1   Calcium channel blockers and breast cancer incidence: an updated systematic review

2   and meta-analysis of the evidence.

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32   Word count: 4,062

33

34 **Abstract**

35 Controversy exists regarding the potential association between taking calcium channel

36 blockers (CCBs) and the development of breast cancer. As a positive association

37 would have important public health implications due to the widespread use of CCBs,

38 this study aimed to incorporate new evidence to determine whether an association is

39 likely to exist. We searched MEDLINE, EMBASE and the Cochrane Library to 28

40 June 2016 for relevant literature. References and citing articles were checked and

41 authors contacted as necessary. Two authors independently selected articles and

42 extracted data. Twenty-nine studies were reviewed; 26 were non-randomised studies

43 (NRS). Meta-analysis of study data where adjustment for 'confounding by indication'

44 was judged to be present suggests that an association, if any, is likely to be modest in

45 magnitude (pooled odds/risk ratio 1.09 (95% confidence interval (CI) 1.03 – 1.15, I^2 =

46 0%, 8 sub-studies; pooled hazard ratio 0.99 (95% CI 0.94 – 1.03, I^2 = 35%, 9 sub-

47 studies)). There are credible study data showing an increased relative risk with long-

48 term use of CCBs, but the results of our meta-analysis and of meta-regression of log

49 relative risk against minimum follow-up time are mixed. The current summative

50 evidence does not support a clear association between taking CCBs and developing

51 breast cancer. However, uncertainty remains, especially for long-term use and any

52 association might not be uniform between different populations and/or breast cancer

53 sub-types. We thus recommend further NRS in settings where CCB use is highly

54 prevalent and population-based cancer, prescription and health-registries exist, to

55 resolve this continuing uncertainty. PROSPERO, CRD42015026712.

56

57 **Keywords:** calcium channel blockers, breast neoplasms, dihydropyridines,

58 amlodipine, nifedipine, verapamil.

59

60   **Highlights**

61   • In 2013 a large case-control study linked long-term calcium channel blocker

62   (CCB) use with breast cancer.

63   • Since then, research groups have conducted studies to confirm/refute this

64   association.

65   • Our systematic review and meta-analysis critically reviewed relevant studies

66   to 2016.

67   • While an association seems unlikely, there remains uncertainty for use beyond

68   10 years.

69   • We recommend further investigation of long-term use to provide further

70   reassurance.

71

1. Introduction[1]

72

73 Calcium channel blockers (CCBs) are considered first-line treatment for hypertension,

74 with a common aim of preventing downstream morbidity and premature mortality (1).

75 In Australia during 2015, amlodipine was the fourth most commonly dispensed drug

76 in the community, with 41.35 doses prescribed/1000 population daily (equating to

77 over 350 million doses annually) (2). Whether CCBs have a role in the development

78 of breast cancer has been a topic of interest to many research groups (editorialised in

79 (3)). With one in eight Australian women by age 85 years diagnosed with breast

80 cancer, and 15,902 Australian women diagnosed with breast cancer in 2013, breast

81 cancer is second only to lung cancer as the most common cause of death from cancer

82 in Australian women (4, p. 86). One study found that in American women 58% of

83 early stage breast cancer patients were prescribed an antihypertensive medication (5).

84 Because of the widespread use of CCBs and the commonly preventive therapeutic

85 aim, ongoing risk assessment is appropriate.

86

87 The hypothesised mechanism for CCBs increasing the risk of developing cancer is

88 through decreased influx of calcium inhibiting apoptosis. The plausibility of this

89 hypothesis was reviewed by Mason (6), who considered studies showing CCB-related

90 inhibited apoptosis of non-cancerous cells (7-10), and others showing the opposite

91 effect (11-14). Despite inconclusive evidence supporting a biological mechanism for

92 breast cancer potentiation by CCBs, observational data supporting an association has

93 continued to emerge. Known risk factors for cancer, such as obesity (15, 16) and

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[1] Abbreviations used in this paper: AHT = antihypertensive drug, CCB = calcium channel blocker, CI = confidence interval, HR = hazard ratio, NRS = non-randomised study, OR = odds ratio, PICOS = population, intervention, comparator, outcome, setting, RCT = randomised controlled trial, SIR = standardised incidence ratio.

5

94 excessive alcohol consumption (17, 18), may confound the association between CCBs

95 and breast cancer, or conversely interact to potentiate breast cancer, in a way difficult

96 to predict via pre-clinical studies or detect through randomised controlled trials

97 (RCTs).

98

99 As this remains a source of controversy, a critical review assessing whether there is an

100 association is warranted. This study aimed to either: confirm whether an association

101 between taking CCBs and developing breast cancer is plausible, or conclude that a

102 definitive answer is not possible at this time and make measured recommendations for

103 further research to resolve continuing uncertainty.

104 # 2. Methods

105 Cochrane guidelines formed the basis of this study design (19); the reporting follows

106 the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement

107 (20).

108 ## 2.1 Protocol and registration

109 On 7 September 2015, a crude PubMed search was conducted: 'calcium AND channel

110 AND blockers AND breast AND cancer'. This search indicated that two meta-

111 analyses have recently been published on the same topic, though no comprehensive

112 and critical systematic review was returned from this search (21, 22). Given the

113 importance of critical appraisal, as well as meta-analysis of the literature, and that

114 there has been progress in this area since 2013 when the searches for these meta-

115 analyses were conducted, we considered there was scope to expand upon existing

116 meta-analyses. A study protocol including study eligibility criteria was registered on

117 PROSPERO on 6 October 2015 (Appendix A), at which time there were no other

118 registered reviews on this topic (CRD42015026712) (23).

119 **2.2 Eligibility criteria**

120 Eligibility criteria followed the population, intervention, comparator, outcome, setting

121 (PICOS) format.

122 **2.2.1 Inclusion criteria**

123 P: the general human population from any setting, or any specified subpopulation (not

124 including studies utilising cell lines, even if human-derived). Even though breast

125 cancer affects predominantly females, there was no restriction placed on sex for this

126 criterion;

127 I: taking a CCB (Anatomical Therapeutic Classification System: C08 (24)), of any

128 sub-class (i.e. (non)-dihydropyridine) or release-type (i.e. immediate- or sustained-

129 release);

130 C: persons not taking a CCB (i.e. taking another class/es of antihypertensive drug

131 (AHT) or no AHT);

132 O: development of newly diagnosed breast cancer of any type or level of severity,

133 however diagnosed or assessed. If cancer overall was reported for a study, this could

134 still be included as long as breast cancer as an outcome in the context of CCB as an

135 exposure had a separate relative risk reported;

136 S: any original research (therefore, not including editorials or commentary where no

137 new data are generated or syntheses performed), regardless of quality.

138 **2.2.2 Exclusion criteria**

139 Systematic or narrative reviews, case studies, case reports or studies without a full-

140 text version in English were excluded.

2.3 Information sources and search strategy

MEDLINE (via OVID), EMBASE (via OVID) and the Cochrane Library were searched from inception to 28 June 2016. Search terms (Appendix B), chosen in consultation with a specialist librarian, included Medical Subject Headings/EMTREE and free-text terms and were grouped into: <terms related to CCBs (e.g. "exp calcium channel blockers/")> AND <terms relating to breast cancer (e.g. "exp breast neoplasms/") > AND <limits to restrict to studies in humans only>. Unduplicated references of included studies and relevant meta-analyses (21, 22) were screened, along with unduplicated citing articles, identified via Web of Science on 28 June 2016. We contacted the authors of eligible conference abstracts, requesting a copy of the conference poster or presentation slides.

2.4 Study selection and data collection

Two authors independently selected articles (CMW & JDH), assessing the title/abstract and then the full-text articles against each eligibility criterion in-turn. Data were extracted by three co-authors (CMW, n = 29, JDH, n = 7, EKC, n=22), using a pre-specified template (based on (25)). Disagreements in article selection or data extraction were resolved through discussion between the two relevant co-authors.

2.5 Synthesis of results

We performed a DerSimonian-Laird random effects meta-analysis (26). Studies were separated into: a) CCB versus no CCB, and; b) CCB versus another AHT, or CCB versus no CCB but with only hypertensive patients analysed, or CCB versus no CCB where adjustment was made for hypertension and/or use of other AHTs. Mutually exclusive sub-cohorts for which relative risks were reported within a single study, or where analyses were only performed separating by breast cancer type, or sub-

165   analysed versus another AHT or in hypertensive patients only, were treated as

166   separate studies. Where studies compared CCBs to no CCBs, adjusted for

167   hypertension/other AHTs and sub-analysed for only those taking AHTs or with a

168   diagnosis of hypertension, the main analysis was included in the CCB versus no CCB

169   meta-analysis (i.e. a)) and the sub-analysis/es included in the CCB versus other AHT

170   meta-analysis (i.e. b)). This meant that analysis/es from a given study most adjusted

171   for 'confounding by indication' was included in the CCB versus other AHT meta-

172   analysis. As there was some question as the suitability of combining such diverse

173   studies, we did not perform further meta-analysis for sub-type of CCB/breast cancer.

174   Studies reporting risk and odds ratios were analysed together, as breast cancer was

175   generally a rare outcome. Studies reporting standardised incidence ratios or hazard

176   ratios were analysed separately to one another and to studies reporting a risk or an

177   odds ratio, as these relative risk measurements communicate different information.

178   The adjusted relative risks reported were used for the meta-analysis, with the standard

179   error back calculated by the mean of the difference between the point estimate and the

180   upper and lower 95% confidence intervals, divided through by 1.96. No studies were

181   excluded based on quality, though this was subject to some sensitivity analysis (see

182   'risk of bias' section below). We performed meta-regression of log-relative risk

183   versus minimum follow-up time in single years, separating studies as described

184   above. Finally, we repeated analyses for studies including female breast cancer only.

