

Original Article

Calcium channel blockers and risk of breast cancer: a meta-analysis

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Abstract: Purpose: Studies on the association between the use of calcium channel blockers (CCBs) and breast cancer risk have reported inconsistent results. We quantitatively evaluated this association by conducting a meta-analysis based on the evidence from all studies. Methods: We searched PubMed, MEDLINE, EMBASE and the Cochrane Library for relevant studies published up to and including December 15, 2015. We calculated pooled risk ratios (RRs) for breast cancer risk. Results: A total of 24 studies were selected for further study. These studies included 711,479 female subjects, of which 181,492 were CCBs users, who were followed for 3-16 years. The risks of breast cancer among patients receiving CCBs were significantly different for the pooled RRs (95% confidence interval) of cohort studies 1.02 (0.97, 1.07) and case-control studies 1.03 (1.01, 1.06). Differences were also noted for breast cancer risk, for CCBs use of <10 years 1.07 (1.02, 1.11), and for >10 years 1.02 (0.99, 1.04). Conclusions: The long-term use of CCBs appears to have a significant relationship with breast cancer. Well-designed clinical trials are needed to optimize the doses and types of these drugs needed to minimize their carcinogenic potential.

Keywords: Calcium channel blockers, breast cancer, meta-analysis

Introduction

Calcium channel blockers (CCBs) are prescribed primarily for treatment of hypertension and coronary heart disease [1, 2]. CCBs are also used to treat esophageal diseases [3]. These drugs are potent drugs that affect various organ systems, and can cause constipation [4], increase the risk of hemorrhage and cancer [5-7], and impair differentiation during embryogenesis [8]. Furthermore, cases of lupus after use of diltiazem have been reported [9].

CCBs, which can inhibit apoptosis and so facilitate the division of cells with malignant potential [10], have been found to increase breast cancer risk in some studies [11-34]. Nifedipine, one type of CCBs can promote the proliferation and migration of breast cancer cells [35]. Numerous observational studies have suggested that traditional antihypertensive agents, such as calcium channel blockers (CCBs) [36-39] are associated with an increased risk of cancer. Therefore the debate has been fuelled

by conflicting data. We conducted a meta-analysis of observational studies of CCBs, to examine their effect on the occurrence of breast cancer.

In total, the current literature on CCBs and breast cancer incidence is contradictory, incomplete, and based almost completely on observational studies. While observational trials are important in research, they do have inherent selection, publication, and interpretation biases which can impact whether an association is found or not.

Methods

Data sources and search strategy

Observational studies (case-control, nested case-control, and cohort studies) on CCB use and breast cancer risk were included in our meta-analysis, not taking into account language, publication status, or article type. Two investigators conducted a systematic literature search using the electronic databases such as

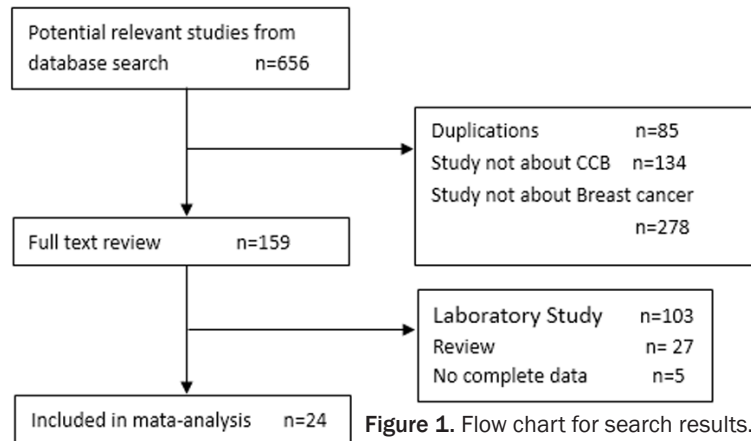


Figure 1. Flow chart for search results.

