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Calcium intake and breast cancer risk: meta-analysis of prospective cohort studies

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Abstract

Findings from observational studies have suggested a possible relation between Ca and breast cancer risk. However, the results of these studies are inconclusive, and the dose–response relationship between Ca intake and risk of breast cancer remains to be determined. A meta-analysis of prospective studies was conducted to address these issues. PubMed and Embase databases were searched for relevant studies concerning the association between Ca intake and breast cancer up to March 2016. The summary relative risks (RR) with 95 % CI were calculated with a random-effects model. The final analysis included eleven prospective cohort studies involving 26 606 cases and 872 895 participants. The overall RR of breast cancer for high *v.* low intake of Ca was 0·92 (95 % CI 0·85, 0·99), with moderate heterogeneity ($P=0·026$, $I^2=44·2$ %). In the subgroup analysis, the inverse association appeared stronger for premenopausal breast cancer (RR 0·75; 95 % CI 0·59, 0·96) than for postmenopausal breast cancer (RR 0·94; 95 % CI 0·87, 1·01). Dose–response analysis revealed that each 300 mg/d increase in Ca intake was associated with 2 % (RR 0·98; 95 % CI 0·96, 0·99), 8 % (RR 0·92; 95 % CI 0·87, 0·98) and 2 % (RR 0·98; 95 % CI 0·97, 0·99) reduction in the risk of total, premenopausal and postmenopausal breast cancer, respectively. Our findings suggest an inverse dose–response association between Ca intake and risk of breast cancer.

Key words: Breast cancer: Calcium: Dose–response associations: Meta-analyses

Globally, breast cancer ranks first for cancer incidence and fifth for cancer mortality in women[1]. Dietary and lifestyle factors may have an important role in the development of breast cancer[2–4], among which Ca intake has been suggested as a potential protective factor in mounting experimental research[5–10] and several observational studies[11–13]. A meta-analysis by Chen *et al.*[14] involving six prospective cohorts and nine case–control studies suggested a significant inverse association between Ca intake and risk of breast cancer, with a summary relative risk (RR) of 0·81 (95 % CI 0·72, 0·90) for the highest compared with the lowest intake of Ca, with a significant publication bias. Their results became statistically non-significant after correcting for publication bias. The meta-analysis was followed by several subsequent prospective studies[15–19] that also focused on the same topic, but their findings continued to be inconsistent. To clarify the association between Ca intake and risk of breast cancer, we performed an updated meta-analysis of prospective studies. Given the fact that high amounts of Ca, particularly from supplements, might increase risks of certain diseases, such as CVD[20–24] and kidney stones[25,26], we also attempted to explore the shape of the dose–response association between Ca intake and breast cancer that has not been investigated in the previous meta-analysis.

Methods

Search strategy

This meta-analysis was planned, conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendation[27]. PubMed and Embase databases were searched for studies assessing the association between Ca intake and breast cancer up to March 2016. The following search terms were used to retrieve the relevant literature in the databases: ('calcium' OR 'dairy products' OR 'dairy' OR 'milk' OR 'cheese' OR 'yogurt' OR 'butter' OR 'cream') AND ('breast cancer' OR 'mammary gland cancer' OR 'breast neoplasms' OR 'mammary gland neoplasms' OR 'neoplasm of the breast' OR

Abbreviation: ER, oestrogen receptor; PR, progesterone receptor; RR, relative risk.

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British Journal of Nutrition

'neoplasm of the mammary gland') AND ('cohort' OR 'prospective' OR 'nested case-control' OR 'case-cohort' OR 'observational study'). The search strategy had no language, publication date or publication type restriction. In addition, the reference lists of retrieved full publications and previous meta-analysis were reviewed to complement the search and to identify relevant studies that were missed during electronic database search. We also contacted the authors of the primary studies for further information.

Study selection

To be included in this meta-analysis, the studies had to meet the following inclusion criteria: (a) the study design was a prospective study (including a prospective cohort study, nested case–control study and a case–cohort study); (b) the exposure of interest was Ca intake (dietary and/or supplemental Ca); (c) the outcome of interest was breast cancer incidence; (d) female participants; and (e) risk estimates with corresponding 95 % CI were available. Accordingly, retrospective studies, or studies on breast cancer mortality or recurrence, were excluded. If one study was reported in overlapping publications, the publication containing more detailed information (i.e. reporting data for subgroup or dose–response analyses) was selected.