185   Heterogeneity was described using the I^2 statistic, where 0% indicates no inter-study

186   heterogeneity up to 100% (27). Publication bias was explored through visual

187   examination of Funnel plots and calculation of the Egger's statistic (28). Analyses

188   were performed using Stata SE (Version 13.1, College Station, Texas), using the

189   metaan command for the meta-analyses (29).

9

190

2.6 Risk of bias

The RTI Item Bank was used to qualitatively assess the risk of bias for both randomised and non-randomised studies (30). The Newcastle-Ottawa scale was used to assess the quality of non-randomised studies, with different criteria for (nested) case-control studies and cohort studies in the areas of selection (four possible stars), comparability (two possible stars), and exposure (three possible stars). In keeping with the authors of one of the 2014 meta-analyses (21), we considered seven or more stars to be 'high quality' (31). The quality of included randomised controlled trials was assessed as very low, low, moderate, or high, using the Grading of Recommendations, Assessment, Development and Evaluation criteria (32). For the meta-analysis some sensitivity analysis was performed removing low quality studies. Risk of bias and quality assessments were undertaken by one author (CMW).

3. Results

3.1 Study selection

Database searching returned 2,099 unduplicated records of which 58 articles underwent full-text review. Twenty articles fulfilled the eligibility criteria (33-52). One conference abstract (53) was excluded after contacting the senior author for this study, who indicated that these data were to be re-analysed prior to writing up the study in full. A further 956 unduplicated articles were identified via reference and citation checking; nine of these fulfilled the eligibility criteria (54-62). For the three eligible records only available as conference abstracts (42, 49, 51), the authors sent a

212 copy of the presentation upon request. Figure 1 details article selection flow.

213 Appendix C lists rejected articles undergoing full-text review.

214 **3.2 Study characteristics**

215 A summary of included study results is provided in Table 1, with full extracted data

216 provided in Appendix D. Studies were published from 1996 through 2016 and

217 included > 1.4 million participants (for some studies the exact participant number was

218 not clear) of varying ages. Not all studies specified the sex of incident breast cancer,

219 but the vast majority of studies (n=21) considered female breast cancer only (34-47,

220 49-52, 57, 58, 61). For example, one study included women aged 55 to 74 years (46),

221 whereas an earlier study had a mean age of 79 years (60). The length of follow-up

222 varied, with some studies conducting a discrete analysis for CCB use exceeding 10

223 years (37, 45, 46, 49, 51). The majority of studies (27/29) used data from Europe or

224 North America, with the exception of two recent studies from Taiwan (35, 44).

225 Twenty-six were non-randomised studies (NRS), utilising nested case-control (33, 35,

226 40, 54, 56), case-control (34, 36, 44-47, 61) or cohort designs (37-39, 41-43, 49-52,

227 55, 58-60). The remainder were RCTs (48, 57, 62). Three sets of studies analysed the

228 same or similar cohort over different time periods ((58) & (37), (38) & (50), (39, 52,

229 59)). Three of the case-control analyses studied a population from he same area (36,

230 45,   46).

Table. F. Summary of included studies (abbreviations not defined in table are defined below).

Study author(s) and year of publication	Setting	Study Design	Number of participants	Main results	Notes, for more details see Appendix C.
Assimes *et al.* 2008 (54)	Saskatchewan Province, Canada Study period 1 January 1980 – 31 December 2003.	Nested case-control CCB (but not thiazide diuretic) versus thiazide diuretic (but not CCB) [ref]	CCB any duration: 92 cases; 927 controls. Thiazide: 972 cases; 9213 controls.	aOR 0.96 (95% CI) 0.76 – 1.22).	• Used population-based registries. • Total use CCB versus thiazide diuretic > 7.5 years – aOR 0.73 (95% CI 0.43 – 1.23)
Azoulay *et al.* 2012 (33)	United Kingdom Study period 1 January 1995 – 31 December 2010.	Nested case-control CCB versus diuretics +/- beta-blockers [ref]	CCB use: 2,070 cases; 21,160 controls. Diuretics +/- beta-blockers: 2,153 cases; 24,426 controls.	aRR 0.98 (95% CI 0.92 – 1.04)	• Used UK General Practice Research Database (GPRD).
Bergman *et al.* 2014 (34)	Sweden Study period 1 January 2006 – 31 December 2011.	Case-control Continuous use (2006 – 10), versus no continuous use [ref]	CCB continuous use: 148 cases; 719 controls. No continuous use: 3,134 cases; 15,765 controls.	aOR 1.1 (95% CI 0.9 – 1.3)	• Used population-based registries. • 95% CI of aOR for duration-response analysis all crossed unity value of 1.
Chang *et al.* 2016 (35)	Taiwan, national coverage. Study period 1 January 2001 – 31 December 2011.	Nested case-control CCB use versus never use [ref]	Main cohort. Any CCB use: 3,529 cases; 10,909 controls. No CCB use: 5,868 cases; 26,679 controls.	aOR 1.39 (95% CI 1.14 – 1.69).	• Used population-based registries. • For sub-cohort of AHT users, aOR = 1.21 (95% CI 0.88 – 1.67). • For sub-cohort diagnosed with hypertension, aOR = 1.71 (95% CI 0.99 – 2.95).
Davis & Mirick 2007 (36)	Seattle, United States Study interviews: March 2000 – December 2001.	Case-control CCB ever user versus CCB never use [ref]	CCB ever use: 38 cases; 36 controls. CCB never use: 509 cases; 560 controls.	aOR 1.4 (95% CI 0.9 – 2.4).	• Questionnaire-based study utilising participants from a case-control study conducted five years previously. Cases originally diagnosed with breast cancer between November 1992 and March 1995. • No clear duration/recency-response trend.
Devore *et al.* 2015 (37)	United States Study period: Assessment of outcome 1 June 1988 – 1 June 2012 for Nurses' Health Study (NHS) cohort; 1 June 1989 – 1 June 2011 for NHS II cohort.	Cohort CCB current use versus past/never us [ref]	**NHS I –** CCB current use: 640 events/144,242 PYs Past/never use: 6,077 events/1,634,906 PYs **NHS II –** CCB current use: 87 events/47,431 PYs Past/never use: 3,025 events/1,925,448 PYs	**NHS I –** aHR 1.07 (95% CI 0.99-1.17) **NHS II –** aHR 0.97 (95% CI 0.78-1.20)	• Questionnaire-based data collection, some of same cohort as earlier study by Michels *et al.* (58). • Restriction to hypertensive women only and assessment of consistency of use yielded aHR with 95% CIs crossing unity value of 1. • For NHS I, aHR of 1.36 (95% CI 1.09 – 1.70) for oestrogen-receptor –ve breast cancer, though 95% CI for aHR for this analysis in NHS II crossed unity value.
Fitzpatrick *et al.* 1997 (38)	United States Study period 1989/90 – December 1994 for original cohort; 1992/93 – December	Cohort CCB use versus no use [ref]	CCB use: 20 events/ 759 participants. No use: 55 events/ 2,439 participants	aHR 2.57 (95% CI 1.47 – 4.49)	• Outcome based on hospital records, exposure based on questionnaire. • aHR 2.91 (95% CI 1.41 – 6) when [ref] is users of other AHTs. • Higher than modal dose has stronger

Study author(s) and year of publication	Setting	Study Design	Number of participants	Main results	Notes, for more details see Appendix C.
	1994 for African American cohort.				association, though clear trend absent. • aHR 4.48 (95% CI 1.58 – 12.75) for CCB + oestrogen use, versus no use of either.
Fryzek *et al.* 2006 (39)	North Jutland, Denmark <u>Study period:</u> 1 January 1989 – 31 December 2002.	<u>Cohort</u> CCB ever use versus never use [ref]	Number of events for CCB ever users/never users, not reported.	aRR 0.80 (95% CI 0.59 – 1.09).	• Used population-based registries. • CCB exclusive use versus never use [ref] – aRR 1.19 (95% CI 0.87 – 1.65).
González-Pérez 2004 *et al.* (40)	United Kingdom <u>Study period</u> January 1995 – December 2001.	<u>Nested case-control</u> CCB use (<1 year, 1-3 years, > 3 years), past use) versus no use [ref]	CCB use <u><1 year:</u> 63 cases; 377 controls <u>1 – 3 years:</u> 66 cases; 419 controls <u>> 3 years:</u> 128 cases; 703 controls <u>Past use:</u> 118 cases; 657 controls	< 1 year & 1 – 3 years: aOR 0.8 (95% CI 0.6 – 1.1) > 3 years: aOR 1.0 (95% CI 0.6 – 1.2) Past use: aOR 0.9 (95% CI 0.8 – 1.2)	• Used the UK GPRD.
Grimaldi-Bensouda 2016 *et al.* (41)	United Kingdom <u>Study period:</u> 1996 – 2009.	<u>Cohort</u> CCB use versus other AHT use [ref]	<u>CCB use:</u> 1,397/457,417 PYs <u>Other AHT use [ref]:</u> 1,194 events/514,400 PYs	aHR 0.95 (95% CI 0.87-1.04)	• Used population-based registries.
Hole *et al.* 1998 (55)	Glasgow, Scotland <u>Study period:</u> 1 January 1980 – 31 December 1995.	<u>Retrospective, cohort</u> CCB use versus no use [ref]	CCB use: 14 events observed; 12.86 expected. No use: 17 events observed; 22.67 expected.	Ratio of RRs – 1.45	• Benchmarked against expected events from population-based registry • No use group also from blood pressure clinic, therefore likely on other AHTs.
Jick *et al.* 1997 (56)	United Kingdom <u>Study period</u>: based on outcome in 1995.	<u>Nested case-control</u> CCB use versus beta-blockers [ref], both +/- diuretics	80 events amongst CCB users; events amongst beta-blocker group not reported.	aRR 1.32 (95% CI 0.72 – 2.41)	• Used the UK GPRD.
Lam *et al.* 2014 (42) [2]	Intermountain West, United States	<u>Prospective, cohort</u> CCB prescription versus no prescription [ref]	General patient cohort Coronary angiography (CV) cohort	GP group: aHR 1.71 (95% CI 1.20 – 2.44) CV group: aHR 0.68 (95% CI 0.37 – 1.25)	• Used healthcare provider database. • Reported relative risks are from conference presentation and differ slightly from abstract (aHR point estimates of 1.58 and 0.51 respectively). • Conference abstract and poster only, event numbers not reported, only relative risks.
Largent *et al.* 2010 (43)	California, United States <u>Study period:</u> 2000 – 31 December	<u>Prospective, cohort</u> CCB regular use within 2 years versus	CCB regular use: 84 events/ 17,208 PYs No regular use:	aRR 1.05 (95% CI 0.84 – 1.31)	• Outcome identified through population-based cancer registry; exposure via questionnaire.