PubMed, Embase, and Web of Science from their inception to December 15, 2015. Searches were performed using MeSH terms and the free keywords “calcium channel blockers”, “calcium antagonists”, “verapamil”, “diltiazem”, “nifedipine”, “dihydropyridines”, “amlodipine”, “breast cancer”, “breast malignancy”, “breast carcinoma”, and “breast neoplasm”. Additionally, manual searches of references cited in all relevant original and review articles were conducted.

Selection criteria

Eligible studies had to meet the following inclusion criteria: (1) any type of observational study (case-control study, nested case-control study, and cohort study) investigating the relationship between CCB use and risk of breast cancer and (2) a study reporting the relative risk (RR) or odds ratio (OR) and its 95% confidence interval (CI) for the association between CCB use and risk of breast cancer. Studies not documenting cancer incidence, animal or experimentation studies, and mechanistic research studies were excluded. If more than one article reported data from the same population, the recent and most complete articles were included in our meta-analysis. Selection of studies was conducted independently by two investigators.

Data extraction and quality assessment

Data extraction and quality assessment were independently performed by two reviewers. The following information was extracted from each eligible studies: first author's surname, year of publication, source of study population, study

design, sample size, age of study population, follow-up time and estimated effect size (OR or RR), corresponding 95% CI. In cases of studies that reported several multi-variate-adjusted effect estimates, the result that was fully adjusted for potential confounding variables was selected. If a study reported different kinds of CCB use and breast cancer risk, we included the effect resulting from the most prolonged CCB use.

Quality assessment was conducted using the nine star Newcastle-Ottawa Scale (NOS) [40]. We considered studies with a NOS score of seven or more to be high-quality studies. After data extraction and assessment, information was examined and adjudicated independently by an investigator who referred to the original articles.

Statistical analysis

We examined the relationship between CCB use and breast cancer risk on the basis of the adjusted OR and RR and 95% CIs reported in each study. Because the incidence of breast cancer was low, the OR in case-control studies approximated the RR [41, 42]. If there was no evidence of heterogeneity, a fixed-effects model was used to estimate the pooled RRs with 95% CIs; otherwise, a random-effects model was used [43]. With regard to the reference category of no CCB use, the pooled RR and 95% CI of breast cancer risk for CCB use was calculated.

Heterogeneity between studies was evaluated by the χ^2 test and I^2 statistic [44]. Subgroup analyses were performed according to the study design type, study quality level and Follow-up time length. Nested case-control studies and cohort studies were classified into prospective studies, and case-control studies were classified into retrospective studies. We also performed a sensitivity analysis and examined the effect size. The probability of publication bias was assessed with the Egger's regression test [44]. If publication bias existed, we tried to evaluate

Table 1. Characteristic of studies included in the meta-analysis

Study	Year	Country	Study type	Sample size (case)	Age (year)	Follow-up (year)	Study quality*
Pahor M	1996	USA	Cohort	3259 (289)	79.3	5	8
Jick H	1997	UK	Case-control	1096 (221)	71.3	5	8
Olsen JH	1997	Danish	Cohort	17911 (17911)	71	3	8
Fitzpatrick AL	1997	USA	Cohort	2439 (759)	72.4	5	8
Hole DJ	1998	UK	Cohort	2910 (2297)	51.7	16	8
Michels KB	1998	USA	Cohort	16274 (2361)	60.8	6	6
Rosenberg L	1998	USA	Case-control	14866 (1139)	40-69	5	6
Sorensen HT	2000	USA	Cohort	11726 (11726)	66.4	3.2	8
Meier CR	2000	UK	Case-control	12312 (925)	>59	5	8
Li CI	2003	USA	Case-control	936 (290)	65-79	3	8
Gonzalez-Perez A	2004	UK	Case-control	21177 (2531)	30-79	7	6
Fryzek JP	2006	Denmark	Cohort	49950 (4381)	50-67	5.7	8
Davis S	2007	USA	Case-control	1069 (74)	20-74	3	8
Assimes TL	2008	Canada	Case-control	10185 (1019)	71.8	7	8
Largent JA	2010	USA	Cohort	70862 (2873)	<85	10	6
Saltzman BS	2013	USA	Cohort	1675 (392)	≥65	12	8
Li CI	2013	USA	Case-control	1489 (270)	55-74	>10	8
Holmes S	2013	Canada	Cohort	2310 (567)	63	5	8
Soldera SV	2015	UK	Cohort	165815 (107337)	>58	≥10	8
Bergman GJ	2014	Swedish	Case-control	15765 (3143)	55-74	5	7
Chen L	2015	USA	Case-control	661 (352)	40-79	≥3	8
Dovore EE	2015	USA	Cohort	7315 (575)	44-47; >63	16	8
Leung HW	2015	Taiwan	Case-control	14012 (11438)	18-85	>4	6
Azoulay L	2012	UK	Case-control	83973 (8622)	72.4	15	6