Data extraction and quality assessment

Using a standardised data-collection form, the following data were abstracted from each study: the first author's last name, publication year, study population, duration of the study, country, length of follow-up, number of cases, dietary assessment method, sources of Ca intake (diet and/or supplement), the multivariable-adjusted risk estimates with their corresponding 95 % CI for each category of Ca intake and statistical adjustment for potential confounding factors. The study quality was assessed using the nine-star Newcastle–Ottawa Scale (NOS)[28], in which each study was judged based on the selection of the study groups, the comparability of the groups and the ascertainment of exposure and outcome. Two investigators (K. H. and G.-C. C.) participated in literature search, study selection and data extraction independently. Any discrepancies regarding inclusion were solved through group discussion.

Statistical analysis

RR was chosen as the common measure of association across this study, and hazard ratio was directly considered as RR. A DerSimonian & Laird random-effects model[29] was used to calculate the summary risk estimates. The degree of heterogeneity in the relationship between Ca intake and breast cancer across studies was assessed using Q and I^2 statistics. For the Q statistic, $P < 0{\cdot}1$ was considered statistically significant, and for the I^2 statistic the following conventional cut-off points were used: <25 % (low heterogeneity), 25–50 % (moderate heterogeneity) and >75 % (severe heterogeneity). Both Begg's rank correlation test and Egger's linear regression test were performed to investigate potential publication bias[30]. If evidence of publication bias was observed, the trim and fill method was applied to correct the bias[31].

To explore potential sources of heterogeneity, subgroup and meta-regression analyses were performed according to geographic region, duration of follow-up, sources of Ca, menopausal status and quality scores. To investigate the impacts of individual studies on the overall results, we also performed a sensitivity analysis by omitting one study in each turn while pooling results from the remainder. We performed a linear dose–response analysis examining the association between Ca intake and breast cancer risk according to the method proposed by Greenland & Longnecker[32] and Orsini *et al.*[33]. This method requires the number of cases and person-years and the risk estimates with their variance estimates for at least three quantitative exposure categories. For the studies that did not provide the number of cases and/or person-years in each exposure category, we estimated these data from the total number of cases and person-years. For each study, the median or mean level of intake for each category was assigned to each corresponding risk estimate. When the median or mean intake per category was not provided, we considered the midpoint of the upper and lower boundaries in each category as average intake. If the highest or lowest category was open-ended, we assumed the width of the interval to be the same as in the closest category. Forest plots of the linear dose–response meta-analysis were presented for RR for each 300 mg/d increment of Ca intake (the unit equivalent to Ca content in 250 ml or one serving of milk). Potential non-linear dose–response relationship between Ca intake and breast cancer risk was examined by modelling exposure levels using restricted cubic splines with three knots at percentiles 10, 50 and 90 % of the whole Ca distribution[34]. The P value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. All statistical analyses were performed using the STATA software, version 11.0 (StataCorp. LP). All P values were two-sided, and the level of significance was at <0·05, unless explicitly stated.

Results

Study characteristics

A flow chart of study selection, including reasons for exclusion, is presented in Fig. 1. We included eleven studies[11–13,15–19,35–37] that fully met our inclusion criteria for this meta-analysis. The characteristics of the included studies are summarised in Table 1. These studies were published between 2002 and 2013, with a total of 26 606 breast cancer cases diagnosed among 872 895 participants. Ten studies were conducted in Western populations (five in the USA, one in Finland, one in France, one in Norway, one in Sweden and one in ten European countries), and one study consisted of Singaporean Chinese. The duration of follow-up ranged from 7 to 25 years. One study[36] was conducted among postmenopausal women only, six studies[12,13,16,17,19,35] reported results by menopausal status and four studies[11,15,18,37] combined premenopausal and postmenopausal breast cancer. One study[37] further reported results by oestrogen receptor (ER) and progesterone receptor