Study author(s) and year of publication	Setting	Study Design	Number of participants	Main results	Notes, for more details see Appendix C.
	2006.	no regular use [ref]	1,630 events/448,175 PYs		
Leung *et al.* 2015 (44)	Taiwan Study period: 1 January 1998 – 31 December 2011.	Case-control CCB use versus no use [ref]	CCB use: 3,411 cases; 9,290 controls CCB never use: 3,052 cases; 9,697 controls	aOR 1.09 (95% CI 1.03 – 1.16)	• Used population-based insurance database. • Study included only hypertensive patients. • Evidence of a duration-response effect, some evidence of a dose-duration effect.
Li *et al.* 2003 (45)	Seattle – Puget Sound, United States Study period: outcomes from 1 April 1997 – 31 May 1999.	Case-control CCB ever use versus never use of AHTs [ref]	CCB use: 149 cases; 141 controls. Never use: 446 cases; 490 controls.	aOR 1.2 (95% CI 0.9 – 1.5)	• Outcome data via population-based registry, exposure information via participant interviews. • Evidence of association with use of immediate-release CCBs and breast cancer. • No association overall (lower 95% CI of OR crosses unity) in sub-analysis restricting to ever users of AHTs.
Li *et al.* 2013 (46)	Greater Seattle, United States Study period: Outcomes 1 January 2000 – 31 December 2008.	Case-control Current CCB use versus never use [ref]	**Invasive ductal:** CCB use: 94 cases; 74 controls Never use: 477 cases; 456 controls **Invasive Lobular:** CCB use: 102 cases; 74 controls Never Use: 556 cases; 456 controls	**Invasive ductal:** aOR 1.3 (95% CI 0.9 – 1.8) **Invasive Lobular:** aOR 1.3 (95% CI 0.9 – 1.8)	• Outcome data via population-based registry, exposure data via participant interview. • Evidence of duration-response relationship, especially with use ≥ 10 years: aOR 2.4 (95% CI 1.2 – 4.9) for **invasive ductal** and 2.6 (95% CI 1.3 – 5.3) for **invasive lobular** breast cancer. Also the case when analysis restricted to women using AHTs only and when separating into subclasses (non/dihydropyridine, long/short acting). • For use ≥ 10 years oestrogen receptor-positive breast cancer **invasive ductal** aOR 2.3 (95% CI 1.1 – 4.8) **invasive lobular** aOR 2.6 (95% CI 1.3 – 5.2), oestrogen receptor-negative **invasive ductal** aOR 3.1 (1.1 – 8.8), **invasive lobular** not reported.
Lindholm *et al.* 2001 (57)	Sweden Recruitment from 1 September 1992 – 31 December 1998, with mean 5 years follow-up.	Randomised, controlled trial CCB (felodipine or isradipine, both 2.5 – 5mg daily) versus expected incidence for Swedish population	19 cases observed; 22.54 expected.	Standardised incidence ratio (SIR): 0.84 (95% CI 0.51 – 1.32)	• Note previous history of breast cancer was not an exclusion criterion for this trial, with authors conducting a sub-analysis to exclude these participants yielding similar results (data not shown). • SIRs adjusted for age, sex and calendar year.
Meier *et al.* 2000 (47)	United Kingdom	Case-control	CCB use:	aOR 1.0 (95% CI 0.8 –	• Used the UK GPRD

Study author(s) and year of publication	Setting	Study Design	Number of participants	Main results	Notes, for more details see Appendix C.
	Study period: outcomes 1 January 1992 – 30 September 1997.	CCB use versus use of neither CCB, ACEI, or beta-blocker [ref]	190 cases; 735 controls No CCB/ACEI/beta-blocker: 2,567 cases; 9,745 controls	1.1)	• Duration-response analysis yielded aOR of: 1.0 (95% CI 0.8 – 1.3) for 1 – 2 years; 1.0 (95% CI 0.6 – 1.6) for 3 – 4 years and; 0.9 (95% CI 0.7 – 1.2) for ≥5 years. • CCB subclass analysis, all 95% CI crossed unity value of 1.
Michels *et al.* 1998 (58)	United States Study period: 1988 – 1 May 1994.	Prospective, cohort CCB use versus no use [ref]	CCB use: 51 events/ 11,807 PYs No use: 304 events/ 82, 524 PYs	aRR 1.07 (95% CI 0.78 – 1.48)	• Questionnaire-based study, some of the same cohort as later study by Devore *et al.* (37).
Olsen *et al.* 1997 (59)	North Jutland, Denmark Study period: 1 January 1991 – 31 December 1993.	Cohort CCB prescription versus population expected incidence.	32 cases observed; 40.3 expected	SIR 0.8 (95% CI 0.5 – 1.1)	• Used population-based registries.
Pahor *et al.* 1996 (60)	United States Study period: 1988 – 31 December 1992.	Prospective, cohort CCB use versus no use [ref]	CCB use: 31 events	aHR 1.65 (95% CI 0.49 – 5.55)	• Outcome/exposure assigned via interview, outcome confirmed against medical records.
Poole-Wilson *et al.* 2006 (48)	Nineteen countries	Randomised controlled, trial Nifedipine GITS versus placebo [ref]	Nifedipine GITs: 16 events/ 3,655 patients for rate = 0.09 Placebo: 8 events/3,654 patients for rate of 0.04	HR ~ 2.25, 95% CIs not reported though cross 'unity' value of 1.	
Raebel *et al.* 2015 (49) [2]	United States Study period: 1997 to 30 April 2013	Retrospective, cohort **For conference abstract:** CCB use > 1 year versus CCB use < 1 year [ref] **For presentation:** CCB versus ACEI use [ref]	29,830 taking a CCB, Amongst CCB group, 572 (1.9%) with breast cancer.	**From abstract:** At 9 years, aHR 1.09 (95% CI 0.6 – 2) At 12 years, aHR 0.88 (95% CI 0.28-2.78). **From presentation:** Cox Regression aHR 1.02 (95% CI 0.93-1.12) Discrete time survival aHR 0.91 (95% CI 0.83-1.00)	
Rosenberg *et al.* 1998 (61)	United States Study period: 1983 – 1996.	Case-control CCB use versus never use [ref]	CCB use: 92 cases; unclear how many controls. Never use: unclear number of cases/controls	aRR 1.1 (95% CI 0.8 – 1.4).	• Hospital-based controls used. Outcome data from discharge summaries/pathology reports; exposure data via interview.
Sajadieh *et al.* 1999	Denmark	Randomised	2 cases observed; 2.5	SIR 0.4 (95% CI 0.1 – 2.9)	• SIRs adjusted for age, sex and calendar year.

Study author(s) and year of publication	Setting	Study Design	Number of participants	Main results	Notes, for more details see Appendix C.
(62)	Study period 1985 – 31 December 1993.	controlled, trial Verapamil use versus Danish population [ref]	expected		• SIR for placebo group (1 observed; 2.5 expected) of 0.4 (95% CI 0.01 – 2.2)
Saltzman *et al.* 2013 (50)	United States Study period 1989/90 – 31 December 2001 for original cohort; 1992/93 – 31 December 2001 for African American cohort.	Prospective, cohort CCB 'ever use' versus never use of AHTs [ref]	CCB use: 55 events/9,916 PYs Never use of AHTs: 69 cases/ 14,081 PYs	aHR 1.1 (95% CI 0.7 – 1.6)	• Outcome assigned via population-based registry, exposure via interview and label checking. • For use in past 2 years, aHR 1.6 (95% CI 1.0 – 2.5) for all types of CCB; 2.4 (95% CI 1.3 – 4.5) for immediate-release and 1.4 (95% CI 0.8 – 2.3) for sustained-release.
Soldera *et al.* 2015 (51) [2,3]	United Kingdom Study period: to 31 December 2010.	Cohort CCB versus use of other AHTs [ref]	CCB use: 1,518 events/491,768 PYs Other AHTs: 3,002 events/1,075,336 PYs	aHR 0.98 (95% 0.92 – 1.04)	• Used UK Clinical Practice Research Data link. • Duration-response analysis (from presentation): <5 years, aHR 0.96 (95% CI 0.90 – 1.03); 5 – 10 years, 1.05 (95% CI 0.9 – 1.22); > 10 years, 0.61 (95% CI 0.32 – 1.20)
Sorensen *et al.* 2000 (52)	North Jutland, Denmark Study period: 1 January 1989 – 31 December 1995.	Cohort CCB prescription (>2) versus Danish Population [ref]	84 cases observed; 86.7 cases expected	SIR 0.97 (95% CI 0.77 – 1.20)	• Used population-based registries.

232   1.   Abbreviations: ACEI = Angiotensin-converting enzyme Inhibitor, AHT = antihypertensive drug(s), aOR = adjusted odds ratio, aHR = adjusted hazard ratio, aRR = adjusted relative risk, CCB = calcium channel blocker,
233   CI = confidence interval, GITS = gastro-intestinal therapeutic system, HRT = hormone replacement therapy, NSAIDs = non-steroidal anti-inflammatories, PY = person-year.
234   2.   Available as a conference abstract only and author-forwarded presentation only.
235   3.   Full paper indexed after the latest database search update for this review (63); the main results are unchanged from the abstract.

