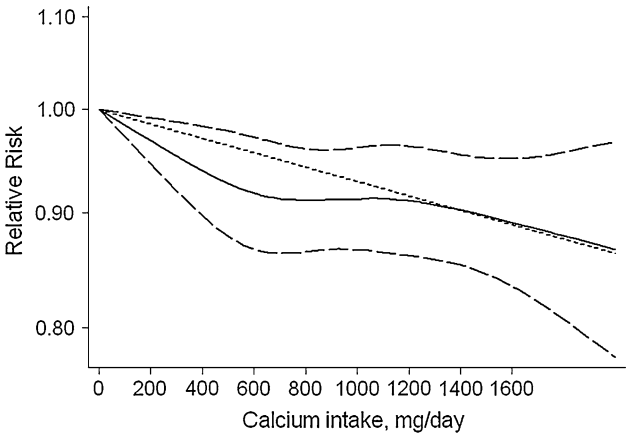

Fig. 1 The dose–response analysis between calcium intake and risk of breast cancer with restricted cubic splines in a multivariate random-effects dose–response model. The *solid line* and the *long dash line* represent the estimated relative risk and its 95 % confidence interval. *Short dash line* represents the linear relationship

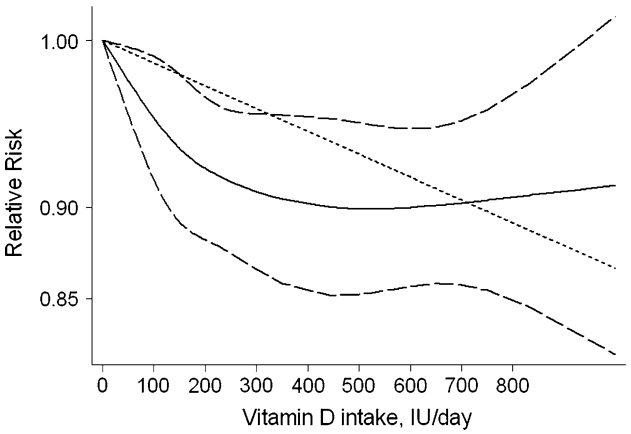

Fig. 2 The dose–response analysis between vitamin D intake and risk of breast cancer with restricted cubic splines in a multivariate random-effects dose–response model. The *solid line* and the *long dash line* represent the estimated relative risk and its 95 % confidence interval of the nonlinear relationship. *Short dash line* represents the linear relationship

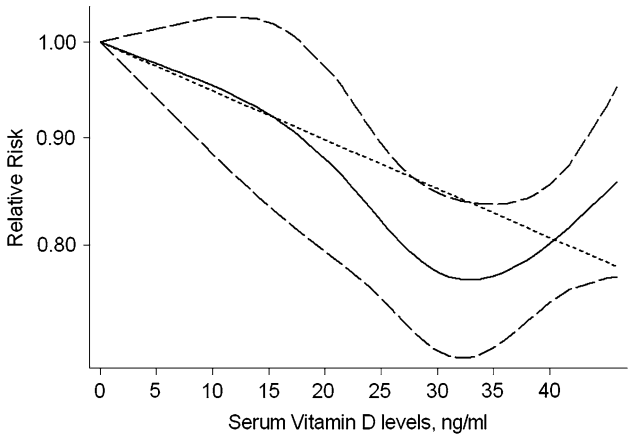

Fig. 3 The dose–response analysis between serum vitamin D levels and risk of breast cancer with restricted cubic splines in a multivariate random-effects dose–response model. The *solid line* and the *long dash line* represent the estimated relative risk and its 95 % confidence interval of the nonlinear relationship. *Short dash line* represents the linear relationship

Conflict of interest None.