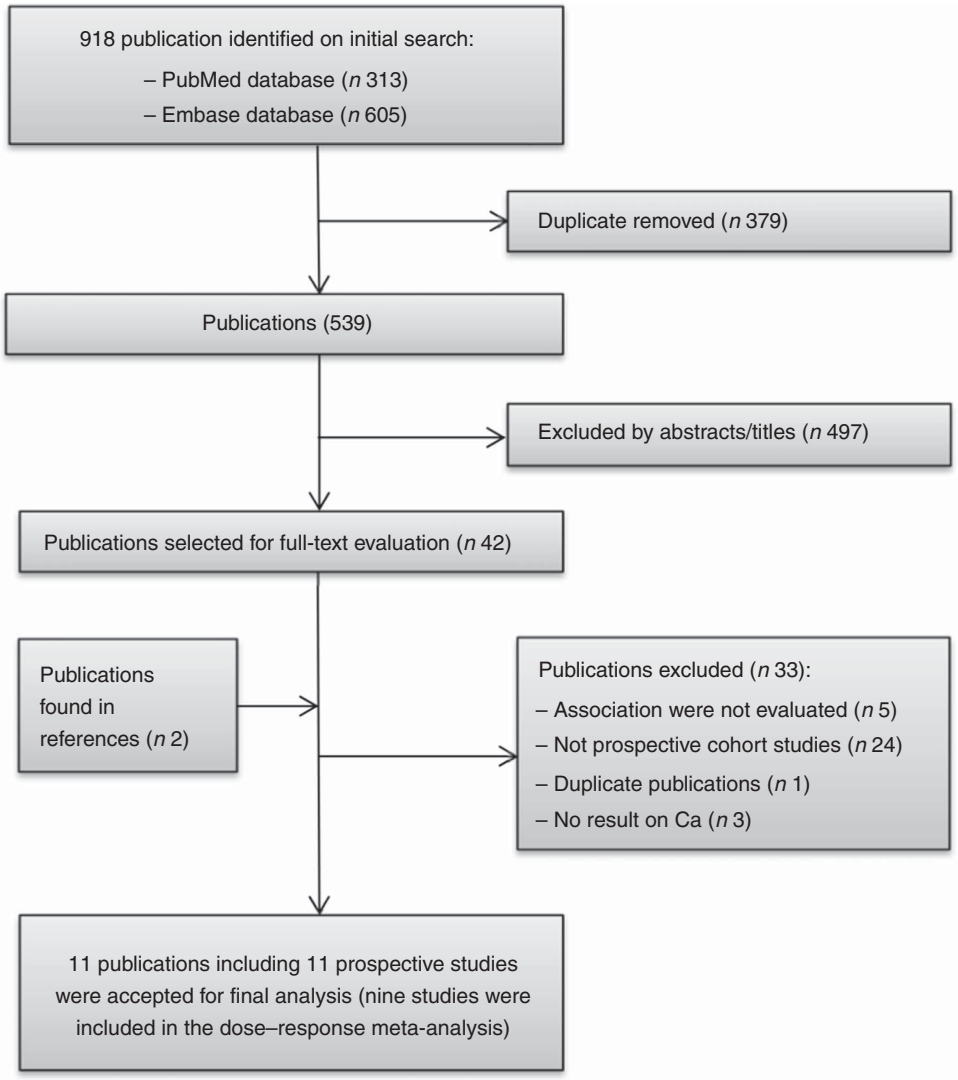

Fig. 1. Flow chart of study selection.

(PR) status of the tumour[37]. Either FFQ or 24-h recall was used as a dietary assessment tool. Ca intakes in the highest categories across studies ranged from >345 to >1750 mg/d, and the intakes in the lowest categories ranged from <203·2 to <807 mg/d. Most individual studies adjusted for a wide range of potential confounding factors, such as age, BMI, family history of breast cancer, hormone replacement therapy use and total energy intake. The details of quality assessment according to the nine-star NOS are presented in the online Supplementary Table S1. Nine of these studies were given scores of ≥7.

Calcium intake and breast cancer risk, high v. low intake

The combined multivariable-adjusted RR for the highest *v.* lowest Ca intake was 0·92 (95 % CI 0·86, 0·99) (online Supplementary Fig. S1), with evidence of moderate heterogeneity ($P=0·026$, $I^2=44·2\%$). Both the Begg's rank correlation test and Egger's linear regression test suggested the presence of publication bias (Begg, $P=0·029$; Egger, $P=0·016$). However, because no missing studies were detected to be filled, the results remained unchanged despite the fact that the trim and fill method was performed to correct the bias.