236   While some studies specifically focused on the risk of breast cancer associated with CCB use

237   (34, 38, 42, 47, 49, 51), the remainder either explored the risk of breast cancer or cancer

238   overall associated with AHTs, or the risk of cancer overall associated with CCBs. Older

239   studies tended to include more patients taking immediate-release/short-acting CCBs, as

240   prescribing trends changed to include more sustained-release/longer-acting CCBs in newer

241   studies. Data collection sources included population-based registries (e.g. UK General

242   Practice Research Database (33, 40, 47, 56)), or interview/questionnaires. The choice of

243   comparator group was generally non-users of CCBs. For some studies the reference group

244   was another type/s of AHT (e.g. relative to thiazide diuretics in (54)). In others, hypertension

245   or use of AHTs was adjusted for in the analysis (40) and/or a sub-analysis was conducted

246   restricting to only participants with hypertension and/or taking AHTs (35, 37, 38, 45, 46, 50).

247   **3.3 Results of individual studies**

248   The majority of included studies found no association between CCB use and breast cancer,

249   beyond that which could be explained through chance (33-35, 39-41, 43, 47-49, 51, 52, 54-

250   62). In contrast, the findings of eight studies suggested a positive association between CCB

251   use and breast cancer, to varying degrees (36-38, 42, 44-46, 50). Those with earlier study

252   periods included mainly immediate-release/ short-acting CCBs that are no longer widely used

253   in contemporary practice (36, 38, 45). Two more recent studies found an association for one

254   sub-cohort within the analysis, which could not be reproduced for other sub-cohorts in that

255   same study (37, 42). Analysis of data from the Cardiovascular Health Study suggests that

256   recent use of CCBs, particularly immediate-release CCBs, may be associated with an

257   increased rate of breast cancer relative to no AHT use (50). The only data from outside North

258   America and Europe were from Taiwan, with the two studies covering a similar population

259   producing conflicting findings, one finding an association (44) while the other did not (35).

260

261   Authors of a recent study from Seattle reported an adjusted odds ratio (OR) for developing

262   invasive ductal or lobular cancer respectively of 2.4 and 2.6, for use of CCBs for ≥10 years

263   relative to never use (46), an association which remained when restricting to only users of

264   AHTs.

265   **3.4 Synthesis of results**

266   Two studies were excluded from the meta-analysis as standard errors could not be calculated

267   (48, 55). The pooled odds/risk ratio for the CCB versus no CCB was 1.14 (95% CI 1.04 −

268   1.25, I^2 = 15%, n = 8 studies/sub-studies (34-36, 45-47, 61), the same for female only

269   studies); the combined hazard ratio was 1.02 (95% CI 0.88 − 1.17, I^2 = 49%, n = 9

270   studies/sub-studies (37-39, 42, 43, 50, 60): 1.02 (95% CI 0.87 − 1.17) for female only

271   studies), and; the combined SIR was 0.90 (95% CI 0.74 − 1.05, I^2 = 0%, n = 4 studies (52, 57,

272   59, 62): 0.94 (95% CI 0.75 − 1.13 for female only). For the CCB versus other AHT meta-

273   analyses (Figures 2 and 3) the pooled odds/risk ratio was 1.09 (95% CI 1.03 − 1.15, I^2 = 0:

274   1.10 (95% CI 1.04 − 1.16) for female only studies) and the pooled hazard ratio was 0.99

275   (95% CI 0.94 − 1.03, I^2 = 35%: 0.99 (95% CI 0.94 − 1.05) for female only studies). There

276   was an inconsistent duration-response relationship for the CCB versus other AHT meta-

277   regression. The log relative risk against minimum follow-up time for log odds/risk ratio had a

278   regression coefficient 0.047 (95% CI 0.007 − 0.086, p = 0.02, 5 studies/sub-studies (35, 40,

279   45, 46, 54): 0.06 for female only studies), whilst for log hazard ratio, only one study was

280   included (51), and no duration-response effect was seen (regression coefficient = 0.006, 95%

281   CI -0.024 − 0.036, p = 0.703: 0.006 for female only studies). Visual examination of funnel

282   plots suggested some asymmetry, as higher positive relative risk estimates tended to a higher

283   standard error. The Egger's statistic for CCB versus no CCBs with odds/risk ratios supported

284   this (bias regression coefficient, 1.82, 95% CI 0.21 − 3.43, p = 0.033), while there was only

285   weak quantitative evidence of potential reporting bias for the other meta-analyses.

286 **3.5 Risk of bias**

287 All risk of bias assessments are provided in Appendix E. Overall, the risk of selection bias

288 arising due to factors such as differential follow-up or different selection criteria for

289 compared groups was assessed as low. Recall bias was more of an issue for studies using

290 questionnaires/interviewers to collect data, than for studies using population-based registries.

291 In some cases, aids were used to reduce the risk of misclassification such as using tablet

292 bottles as a visual aid (e.g. (46)) and several studies used more objective measures to assign

293 outcome (e.g. checking health records in (60)). The risk of 'confounding by indication' was

294 reduced when only hypertensive patients were included, when analyses were adjusted for or

295 conducted separately for women using AHTs and/or with hypertension, but this did not

296 always occur. Relatively few studies accounted for latency in development of cancer, where

297 exposure would be expected to precede outcome, though this was explored in several cases

298 via duration-response analysis.

299

300 The quality assessments detailed in Appendix F indicated that four of the studies were of

301 'low quality' (38, 43, 58, 61). Sensitivity analysis via removing these studies from the meta-

302 analysis did not change the pooled risk ratios reported above markedly. The amended pooled

303 odds/risk ratio for the CCB versus no CCB was 1.16 (95% CI 1.04 – 1.29, $I^2 = 27\%$), while

304 the combined hazard ratio was 1.02 (95% CI 0.84 – 1.20, $I^2 = 55\%$). For the pooled SIR and

305 the CCB versus other AHT meta-analyses the results were unchanged.

306 # 4. Discussion

307 This review is unable to definitively refute an association between taking CCBs and

308 developing breast cancer, especially for use beyond 10 years. This was a thorough systematic

309 review, in which data have been analysed quantitatively and interpreted taking study biases

310   into account. Thus while a definitive answer to the study question was not made possible by

311   the published literature to date, our study does comprehensively assess the present 'state of

312   play' for this question and does provide some reassurance that an association with short-term

313   use seems reasonably unlikely. In highlighting continuing uncertainty, we recommend the

314   controversy be resolved by further investigation through population-based NRS. It is

315   reassuring that the majority of the 29 reviewed studies found no important association.

316   However, the strong positive association (adjusted odds ratio >2 for use beyond ten years)

317   and that some duration-response relationship is shown are noteworthy in one recent study

318   (46). This study had differential response rates (80% for cases, 69% for controls), relatively

319   small case numbers and the finding has not yet been subsequently clearly replicated

320   elsewhere ((35, 37, 49, 51) and subsequent to database searching (64)). Our meta-analysis of

321   study data where an attempt was made to correct for 'confounding by indication' suggests

322   that an association, if any, is much lower in magnitude. The pooled odds/risk ratio of 1.09 in

323   our meta-analysis is largely attributable to a single study (weighting of 82% (44)) and the

324   pooling of hazard ratios suggests no association exists. Assessing the result had this single

325   study not been included yields a pooled risk ratio closer to unity (1.08, 95% CI 0.95 – 1.22, I^2

326   = 0%), though it should be noted that this study seemed to have a reasonably low risk of bias

327   (see Appendix F).

328

329   Two meta-analyses on this topic were published during 2014 (21, 22). One group (21)

330   reported a pooled OR of 1.11 (95% CI 0.93 to 1.33) for taking CCBs and developing breast

331   cancer, with a pooled OR of 1.88 (95% CI 1.37 to 2.60) for immediate-release CCBs.

332   Another group (22) concluded that long-term use beyond 10 years "appears to have a

333   significant relationship with breast cancer", based on pooling data from two trials (46, 50).

334   However, the Forest Plot does not match the pooled estimate reported in the text (22). We

335   have combined studies with comparable outcome measures, and have focused the

336   interpretation of the results on studies where there was an attempt to address 'confounding by

337   indication', and have refrained from sub-analysis by CCB or breast cancer subtype, as

338   conservative use of meta-analysis seems appropriate to the relatively methodologically

339   disparate studies included in this review. It would be interesting to see if any association

340   differs between oestrogen receptor-positive and –negative breast cancer, this was explored in

341   some studies (37, 46). Devore and colleagues (37) report a possible positive association

342   between CCBs and oestrogen receptor-negative breast cancer, while Li and colleagues (46)

343   found the positive association in their study was not affected by oestrogen-receptor status

344   (Table 1). However, there is little value in meta-analysing these two studies, especially as

345   they report different relative risk measures. The larger number of studies included in our

346   review relative to previous meta-analyses is attributable to wider eligibility criteria, and that

347   several studies have been published subsequent to the earlier reviews being conducted. Since

348   these reviews were published, there has been further data emerging with longer-term follow-

349   up (34, 35, 37, 41, 42, 44, 49, 51) and subsequent to database searching (64, 65), notably

350   including data from outside North America and Europe. This was partly in response to the

351   2013 study by Li *et al* (46); it is thus timely to reassess the literature to check if the likely risk

352   has moved toward providing a more unequivocal answer to this controversy. While the

353   authors of a previous meta-analysis concluded that, "there is no evidence that CCB use is

354   associated with an increased risk of breast cancer", the meta-analysis approach combined

355   studies with comparators of no CCB use of other AHTs, and also combined different

356   measures of relative risk (21). The approach we have taken in our meta-analysis takes

357   advantage of the now greater number of available, relevant studies, to combine those that are

358   reasonably comparable, amongst a group of relatively heterogeneous studies. The results

359 indicate that, especially for long-term use, we cannot confidently rule out an association at

360 this time.