*Study quality was judged on the basis of the Newcastle-Ottawa Scale (range, 1-9 stars).

the effect of publication bias by trim and fill method.

Stata software Version 12.0 (Stata Corporation, College Station, TX) was used for all analyses, and all statistical tests were two-sided. $P < 0.05$ was considered to be of statistical significance.

Results

Description of the selected studies

A total of 656 potentially relevant articles were retrieved by our search strategy, and 497 records were excluded because of duplications or no information on CCB use and breast cancer. 159 studies were retained for further evaluation by full texts. Finally, 24 studies were included in this meta-analysis, including twelve cohort studies, twelve case-control studies; the flow chart is shown in **Figure 1**; the general characteristics of each study are listed in **Table 1**.

CCB use and breast cancer risk

As shown in **Figure 2**, the overall RR of the association between CCB use and breast cancer was 1.03 (95% CI 1.01-1.05), with heterogeneity ($P = 0.187$, $I^2 = 20.1\%$) and less obvious publication bias (Egger test $P = 0.046$) (**Figure 3**). In the prospective studies, there was no significant connection between CCB use and breast cancer risk (RR 1.02, 95% CI 0.97-1.07), with no heterogeneity ($P = 0.146$, $I^2 = 30.7\%$) and no publication bias (Egger test $P = 0.070$). Concerning the retrospective studies, their results suggested significant increased risk of breast cancer after use of CCB (RR 1.03, 95% CI 1.01-1.06), with heterogeneity ($P = 0.311$, $I^2 = 13.6\%$) and no publication bias (Egger test $P = 0.195$). We also did sensitivity analyses and not found obvious different study. The effect size based on high quality studies (NOS ≥ 7) was associated with a summary RR of 1.03 (95% CI 0.99-1.07); that based on studies with a long-term follow-up, with a summary RR of 1.02 (95% CI 0.99-1.04).

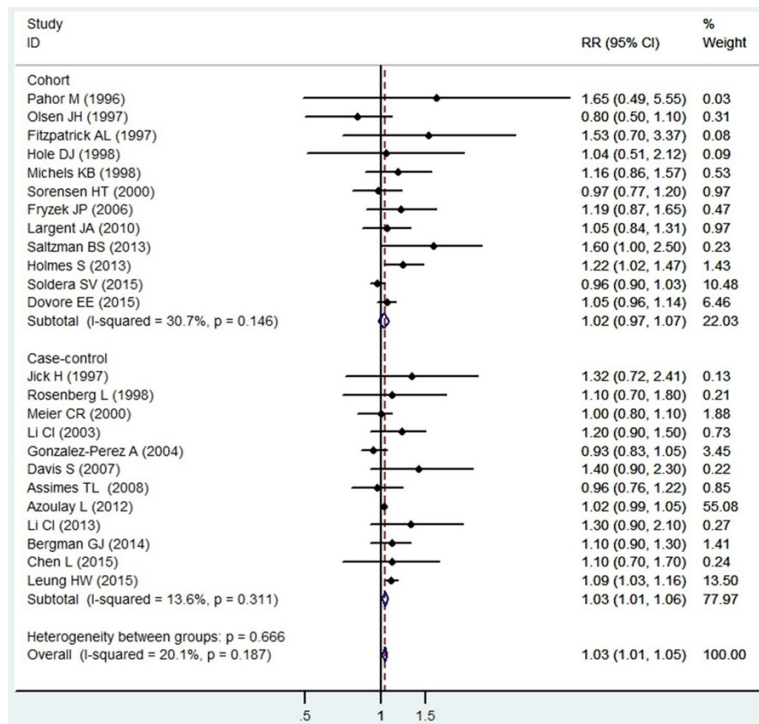


Figure 2. The Forest plot of relative ratios (RR) for breast cancer incidence rate between CCB users and non-users in cohort and case-control studies. Horizontal lines represent 95% CI. The diamond (and dash vertical line) represents the overall RR estimate, with the 95% CI given by its width. The solid vertical line is at the null value (RR=1).