References

1. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H (2010) Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat 2:469–477
2. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H (2010) Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 12:2196–2205
3. Desquilbet L, Mariotti F (2010) Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 9:1037–1057
4. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D (2012) Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 1:66–73
5. Durrleman S, Simon R (1989) Flexible regression models with cubic splines. Stat Med 5:551–561
6. Orsini N, Bellocco RSG (2006) Generalized least squares for trend estimation of summarized dose–response data. Stata J 6:40–57
7. Jackson D, White IR, Thompson SG (2010) Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. Stat Med 12:1282–1297
8. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 11:1301–1309
9. Potischman N, Swanson CA, Coates RJ et al (1999) Intake of food groups and associated micronutrients in relation to risk of early-stage breast cancer. Int J Cancer 3:315–321
10. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC (2002) Intake of dairy products, calcium, and vitamin d and risk of breast cancer. J Natl Cancer Inst 17:1301–1311
11. McCullough ML, Rodriguez C, Diver WR et al (2005) Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 12:2898–2904
12. Abbas S, Linseisen J, Chang-Claude J (2007) Dietary vitamin D and calcium intake and premenopausal breast cancer risk in a German case-control study. Nutr Cancer 1:54–61
13. Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM (2007) Intakes of calcium and vitamin D and breast cancer risk in women. Arch Intern Med 10:1050–1059
14. Larsson SC, Bergkvist L, Wolk A (2009) Long-term dietary calcium intake and breast cancer risk in a prospective cohort of women. Am J Clin Nutr 1:277–282
15. Anderson LN, Cotterchio M, Vieth R, Knight JA (2010) Vitamin D and calcium intakes and breast cancer risk in pre- and post-menopausal women. Am J Clin Nutr 6:1699–1707
16. Kawase T, Matsuo K, Suzuki T et al (2010) Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan. Cancer Sci 5:1234–1240
17. Zhang CX, Ho SC, Fu JH, Cheng SZ, Chen YM, Lin FY (2011) Dairy products, calcium intake, and breast cancer risk: a case-control study in China. Nutr Cancer 1:12–20
18. Adams SV, Newcomb PA, White E (2012) Dietary calcium and risk of invasive postmenopausal breast cancer in the VITAL cohort. Cancer Causes Control 6:845–854
19. Robien K, Cutler GJ, Lazovich D (2007) Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. Cancer Causes Control 7:775–782
20. Rossi M, McLaughlin JK, Lagiou P et al (2009) Vitamin D intake and breast cancer risk: a case-control study in Italy. Ann Oncol 2:374–378
21. Engel P, Fagherazzi G, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F (2011) Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3 N cohort. Cancer Epidemiol Biomarkers Prev 1:187–198
22. Lee MS, Huang YC, Wahlqvist ML et al (2011) Vitamin D decreases risk of breast cancer in premenopausal women of normal weight in subtropical Taiwan. J Epidemiol 2:87–94
23. Fedirko V, Torres-Mejia G, Ortega-Olvera C et al (2012) Serum 25-hydroxyvitamin D and risk of breast cancer: results of a large population-based case-control study in Mexican women. Cancer Causes Control 7:1149–1162
24. Rollison DE, Cole AL, Tung KH et al (2012) Vitamin D intake, vitamin D receptor polymorphisms, and breast cancer risk among women living in the Southwestern US. Breast Cancer Res Treat 2:683–691
25. Bertone-Johnson ER, Chen WY, Holick MF et al (2005) Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 8:1991–1997
26. Almquist M, Bondeson AG, Bondeson L, Malm J, Manjer J (2010) Serum levels of vitamin D, PTH and calcium and breast cancer risk-a prospective nested case-control study. Int J Cancer 9:2159–2168
27. Engel P, Fagherazzi G, Boutten A et al (2010) Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. Cancer Epidemiol Biomarkers Prev 9:2341–2350
28. Freedman DM, Looker AC, Chang SC, Graubard BI (2007) Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 21:1594–1602
29. Abbas S, Linseisen J, Slanger T et al (2008) Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer—results of a large case-control study. Carcinogenesis 1:93–99
30. Abbas S, Chang-Claude J, Linseisen J (2009) Plasma 25-hydroxyvitamin D and premenopausal breast cancer risk in a German case-control study. Int J Cancer 1:250–255
31. Crew KD, Gammon MD, Steck SE et al (2009) Association between plasma 25-hydroxyvitamin D and breast cancer risk. Cancer Prev Res (Phila) 6:598–604

32. McCullough ML, Stevens VL, Patel R et al (2009) Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. Breast Cancer Res 4:R64
33. Eliassen AH, Spiegelman D, Hollis BW, Horst RL, Willett WC, Hankinson SE (2011) Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses' Health Study II. Breast Cancer Res 3:R50
34. Neuhouser ML, Manson JE, Millen A et al (2012) The influence of health and lifestyle characteristics on the relation of serum 25-hydroxyvitamin D with risk of colorectal and breast cancer in postmenopausal women. Am J Epidemiol 7:673–684