361

362 Risk of bias and the likelihood of a causal link affect that importance of remaining

363 uncertainty highlighted by our review. Studies using questionnaires (e.g. (36, 38)) had a

364 higher risk of misclassification; earlier work by Beiderbeck and colleagues (66) found that

365 this could be differential and markedly affect reported relative risks. While population-based

366 registries were less susceptible to misclassification bias, two drawbacks are that potential

367 confounders are limited by data stored on the registries, and that collecting a prescription

368 from a pharmacy does not necessarily indicate taking it, though the importance of the latter is

369 less for studies requiring records of ≥ 1 prescription (e.g. (54)). Competing mortality risks

370 through people prescribed CCBs dying of non-cancer causes more often that those not taking

371 CCBs, are not formally factored in to the reviewed analyses, though one group does discuss

372 the possible effect on interpretation (35). This is worth exploring in future studies. Exclusion

373 of patients with cancer reduces the risk of reverse causality (i.e. breast cancer leading to

374 hypertension and subsequent prescription of a CCB) or of breast cancer developing prior to

375 CCBs being taken. However, the few studies which allowed for a 'latent period' did so for ~

376 one year, and in most cases follow-up was relatively short (< 10 years) (38-40, 44, 51).

377 Mason (6) concludes that a CCB-mediated decrease in apoptosis leading to a higher risk of

378 carcinogenesis is unlikely. The lack of a clear biological mechanism is consistent with the

379 majority of epidemiological studies showing no association. The majority of data are from

380 North America or Europe, excepting two recent studies from Taiwan (35, 44), which

381 produced conflicting results. Zhu and colleagues (67) discuss that social and biological

382 differences between African-Americans and Caucasian Americans may affect the association

383 between CCBs and breast cancer, and there may also be differences for Asian populations.

384

385   This review had several limitations. Whilst the selection criteria for the review were broad,

386   they did not allow inclusion of data from papers looking at cancer and CCBs, where either

387   breast cancer was not isolated as an outcome, or CCBs as the exposure (68-74). It is possible

388   that this may have also led to some RCTs being omitted, though reviewing references of a

389   recent systematic review and meta-analysis of relevant RCTs indicates that no eligible studies

390   were missed (75). That long-term drug effects often emerge beyond the length of a typical

391   RCT has also been demonstrated for the potential inverse association between low-dose

392   aspirin and colorectal cancer (76), highlighting the important role of well-designed

393   observational studies as part of effective post-marketing surveillance. Subsequent to database

394   searching, a study from Puerto Rico corroborates a lack of association with long-term use

395   (64), while a study from Spain indicates that use of CCBs beyond five years may be

396   associated with developing breast cancer, especially for overweight or postmenopausal

397   women (65). Incorporation of these data into the meta-analyses does not materially change

398   the results. Finally, during the timeframe over which included studies were published there

399   have been marked changes to hypertension and breast cancer epidemiology. If CCBs were

400   independently associated with incident breast cancer, we would expect this to appear over

401   time, notwithstanding the increasing proportion of longer acting CCBs over time. Thus to

402   choose a time cut off to include studies appears somewhat arbitrary. For this reason we have

403   included all studies fulfilling the eligibility criteria, regardless of the date of publication. That

404   only three of the 17 sub studies where an attempt was made to correct for 'confounding by

405   indication' were published prior to 2003 also limits the temporal impact on interpretation of

406   the pooled data for the meta-analysis.

407

408   In view of continuing controversy, especially for any association between long-term CCB use

409   and breast cancer, we recommend further NRS using population-based cancer, prescription

410   and health data registries, where these are available in settings where CCB use is prevalent.

411   These studies should include assessment of use beyond 10 years and adjust for important

412   confounders.

413

Acknowledgements

Several study authors were contacted while conducting this study; we thank them for

providing additional information upon request. Thanks also to Diana Blackwood, Librarian,

Curtin University, for assistance in developing the search strategy.

Funding

Ethics approval and consent to participate

As this study involved publicly accessible data, no ethical approval was required.

Conflicts of interest

None.

Authorship contribution

Study design; CMW, study conceptualisation; REM, JDH, article selection; CMW, JDH, data

extraction; CMW ($n = 29$), JDH ($n = 7$), EKC ($n = 22$), risk of bias and quality assessments;

CMW, manuscript draft; CMW, meta-analysis; CMW, critical revision of manuscript; CMW,

REM, EKC, BHS, CMR, CMS, JDH.

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577 47. Meier CR, Derby LE, Jick SS, Jick H. Angiotensin-converting enzyme inhibitors,

578   calcium channel blockers, and breast cancer. *Arch Intern Med.* 2000;160(3):349-53.

579   48.   Poole-Wilson PA, Kirwan BA, Voko Z, De Brouwer S, Van Dalen FJ, Lubsen J.

580   Safety of nifedipine GITS in stable angina: The ACTION trial. *Cardiovasc Drugs*

581   *Ther.* 2006;20(1):45-54.

582   49.   Raebel MA, Zeng C, Feigelson HS, Shetterly S, Carroll NM, Goddard K, et al. Breast

583   cancer risk with long-term use of calcium channel blockers or angiotensin-converting

584   enzyme inhibitors among postmenopausal women [abstract]. *Pharmacoepidemiol*

585   *Drug Saf.* 2015;24:552-3.

586   50.   Saltzman BS, Weiss NS, Sieh W, Fitzpatrick AL, McTiernan A, Daling JR, et al. Use

587   of antihypertensive medications and breast cancer risk. *Cancer Causes Control.*

588   2013;24(2):365-71.

589   51.   Soldera SV, Bouganim N, Asselah J, Yin H, Maroun R, Azoulay L. The long-term

590   use of calcium channel blockers and the risk of breast cancer [abstract]. *J Clin Oncol.*

591   2015; 33 (S1588).

592   52.   Sorensen HT, Olsen JH, Mellemkjaer L, Marie A, Steffensen FH, McLaughlin JK, et

593   al. Cancer risk and mortality in users of calcium channel blockers. A cohort study.

594   *Cancer.* 2000;89(1):165-70.

595   53.   Lip S, Carlin C, McCallum L, Touyz RM, Dominiczak AF, Padmanabhan S.

596   Incidence and prognosis of cancer associated with digoxin and common

597   antihypertensive drugs [abstract]. *J Hypertens.* 2015;33:e45.

598   54.   Assimes TL, Elstein E, Langleben A, Suissa S. Long-term use of antihypertensive

599   drugs and risk of cancer. *Pharmacoepidemiol Drug Saf.* 2008;17(11):1039-49.

600   55.   Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL, Meredith PA, et al.

601   Cancer risk of hypertensive patients taking calcium antagonists. *J Hypertens.*

602   1998;16(1):119-24.

603   56.   Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR. Calcium-channel
604   blockers and risk of cancer. *Lancet.* 1997;349(9051):525-8.

605   57.   Lindholm LH, Anderson H, Ekbom T, Hansson L, Lanke J, Dahlof B, et al. Relation
606   between drug treatment and cancer in hypertensives in the Swedish Trial in Old
607   Patients with Hypertension 2: a 5-year, prospective, randomised, controlled trial.
608   *Lancet.* 2001;358(9281):539-44.

609   58.   Michels KB, Rosner BA, Walker AM, Stampfer MJ, Manson JE, Colditz GA, et al.
610   Calcium channel blockers, cancer incidence, and cancer mortality in a cohort of U.S.
611   women: the nurses' health study. *Cancer.* 1998;83(9):2003-7.

612   59.   Olsen JH, Sorensen HT, Friis S, McLaughlin JK, Steffensen FH, Nielsen GL, et al.
613   Cancer risk in users of calcium channel blockers. *Hypertension.* 1997;29(5):1091-4.

614   60.   Pahor M, Guralnik JM, Ferrucci L, Corti MC, Salive ME, Cerhan JR, et al. Calcium-
615   channel blockade and incidence of cancer in aged populations. *Lancet.*
616   1996;348(9026):493-7.

617   61.   Rosenberg L, Rao RS, Palmer JR, Strom BL, Stolley PD, Zauber AG, et al. Calcium
618   channel blockers and the risk of cancer. *JAMA.* 1998;279(13):1000-4.

619   62.   Sajadieh A, Storm HH, Hansen JF. Verapamil and risk of cancer in patients with
620   coronary artery disease. DAVIT Study Group. Danish Verapamil Infarction Trial. *Am
621   J Cardiol.* 1999;83(9):1419-22, A9.

622   63.   Azoulay L, Soldera S, Yin H, Bouganim N. Use of Calcium Channel Blockers and
623   Risk of Breast Cancer: A Population-based Cohort Study. *Epidemiology.*
624   2016;27(4):594-601.

625   64.   Wilson LE, D'Aloisio AA, Sandler DP, Taylor JA. Long-term use of calcium channel
626   blocking drugs and breast cancer risk in a prospective cohort of US and Puerto Rican
627   women. *Breast Cancer Res.* 2016;18(1):61.

628 65. Gomez-Acebo I, Dierssen-Sotos T, Palazuelos C, Perez-Gomez B, Lope V, Tusquets

629   I, et al. The Use of Antihypertensive Medication and the Risk of Breast Cancer in a

630   Case-Control Study in a Spanish Population: The MCC-Spain Study. *PLoS ONE.*

631   2016;11(8):e0159672.

632 66. Beiderbeck AB, Sturkenboom MC, Coebergh JW, Leufkens HG, Stricker BH.

633   Misclassification of exposure is high when interview data on drug use are used as a

634   proxy measure of chronic drug use during follow-up. *J Clin Epidemiol.*

635   2004;57(9):973-7.

636 67. Zhu K, Daling JR, Pahor M. African-American ethnicity in epidemiological studies of

637   calcium antagonists in relation to cancer. *Ethn Dis*. 2002;12(1):144-8.

638 68. Finn R, Winstanley J. Regular medication in women who develop breast cancer: A

639   pilot study. *Breast.* 2001;10(3):260-2.

640 69. Friis S, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, et al.

641   Cancer risk among statin users: A population-based cohort study. *Int J Cancer.*

642   2005;114(4):643-7.