Subgroup and sensitivity analyses

The results of subgroup analyses stratified by geographic area, duration of follow-up, type of Ca intake, source of Ca, menopausal status and quality scores are presented in Table 2. The inverse association between Ca intake and breast cancer risk was not significantly affected by these factors (P difference >0·130). By menopausal status, the summary RR were 0·75 (95 % CI 0·59, 0·96) for premenopausal breast cancer and 0·94 (95 % CI 0·87, 1·01) for postmenopausal breast cancer. By sources of Ca, the summary RR were 0·93 (95 % CI 0·84, 1·03) for total Ca, 0·90 (95 % CI 0·84, 0·97) for dietary Ca and 0·98 (95 % CI 0·92, 1·03) for supplemental Ca. Few studies[12,35] also reported results for dairy Ca intake, and the summary RR were 0·80 (95 % CI 0·53, 1·21) for dairy Ca and 1·00 (95 % CI 0·78, 1·29)

Table 1. Prospective cohort studies of calcium intake and breast cancer risk (Adjusted relative risks (RR) and 95 % confidence intervals)

References (country)	Study population	Duration of follow-up (years)	No. of cases	Dietary assessment	Type of intake	Comparison	Adjusted RR (95 % CI)	Adjustment
Knekt *et al.*[11] (Finland)	4697 women aged 15–90 years	25	88	Questionnaire	Dietary Ca	High *v.* low	0·44 (0·24, 0·80)	Age, total energy intake and other potential confounding factors
Shin *et al.*[35] (USA)	88 691 women with a mean age of 46·7 years	16	3842	FFQ	Total Ca	>1250 *v.* ≤500 mg/d	PRM: 0·80 (0·58, 1·12) POM: 0·93 (0·77, 1·12)	Age, BMI, physical activity, history of BBD, family history of breast cancer, height change, age at menarche, parity, age at first birth, alcohol intake, total energy and fat intake, glycaemic index value and intake of β-carotene, alcohol, vitamin E
					Dietary Ca	>1000 *v.* ≤500 mg/d	PRM: 0·67 (0·49, 0·92) POM: 0·99 (0·81, 1·21)	
					Supplemental Ca	≥900 mg/d *v.* non-user	PRM: 1·10 (0·81, 1·50) POM: 0·93 (0·81, 1·08)	
					Dairy Ca	>800 *v.* ≤200 mg/d	PRM: 0·69 (0·48, 0·98) POM: 1·11 (0·88, 1·40)	
					Non-dairy Ca	>600 *v.* ≤200 mg/d	PRM: 1·28 (0·91, 1·80) POM: 0·93 (0·75, 1·15)	
McCullough *et al.*[36] (USA)	68 567 postmenopausal women aged 50–74 years	7·8	2855	FFQ	Total Ca Dietary Ca Supplemental Ca	>1750 *v.* ≤500 mg/d >1250 *v.* ≤500 mg/d >1000 *v.* ≤250 mg/d	0·91 (0·79, 1·06) 0·80 (0·67, 0·95) 0·98 (0·86, 1·12)	Age, energy, history of breast cyst, family history of breast cancer, race, height, weight gain, alcohol intake, age at first birth, parity, education, mammography history, and HRT use
Kesse-Guyot *et al.*[12] (France)	3627 women aged 35–60 years	7·7	92	24-h recall	Total Ca	>1144 *v.* <807 mg/d	All women: 0·50 (0·27, 0·91) PRM: 0·26 (0·10, 0·71) POM: 0·76 (0·34, 1·70)	Age, BMI, educational level, parity, marital status, energy from fat and other sources, alcohol intake, family history of breast cancer, menopausal status, smoking status, supplementation, HRT use and consumption of SFA, vegetable, meat
					Dairy Ca	>733 *v.* <422 mg/d	All women: 0·58 (0·32, 1·04) PRM: 0·32 (0·12, 0·82) POM: 0·87 (0·40, 1·92)	
					Non-dairy Ca	>451 *v.* <308 mg/d	All women: 0·76 (0·42, 1·36) PRM: 0·34, 1·67) POM: 0·84 (0·35, 1·98)	
Lin *et al.*[13] (USA)	31 487 women aged ≥45 years	10	1019	FFQ	Total Ca	≥1366 *v.* <617 mg/d	PRM: 0·61 (0·40, 0·92) POM: 1·17 (0·92, 1·50)	Age, BMI, physical activity, family history of breast cancer, history of benign breast disease, age at menarche, age at first birth, multivitamin, smoking, alcohol, total energy intake, age at menopause and baseline HRT use
					Dietary Ca	≥998 *v.* <557 mg/d	PRM: 0·84 (0·57, 1·22) POM: 1·10 (0·86, 1·39)	
					Supplemental Ca	≥500 *v.* 0 mg/d	PRM: 0·71 (0·47, 1·07) POM: 1·05 (0·86, 1·30)	
Park *et al.*[15] (USA)	198 903 women	7	5856	FFQ	Total Ca Dietary Ca Supplemental Ca	1530 *v.* 526 mg/d 1247 *v.* 478 mg/d ≥1000 *v.* 0 mg/d	0·98 (0·90, 1·07) 0·94 (0·86, 1·03) 0·98 (0·91, 1·06)	Race/ethnicity, BMI, age at first birth, number of children, age at menopause, education, marital status, family history of cancer, physical activity, HRT use, smoking, and intakes of red meat, alcohol, fat and total energy
Larsson *et al.*[37] (Sweden)	61 433 women	17·4	2952	FFQ	Total Ca	≥1125 *v.* <727 mg/d	Overall: 0·97 (0·87, 1·09) ER + /PR + tumours: 1·01 (0·85, 1·21) ER + /PR – tumours: 0·97 (0·70, 1·34) ER – /PR – tumours: 0·66 (0·44, 0·99)	Age, education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer, history of benign breast disease and intakes of alcohol, dietary fibre and total energy