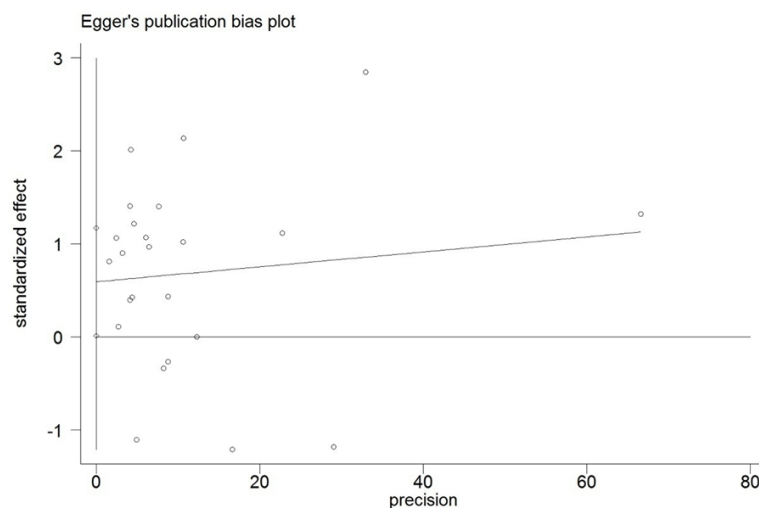


Figure 3. Egger's funnel plot of studies included in the analysis.

Discussion

To the best of our knowledge, this is a new meta-analysis to investigate the association between CCB use and risk of breast cancer. Considering the clinical importance of both

evidence to prove the association between CCB and breast cancer.

Our meta-analysis had several limitations. First, our study was based on aggregate-level data, which may not provide a robust estima-

CCB and breast cancer, we conducted a meta-analysis to investigate the relationship between CCB use and breast cancer in light of conflicting results of several observational studies [11-34]. Our findings show slight significant association between CCB use and risk of breast cancer; long-term use of CCB use may be related to an increased risk of breast cancer.

Although there was no heterogeneity among included studies, it is necessary to assess the possible source of bias that might have led to an inaccurate conclusion. First, extensive long-term observational studies are the best methods to investigate the rare adverse effects of long-term medication use in general population [45]. Second, the increase in breast cancer risk may not be caused by CCB use but rather by the indication for which CCBs are used [46]. Third, observational studies are vulnerable to recall bias, which may lead to under-estimation or over-estimation of the association between CCB use and breast cancer [47]. Finally, the findings of prospective studies and studies with a high NOS score (≥ 7), which were considered to be high-quality studies, suggested there was no significant association between CCB and risk of breast cancer. In short, there is still not sufficient evi-

tion for the association. The quality of our study could not be improved beyond the quality of the individual-level data studies. Second, as a meta-analysis of observational studies, we could not resolve problems arising because of confounding factors that could be inherent in the primary studies included in this meta-analysis. Most of the included studies had adjusted for the age, but other important confounding factors were not standard, such as smoking status, genetic factors and alcohol consumption. Third, the definition of CCB use in the included studies differed among the studies, and this might have caused heterogeneity in our meta-analysis.

Conclusions

In conclusion, the long-term use of CCBs appears to have a significant relationship with breast cancer. These findings provide support for the appropriate use of CCBs for those patients who have potentially increased risk of breast cancer. However, more well-designed clinical trials are needed to determine the effect of CCBs on breast cancer risk, and to optimize the doses and types of these drugs needed to minimize their carcinogenic potential.

Disclosure of conflict of interest

None.

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