643 70. Friis S, Sorensen HT, Mellemkjaer L, McLaughlin JK, Nielsen GL, Blot WJ, et al.

644   Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based

645   cohort study in Denmark. *Cancer.* 2001;92(9):2462-70.

646 71. Magliano DJ, Davis WA, Shaw JE, Bruce DG, Davis TM. Incidence and predictors of

647   all-cause and site-specific cancer in type 2 diabetes: the Fremantle Diabetes Study.

648   *Eur J Endocrinol.* 2012;167(4):589-99.

649 72. Hallas J, Christensen R, Andersen M, Friis S, Bjerrum L. Long term use of drugs

650   affecting the renin-angiotensin system and the risk of cancer: A population-based

651   case-control study. *Brit J Clin Pharmacol.* 2012;74(1):180-8.

652   73.   Lin CS, Hsu CW, Lin WS, Kao CH. Carvedilol use and specific cancer risk in the

653   population with hypertension: Reply. *Int J Cardiol.* 2015;190:159-60.

654   74.   Kanamasa K, Kimura A, Miyataka M, Takenaka T, Ishikawa K. Incidence of cancer

655   in postmyocardial infarction patients treated with short-acting nifedipine and

656   diltiazem. *Cancer.* 1999;85(6):1369-74.

657   75.   Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood

658   pressure lowering for prevention of cardiovascular disease and death: a systematic

659   review and meta-analysis. *Lancet.* 2016;387(10022):957-

660   76.   Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-

661   term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up

662   of five randomised trials. *Lancet.* 2010;376(9754):1741-50.

663

Figure 1. Flow diagram of study selection.

Identification

Records identified through
database searching
MEDLINE, n = 534
EMBASE, n = 1,992
Cochrane Library, n = 43
N = 2,569

Additional records identified
through other sources:
From selected articles, n = 714
From review articles, n = 68
From Web of Science citation
search, n = 1,225
N = 2,007

Screening

Records after duplicates removed:
From database searching (DS), n = 2,099
From other sources (OS), n = 956
N = 3,055

Records excluded based on
title, abstract:
DS, n = 2,041
OS, n = 891
N = 2,932

Eligibility

Full-text articles assessed
for eligibility:
DS, n = 58
OS, n = 65
N = 123

Full-text articles excluded:
· P, n = 0
· I, n = 5 (DS) + 17 (OS) = 22
· C, n = 7 + 1 = 8
· O, n = 5 + 16 = 21
· S, n = 17 + 18 = 35
· Review article, n = 0 + 4 = 4
· Rejected based on authors'
advice, n = 1 + 0 = 1
· Same data in two abstracts,
n = 1 + 0 = 1
· Data in paper and abstract
form, full paper included, n
= 2 + 0 = 2.
N = 94

Included

Studies included in
systematic review:
DS, n = 20
OS, n = 9
N = 29

Figure 2. Forest plot of pooled odds/risk ratio of breast cancer diagnosis for CCB versus other antihypertensive*
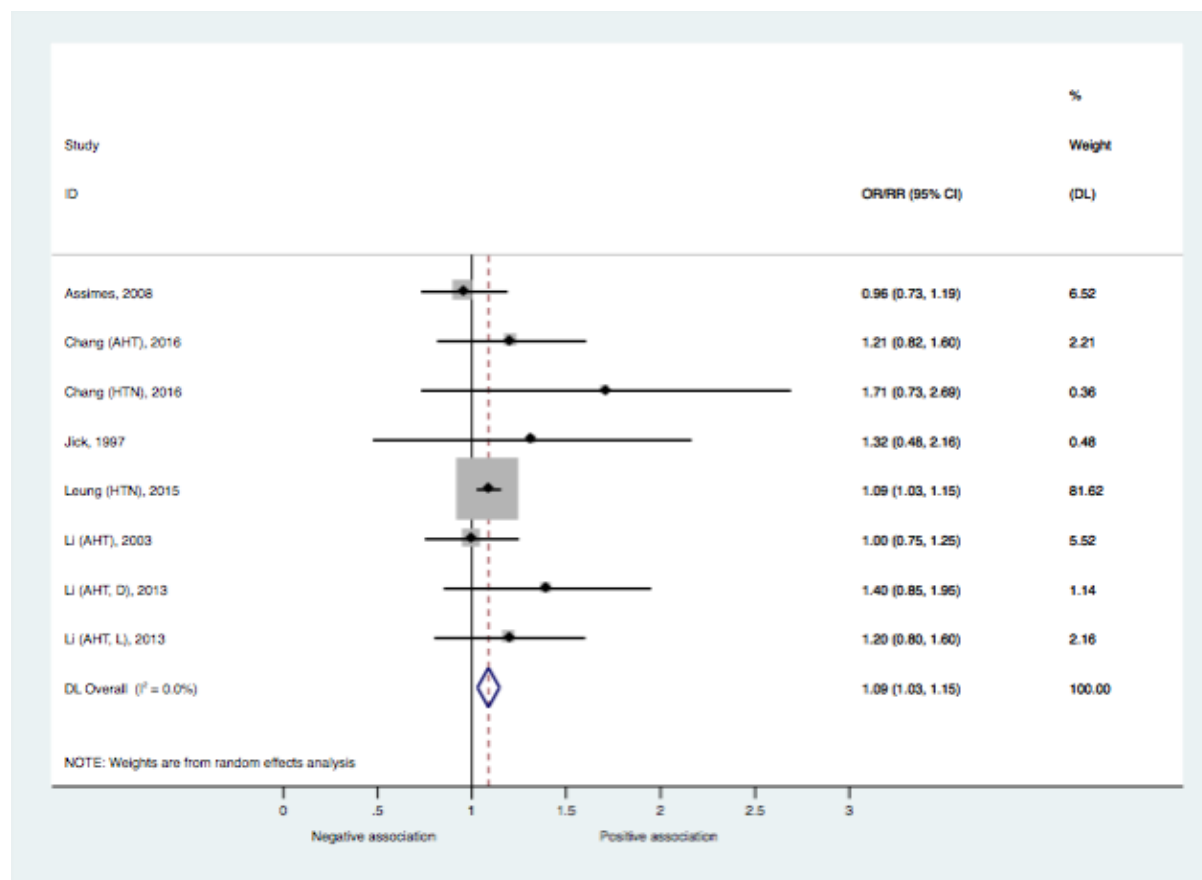
*Versus another antihypertensive drug or only amongst hypertensive patients, or with adjustment for hypertension/use of other antihypertensive drugs. The size of the box is proportionate to study weighting in the meta-analysis (inversely proportionate to the standard error), the horizontal lines indicates 95% confidence intervals (CI), and the diamond shows the pooled risk/odds ratio (1.09). Some 95% CIs differ slightly from original study due to rounding. AHT = antihypertensive drug, D = invasive ductal, HTN = patients with hypertension only, L = invasive lobular. Included study full references (35, 44-46, 54, 56)

Figure 3. Forest plot of pooled hazard ratio of breast cancer diagnosis for CCB versus other antihypertensive*.
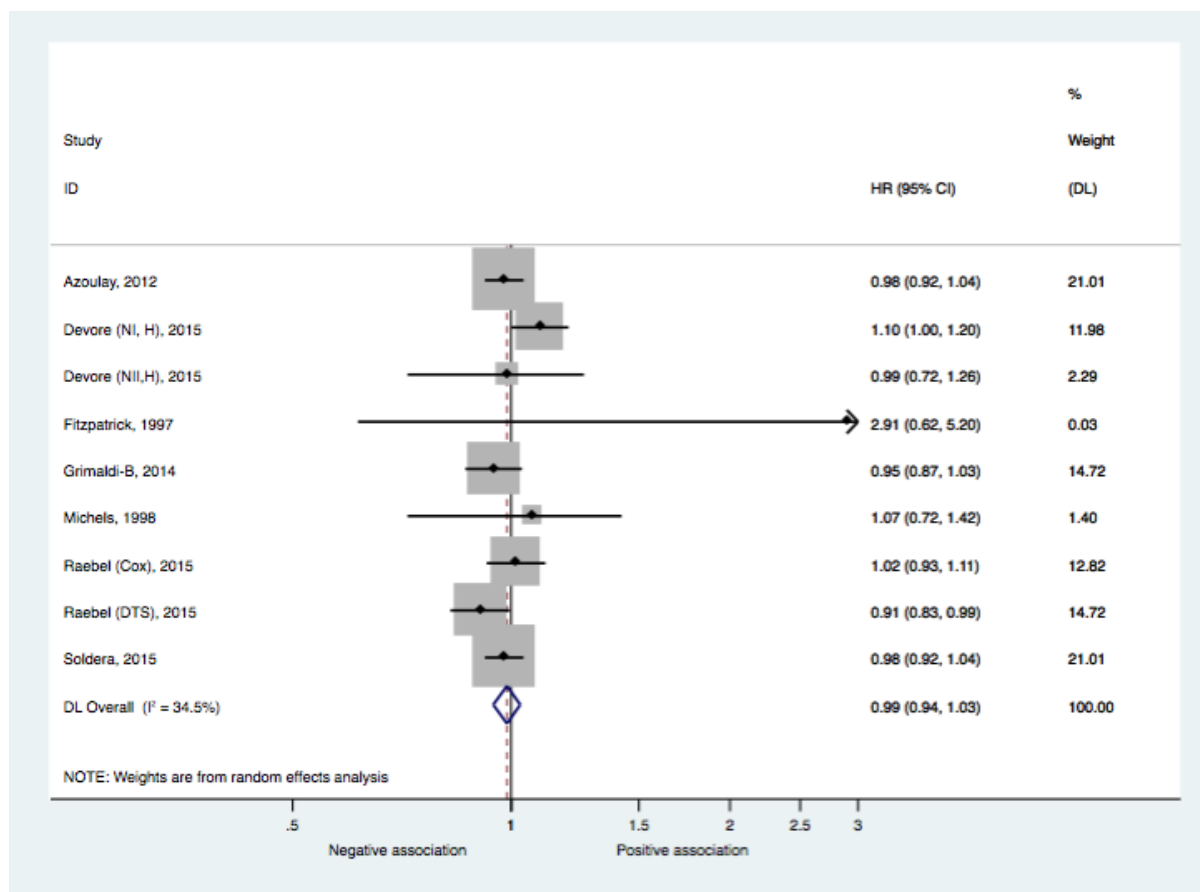
		%
Study		Weight
ID	HR (95% CI)	(DL)
Azoulay, 2012	0.98 (0.92, 1.04)	21.01
Devore (NI, H), 2015	1.10 (1.00, 1.20)	11.98
Devore (NII,H), 2015	0.99 (0.72, 1.26)	2.29
Fitzpatrick, 1997	2.91 (0.62, 5.20)	0.03
Grimaldi-B, 2014	0.95 (0.87, 1.03)	14.72
Michels, 1998	1.07 (0.72, 1.42)	1.40
Raebel (Cox), 2015	1.02 (0.93, 1.11)	12.82
Raebel (DTS), 2015	0.91 (0.83, 0.99)	14.72
Soldera, 2015	0.98 (0.92, 1.04)	21.01
DL Overall (I^2 = 34.5%)	0.99 (0.94, 1.03)	100.00