Table 1. *Continued*

References (country)	Study population	Duration of follow-up (years)	No. of cases	Dietary assessment	Type of intake	Comparison	Adjusted RR (95 % CI)	Adjustment
Hjartåker *et al.*[16] (Norway)	64 904 women	8·6	1407	FFQ	Dietary Ca	≥814·2 *v.* < 552·6 mg/d	PRM: 0·65 (0·39, 1·08) POM: 0·85 (0·70, 1·04)	Age, energy intake, alcohol intake, height, weight increase since the age of 18 years, level of physical activity, years of education, maternal history of breast cancer, mammography practice, age at menarche, number of children and age at first birth, and use of oral contraceptives
Li *et al.*[17] (Singapore)	35 298 women aged 45–74 years	14·2	823	FFQ	Total Ca	>345 *v.* <203·2 mg/d	PRM: 0·87 (0·59, 1·28) POM: 1·09 (0·86, 1·38)	Age, BMI, dialect group, interview year, education, family history of breast cancer, age when period become regular and number of live births
Genkinger *et al.*[18] (USA)	52 062 women aged 21–69 years	12	1268	FFQ	Dietary Ca	≥1000 *v.* <200 mg/d	1·10 (0·79, 1·53)	Energy intake, age at first menarche, BMI, family history of breast cancer, education, parity and age at first live birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous physical activity and alcohol intake
Abbas *et al.*[19] (ten European countries)	319 985 women	8·8	7760	Questionnaire	Dietary Ca	≥1231 *v.* <635 mg/d	All women: 0·91 (0·83, 1·01) PRM: 0·98 (0·80, 1·19) POM: 0·90 (0·79, 1·02)	Age, centre, non-fat, non-alcohol energy, fat, alcohol consumption, weight, height, smoking status, education level, menopausal status, current use of contraceptives or hormones, physical activity, age at menarche

PRM, premenopausal women; POM ,postmenopausal women; BBD, benign breast disease; HRT, hormone replacement therapy; ER/PR, oestrogen and progesterone receptors.

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Table 2. Subgroup analysis of breast cancer in relation to calcium intake (Relative risks (RR) and 95 % confidence intervals)

Groups	No. of studies	RR	95 % CI	*P**	I^2 (%)	*P*†
Total	11	0·93	0·87, 0·99	0·094	36	
Geographic area						
North America	5	0·95	0·86, 1·04	0·136	38·4	
Europe	5	0·84	0·72, 0·97	0·027	60·5	0·409‡
Asia	1	1·03	0·84, 1·25	0·330	0	0·630‡
Duration of follow-up (years)						
≥10	7	0·93	0·84, 1·03	0·041	48·6	0·704
<10	4	0·88	0·77, 1·00	0·085	51·1	
Type of intake						
Total	6	0·93	0·84, 1·03	0·063	46·1	
Dietary	9	0·90	0·84, 0·97	0·051	43·9	0·467§
Supplemental	4	0·98	0·92, 1·03	0·426	0	0·669§
Source of Ca						
Dairy Ca	2	0·80	0·53, 1·21	0·025	72·8	0·472
Non-dairy Ca	2	1·00	0·78, 1·29	0·193	29·1	
Menopausal status						
Premenopausal	6	0·75	0·59, 0·96	0·048	55·2	0·130
Postmenopausal	7	0·94	0·87, 1·01	0·373	7·3	
Quality scores						
≥7	9	0·93	0·87, 0·99	0·094	36	0·805
<7	2	0·92	0·85, 0·99	0·009	85·4	

* *P* value for heterogeneity among studies.
† *P* value for heterogeneity between groups according to meta-regression.
‡ Studies conducted in the North America as a reference group.
§ *P* Total Ca intake data as a reference group.

for non-dairy Ca. Results of the sensitivity analysis indicated that the overall risk estimates were not dominated by any single study, with summary RR ranging from 0·90 (95 % CI 0·83, 0·98) to 0·93 (95 % CI 0·87, 0·99). The summary RR was 0·91 (95 % CI 0·84, 0·98) after an exclusion of the only Asian study. In addition, one study[37] reported results by ER and PR status of the tumour, and the inverse association of Ca intake with breast cancer risk appeared to be restricted to women with ER-negative and PR-negative tumours (RR 0·66; 95 % CI 0·44, 0·99).

Dose–response analysis

Two studies[11,18] that did not report sufficient data for the dose–response analysis were excluded, and the remaining nine studies were eligible to be included in this analysis. In the linear dose–response analysis (Fig. 2), the summary RR for every 300 mg/d increase in Ca intake was 0·98 (95 % CI 0·96, 0·99, $P_{\text{heterogeneity}} = 0{\cdot}123$, $I^2 = 30{\cdot}8\,\%$) for all women, without evidence of a non-linear relationship ($P_{\text{non-linearity}} = 0{\cdot}17$), although the reduction in breast cancer risk appeared somewhat steeper in the lower range of Ca intake (<800 mg/d) than in the higher range (online Supplementary Fig. S2). By menopausal status (Fig. 2), the summary RR were 0·92 (95 % CI 0·87, 0·98) for premenopausal breast cancer and 0·98 (95 % CI 0·97, 0·99) for postmenopausal breast cancer. By sources of Ca, the summary RR were 0·97 (95 % CI 0·95, 0·98) for dietary Ca and 0·99 (95 % CI 0·97, 1·01) for supplemental Ca (online Supplementary Fig. S3).

Discussion

The present meta-analysis of eleven prospective studies supports an inverse association between Ca intake and breast cancer. Dose–response analysis revealed that each 300 mg/d increase in Ca intake was significantly associated with 2, 8 and 2 % reduced risk of total, premenopausal and postmenopausal breast cancer, respectively.

Although the exact mechanisms by which Ca may reduce the risk of breast cancer remain unclear, the ability of Ca in regulating cell proliferation, differentiation and apoptosis makes it biologically plausible as a potential protective factor against breast cancer[5–7]. Evidence from animal studies suggests that Ca has anti-proliferative and pro-differentiation actions on mammary gland cells of rats fed the high-fat diet, and can reduce the incidence of mammary tumours in rats[8,9]. Much of the evidence indicates that the anti-carcinogenic potential of Ca relies on its interrelation and correlation with vitamin D. However, experimental evidence suggests that an increased level of Ca alone is sufficient to trigger apoptosis[10]. Increased risk of breast cancer has been linked with several chronic diseases such as diabetes, obesity and the metabolic syndrome[38–41], all of which have been suggested to be inversely associated with Ca intake[42–44]. Therefore, Ca intake may indirectly be associated with lower breast cancer risk through its association with these disorders.