NOTE: Weights are from random effects analysis

Negative association   Positive association

*Versus another antihypertensive drug or only amongst hypertensive patients, or with adjustment for hypertension/use of other antihypertensive drugs. The size of the box is proportionate to study weighting in the meta-analysis (inversely proportionate to the standard error), the horizontal lines indicates 95% confidence intervals (CI), and the diamond shows the pooled hazard ratio (0.99). Some 95% CIs differ slightly from original study due to rounding. B = Bensouda, DTS = discrete time survival, H = patients with hypertension only, N = Nurses' Health Study. Included study full references (33, 37, 38, 41, 49, 51, 58)).

Appendix A. Prospero protocol.

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015026712

Appendix B. Database search strategies

MEDLINE

1. exp Calcium Channel Blockers/
2. "calcium channel block$".af.
3. CCB$.af.
4. "calcium antagonist$".af.
5. exp Dihydropyridines/ or dihydropyridine$.af.
6. exp Amlodipine/ or amlodipine.af.
7. clevidipine.af.
8. exp Diltiazem/ or diltiazem.af.
9. exp Felodipine/ or felodipine.af.
10. lercanidipine.af.
11. exp Nifedipine/ or nifedipine.af.
12. exp Nimodipine/ or nimodipine.af.
13. exp Verapamil/ or verapamil.af.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp Breast Neoplasms/
16. (breast adj6 neoplasm$).af.
17. (breast adj6 cancer$).af.
18. (breast adj6 carcinoma$).af.
19. (breast adj6 tumour$).af.
20. (breast adj6 tumor$).af.
21. 15 or 16 or 17 or 18 or 19 or 20
22. 14 and 21
23. exp animals/ not humans/
24. 22 not 23

EMBASE

1. exp calcium channel blocking agent/
2. "calcium channel block$".af.
3. CCB$.af.
4. "calcium antagonist$".af.
5. exp dihydropyridine derivative/ or dihydropyridine$.af.
6. exp amlodipine/ or amlodipine.af.
7. exp clevidipine/ or clevidipine.af.
8. exp diltiazem/ or diltiazem.af.
9. exp felodipine/ or felodipine.af.
10. exp lercanidipine/ or lercanidipine.af.
11. exp nifedipine/ or nifedipine.af.
12. exp nimodipine/ or nimodipine.af.
13. exp verapamil/ or verapamil.af.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp breast cancer/
16. exp breast tumor/
17. exp breast carcinoma/
18. (breast adj6 cancer$).af.
19. (breast adj6 neoplasm$).af.
20. (breast adj6 carcinoma$).af.
21. (breast adj6 tumour$).af.
22. (breast adj6 tumor$).af.
23. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 14 and 23
25. animal/
26. exp animal experiment/
27. nonhuman/
28. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
29. 25 or 26 or 27 or 28
30. exp human/
31. human experiment/
32. 30 or 31
33. 29 not (29 and 32)
34. 24 not 33

Cochrane Library

#1	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#2	calcium NEXT channel NEXT block*
#3	CCB*
#4	calcium NEXT antagonist*
#5	MeSH descriptor: [Dihydropyridines] explode all trees
#6	dihydropyridine*
#7	MeSH descriptor: [Amlodipine] explode all trees
#8	amlodipine
#9	clevidipine
#10	MeSH descriptor: [Diltiazem] explode all trees
#11	diltiazem
#12	MeSH descriptor: [Felodipine] explode all trees
#13	felodipine
#14	lercanidipine
#15	MeSH descriptor: [Nifedipine] explode all trees
#16	nifedipine
#17	MeSH descriptor: [Nimodipine] explode all trees
#18	nimodipine
#19	MeSH descriptor: [Verapamil] explode all trees
#20	verapamil
#21	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 #14 or #15 or #16 or #17 or #18 or #19 or #20
#22	MeSH descriptor: [Breast Neoplasms] explode all trees
#23	breast NEAR neoplasm*
#24	breast NEAR cancer*
#25	breast NEAR carcinoma*
#26	breast NEAR tumour*
#27	breast NEAR tumor*
#28	#22 or #23 or #24 or #25 or #26 or #27
#29	#21 and #28

Appendix C. Rejected articles undergoing full-text review

N = 94.

Rejected under intervention criterion

From database searching, n = 5

- Minerva. *BMJ.* 1993;307(6903):574.

- Safety and efficacy issues. WHO Drug Information. 2013;27(3):218-26.

- Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: A population-based study. *J Clin Oncol.* 2011;29(19):2635-44.

- DeMaria AN, Ben-Yehuda O, Feld GK, Ginsburg GS, Greenberg BH, Lew WYW, et al. Highlights of the Year in JACC 2006. *J Am Coll Cardiol.* 2007;49(4):509-27.

- Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E. Sulphonylureas and cancer: A case-control study. *Acta Diabetologica.* 2009;46(4):279-84.

From other sources, n = 17

- Assimes TL, Suissa S. Age at incident treatment of hypertension and risk of cancer: a population study. *Cancer Causes Control.* 2009; 20: 1811-20.

- Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Cancer risk in association with Parkinson disease: A population-based study. *Parkinsonism Relat Disord.* 2010;16(3):186-90.

- Beji NK, Reis N. Risk factors for breast cancer in Turkish women: a hospital-based case-control study. *Eur J Cancer Care.* 2007; 16(2): 178-84.

- Bhaskaran K, Douglas I, Evans S, van ST, Smeeth L. Angiotensn receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. *BMJ.* 2012; 344: e2697.

- Chae YK, Valsecchi ME, Kim J, Bianchi AL, Khemasuwan D, Desai A, et al. Reduced Risk of Breast Cancer Recurrence in Patients Using ACE Inhibitors, ARBs, and/or Statins. *Cancer Invest.* 2011;29(9):585-93.

- Chang PY, Huang WY, Lin CL, Huang TC, Wu YY, Chen JH, et al. Propranolol Reduces Cancer Risk A Population-Based Cohort Study. *Medicine.* 2015;94(27).

- Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol.* 1991; 134:942-47.

- Hole DJ, Hawthorne VM, Isles GC, McGhee SM, Robertson JWK, Gillis CR, Wapshaw JA, Lever AF. Incidence of an mortality from cancer in hypertensive patients. *BMJ.* 1993; 306: 609-11.

- Kaye JA, Meier CR, Walker AM, Jick H. Statin use, hyperlipidaemia, and the risk of breast cancer. *Br J Cancer.* 2002;86(9):1436-9.

- Largent JA, McEligot AJ, Ziogas A, Reid C, Hess J, Leighton N *et al.* Hypertension, diuretics and breast cancer risk. *J Hum Hypertension.* 2006; 20(10):727-32.

- Lindgren AM, Nissinen AM, Tuomilehto JO, Pukkala E. Cancer pattern among hypertensive patients in North Karelia, Finland. *J Hum Hypertens.* 2005; 19(5): 373-79.

- Mackenzie IS, MacDonald TM, Thompson A, Morant S, Wei L. Spironolactone and risk of incident breast cancer in women older than 55 years: retrospective, matched cohort study. *BMJ.* 2012;345.

- Modugno F, Kip KE, Cochrane B, Kuller L, Klug TL, Rohan TE, et al. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. *Int J Cancer.* 2006;118(5):1292-301.

- Pasternak B, Svanstrom H, Callreus T, Melbye M, Hviid A. Use of Angiotensin Receptor Blockers and the Risk of Cancer. *Circulation.* 2011;123(16):1729-36.

- Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, et al. Cancer linked to Alzheimer disease but not vascular dementia. *Neurology.* 2010;74(2):106-12.

- van der Knaap R, Siemes C, Coebergh JWW, van Duijn CM, Hofman A, Stricker BHC. Renin-anglotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer. *Cancer.* 2008;112(4):748-57.

- Wang KL, Liu CJ, Chao TF, Huang CM, Wu CH, Chen TJ, et al. Long-term use of angiotensin II receptor blockers and risk of cancer: A population-based cohort analysis. *Int J Cardiol.* 2013;167(5):2162-6.

Rejected under comparator criterion

From database searching, n = 7

- Azimi I, Roberts-Thomson SJ, Monteith GR. Calcium influx pathways in breast cancer: Opportunities for pharmacological intervention. *Br J Pharmacol.* 2014;171(4):945-60.

- Davis S, Mirick DK. Residential magnetic fields, medication use, and the risk of breast cancer. *Epidemiology.* 2007;18(2):266-9.

- Finn R, Winstanley J. Regular medication in women who develop breast cancer: A pilot study [3]. *Breast.* 2001;10(3):260-2.