With additional five large prospective studies[15–19] included and comprehensive analyses conducted, our findings are generally consistent with those from the previous meta-analysis[14], and thereby further support a potentially beneficial role of Ca in the development of breast cancer. Indeed, a possible U-shaped association between Ca intake and health outcomes has been widely considered[45,46] Numerous studies also suggested that a high intake of Ca, particularly from supplements, may be associated with increased risks of CVD[19–23] and kidney stones[24,25]. Given concerns about adverse risks of ingesting a high dose of Ca on health, the maximum daily Ca intake from

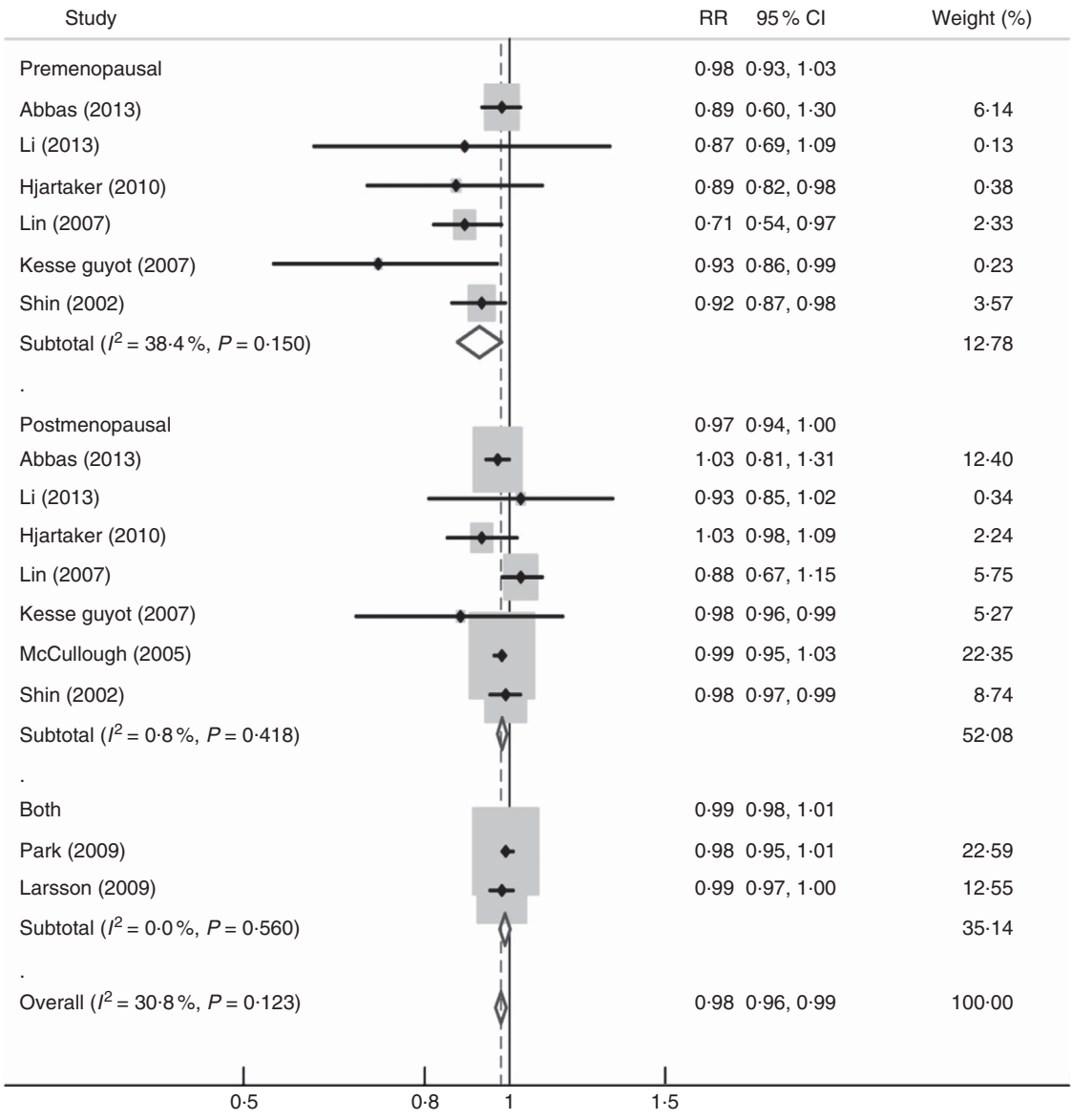

Fig. 2. Dose–response meta-analysis of calcium intake (per 300 mg/d) and breast cancer risk. RR, relative risks.

diet and/or dietary supplement should be carefully considered[47]. Results of our dose–response analysis showed that the inverse association of Ca intake with breast cancer risk remained when the intake was up to 1900 mg/d.

The inverse relation between Ca intake and breast cancer appeared to be stronger in the dietary Ca group (RR 0·90; 95 % CI 0·84, 0·97; *n* 9) than in the supplemental Ca group (RR 0·98; 95 % CI 0·92, 1·03; *n* 6). There were several explanations for these findings. First, it is possible that the interactions between Ca and other nutrient components in diets, such as vitamin D, conjugated linoleic acids and SFA, are necessary for Ca to exert its protection on breast cancer[48]. Second, it is possible that the benefits of Ca may be restricted to the individuals with Ca deficiencies, and Ca supplementation may not bring additional benefits for those who have consumed enough Ca from foods. Third, it is also possible that the observed inverse association may be partly or completely explained by other beneficial nutrients (potential confounders) that share similar food sources with Ca.

Furthermore, the findings from our meta-analysis were consistent with previous meta-analysis showing that inverse association of Ca intake with breast cancer risk is limited to premenopausal women[14]. To date, convincing explanations for the menopause-related difference in the association of Ca intake with the risk of breast cancer have not yet been established. We considered several possible explanations for this difference. First, the complex interactions among Ca, vitamin D and insulin-like growth factors may promote growth inhibition in breast cancer cells[13,49]. Second, Ca may serve as a potential regulator in oestrogen-driven cell proliferation[50]. Third, as Ca inadequacy is more prominent in postmenopausal women[51,52], it is also possible that the beneficial effects of Ca in postmenopausal women might only occur in higher doses.

Strengths and limitations

The present study has several strengths, including incorporated evidence and relevant studies to the date. The enlarged sample size enhanced the power to detect a significant difference and provide more precise estimates of the effects. Most of the original studies included are of long follow-up durations, and all studies used a prospective design, which thereby reduced the likelihood of potential biases (e.g. recall and selection biases). We quantified the association between intake of Ca and risk of breast cancer by carrying out linear and non-linear dose–response analyses. Given the considerably distinct levels of the intake among different populations, a dose–response meta-analysis is necessary in addition to the comparison of the highest *v.* lowest categories of intake.

There are several potential limitations that are worthy of consideration in this meta-analysis. First, there was evidence of publication bias. Although the results did not change after using statistical methods to correct the bias, findings based on evidence of published data should always be interpreted with caution. Second, the strong interrelationship between Ca intake and vitamin D intake makes it difficult to identify the true effects of Ca intake on breast cancer risk as an independent variable in observational studies. Third, the present meta-analysis was unable to assess breast cancer subtypes by hormone receptor status because of the limited studies available. In clinical course of breast cancer, hormonal status is very important for predicting prognosis and efficacy of chemotherapy; thereby, it may also be important to assess whether Ca intake and risk of breast cancer is modified by ER/PR status of the tumour. Fourth, there was moderate heterogeneity across studies. The heterogeneity may be because of the variation in exposure definitions, exposure ranges, dietary assessment methods or population characteristics among studies. Our further analyses indicated that menopausal status was a major potential contributor to the variation in the strength of the association. Finally, although individual studies have considered a wide range of potential confounders in their analyses, the potential impacts of residual/unknown confounding factors on our findings cannot be completely excluded.

Conclusion

In summary, results from this meta-analysis of eleven prospective cohort studies suggest an inverse dose–response association between Ca intake and breast cancer. Additional large prospective studies focusing on the influence of hormone receptor status on this association are necessary to confirm our findings, and such studies would also be helpful for exploring potential mechanisms whereby Ca may reduce breast cancer.

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K. H. and G.-C. C. contributed to the study design, literature search, data extraction and data analyses. K. H. wrote the paper. R. Z. assisted with literature selection. R. Z., X. D. and S.-Y. Z. provided statistical support and created all tables and figures. L.-Q. Q. and B.-M. S. critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

There are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/10.1017/S0007114516001768

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