- Friis S, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, et al. Cancer risk among statin users: A population-based cohort study. *Int J Cancer.* 2005;114(4):643-7.

- Friis S, Sorensen HT, Mellemkjaer L, McLaughlin JK, Nielsen GL, Blot WJ, et al. Angiotensin-converting enzyme inhibitors and the risk of cancer: a population-based cohort study in Denmark. *Cancer.* 2001;92(9):2462-70.

- Magliano DJ, Davis WA, Shaw JE, Bruce DG, Davis TM. Incidence and predictors of all-cause and site-specific cancer in type 2 diabetes: the Fremantle Diabetes Study. *Eur J Endocrinol.* 2012;167(4):589-99.

- Seedat YK. The long-term efficacy and tolerability of nisoldipine in patients with mild-to-moderate hypertension. *Curr Ther Res Clin Exp.* 1997; 58(3):187-99

From other sources, n = 1

- Aromaa A, Hakama M, Hakulinen T, Saxen E, Teppo L, Idä Ian-Keikkila J. Breast cancer and use of Rauwolfia and other antihypertensive agents in hypertensive patients: a nationwide case-control study in Finland. *Int J Cancer.* 1976; 18:727 – 38.

Rejected under outcome criterion

From database searching, n = 5

- Altkorn D, Roach K, Stern S, Levinson W. Update in general internal medicine. *Ann Intern Med.* 1999;131(3):199-206.

- Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJA, Fujii M, et al. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. *Breast Cancer Res Treat.* 2014;144(2):405-16.

- Hallas J, Christensen R, Andersen M, Friis S, Bjerrum L. Long term use of drugs affecting the renin-angiotensin system and the risk of cancer: A population-based case-control study. *Br J Clin Pharmacol.* 2012;74(1):180-8.

- Lin GM, Liu PY, Wu CF, Wang WB, Han CL. Carvedilol use and specific cancer risk in the population with hypertension. *Int J Cardiol.* 2015;186:52-3.

- MacMahon S, Collins R, Chalmers J. Reliable and unbiased assessment of the effects of calcium antagonists: Importance of minimizing both systematic and random errors. *J Hypertens.* 1997;15(11):1201-4.

From other sources, n = 16

- Beiderbeck-Noll AB, Sturkenboom MC, van-der Linden PD, Herings RM, Hofman A, Coeberg JW *et al.* Verapamil is associated with an increased risk of cancer in the elderly: The Rotterdam Study. *Eur J Cancer.* 2003; 39: 98-105.

- Braun S, Bokyo V, Behar S, Reicher-Reiss H, Laniado S, *et al.* Calcium channel-blocking agents and risk of cancer in patients with coronary heart disease. *J Am Coll Cardiol.* 1998; 31:804-8.

- Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet.* 2000;356(9227):366-72.

- Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Principal results from the international nifedipine GITS study: Intervention as a goal in hypertension treatment (INSIGHT). *Europ Heart J.* Suppl. 2001;3(B):B20-B6.

- Cohen HJ, Pieper CF, Hanlon JT, Wall WE, Burchett BM, Havlik RJ. Calcium channel

blockers and cancer. *Am J Med.* 2000;108(3):210-5.

- Daling JR. Calcium channel blockers and cancer: is an association biologically plausible? *Am J Hypertens.* 1996; 9: 713-4.

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- Kuwajima I, Kuramoto K, Ogihara T, Iimura O, Abe K, Saruta T, et al. Tolerability and safety of a calcium channel blocker in comparison with a diuretic in the treatment of elderly patients with hypertension: Secondary analysis of the NICS-EH. *Hypertens Res.* 2001;24(5):475-80.

- Leenen FHH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension.* 2006;48(3):374-84.

- Lever AF, Hole DJ, Gillis CR, McCallum IR, McInnes GT, MacKinnon PL *et al.* Do inhibitors of angiotensin-I-converting enzyme protect against the risk of cancer? *Lancet.* 1998; 352(9123):179-184.

- Lindberg H, Lindblad U, Lo w-Larsen B, Merlo J, Melander A *et al.* Use of calcium channel blockers as antihypertensives in relation to mortality and cancer incidence: a population-based observational study. *Pharmacoepidemiol Drug Saf. 2002*; 11:493-7.

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- Stahl M, Bulpitt CJ, Palmer AJ, Beevers DG, Coles EC, Webster J. Calcium channel blockers, ACE inhibitors, and the the risk of cancer in hypertensive patients: a report from the Department of Health Hypertension Care Computing Project (DHCCP). *J Human Hypertens.* 2000; 14(5): 285-6.

- Trenkwalder PRA, Hendricks P, Hense HW. Calcium-channel blockers do not increase the risk of fatal or non-fatal cancer in an elderly European population: results from STEPHY II. *Circulation.* 1997; 96: I-763.

- Wong MCS, Tam WWS, Lao X, Wang HHX, Kwan MWM, Cheung CSK, et al. The incidence of cancer deaths among hypertensive patients in a large Chinese population: A cohort study. *Int J Cardiol.* 2015;179:178-85.

Rejected under study design criterion

From database searching, n = 17

- Anonymous. Calcium channel blockers and breast cancer. *Harv Heart Lett.* 1998;8(8):7.

- Anonymous. Is this common blood pressure drug risky? Some evidence suggests calcium-channel blockers have an association with breast cancer and kidney problems. *Harv Health Lett.* 2014;39(6):7.

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Appendix D. Data extracted from included studies (number next to publication year is the study reference on the main paper).

Author(s) and year of publication (Reference number on manuscript)	Assimes *et al.* 2008 (54)
Objectives	To examine the relationship between the use of antihypertensive drugs and cancer outcomes.
Methods	
Study design	Nested case-control study.
Setting	Saskatchewan Province, Canada. Study period 1 January 1980 through 31 December 2003.
Participants	**Cohort** formed from users of AHTs, defined by ≥3 prescriptions in one calendar year between 1 January 1980 and 30 June 1987. Follow-up from date of third dispensing in one year through cancer diagnosis, service termination or 31 December 2003, whichever arrived first. **Cases:** ≥1 cancer diagnosis, excluding non-melanoma skin cancer and *in situ* cervical cancer. Date of diagnosis considered as 'index date'. **Controls** (10: 1 case): selected from province-level database, no diagnosis of cancer from 1967, matched to cases on entry into cohort, gender and age (+/- 3 years). **Excluded** if dispensing history for <2 years (modified if entry to cohort after 1 January 1982).
Variables	**Outcome(s):** Primary outcomes: all 35-cancer sites combined, four most common cancers (colorectal, breast, lung, prostate) and kidney. Secondary outcomes: other grouped categories (e.g. "head and neck" included lip, oral cavity, head & neck, larynx, thyroid). Only first cancer within study period considered. **Exposure(s):** Exposure to CCB, beta-blocker or ACEI/ATRA, relative to thiazide diuretic use. **Potential confounder(s):** "common pre-morbid conditions". **Potential effect modifier(s):** Nil stated.
Data sources/measurement	Exposure, outcome and covariate data collected via population-based prescription, cancer and health registries.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with	Conditional logistic regression. Prescription database did not collect individual data from 1 July 1987 to 31 December 1998, so data imputed during this time. CCB use relative to thiazide (but not CCB use), adjusted for age, 'comorbid conditions',

missing data.	use of other AHTs except for potassium-sparing diuretics. Duration-response analysis also conducted for <2.5 years, 2.5 to ≤7.5 years, and >7.5 years).
Results	
Number of participants	Total cohort: 77,887 patients: 11,697 cases matched to 116,970 controls. Total use of any duration: CCB, but not thiazide: 92 cases; 927 controls Thiazide, but not CCB [ref]: 972 cases; 9213 controls Total use > 7.5 years: CCB group: 16 cases; 210 controls. Thiazide group [ref]: 316 cases; 2920 controls.
Description of study group	For total cohort: mean age 71.8 (SD 10.6 years) for cases; 71.7 (SD 10.6) for controls. Male ~ 53%. Mean duration of AHT use: 3.6 to 5.7 years. A subgroup exposed to long-term AHT (mean duration 9.7 – 11.4 years, range 7.5 – 23.1 years).
Outcome(s) overall	Breast cancer cases = 1623 (14% of total incident cancer cases in this study).
Main results	Total use of any duration: aOR 0.96 (95% CI 0.76-1.22). Total use > 7.5 years: For aOR 0.73 (95% CI 0.43-1.23)
Other analyses	Nil relevant
Discussion	
Limitations (author reported)	1) Fewer participants on CCBs and ACEI/ATRAs than expected, even fewer on these exclusively. 2) Some misclassification of exposure as prescription database offline for 18 months of the study period, though the authors did attempt to adjust for this in their analysis. 3) Analysis not adjusted for smoking, BMI, family history. 4) Could not adjust for use of potassium-sparing diuretics (showed co-linearity with thiazide diuretic use). Authors stated "we are not aware of any published studies to date that provide compelling evidence that potassium sparing diuretics are carcinogenic at the population level." 5) Dispensing used as surrogate for 'taking', potential for bias resulting from this. 6) Evidence provided for indirect carcinogenic effects of antihypertensives, not specific genotoxic or carcinogenic effects (this would require a different study design).
Interpretation	No author interpretation for breast cancer specifically, however authors stated "we found no association between the risk of cancer from all sites combined and the use of CCBs but not thiazide diuretics"
Generalisability	Generalisability not specifically mentioned, however authors commented: "Assuming thiazide diuretics are not carcinogenic, our findings provide important reassurance to

	patients that the long-term use of commonly prescribed classes of antihypertensive drugs does not promote or initiate cancer."
Funding	Operating grant from the Canadian Institutes of Health Research. Dr. Assimes supported by a training bursary from Fonds de la Research en santé du Quebec and Dr. Suissa is a recipient of the Distinguished Investigator Award from the CIHR. Phamacoepidemiology Unit is funded by an Equipé grant from the FRSQ.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aOR = adjusted odds ratio, ATRA = angiotensin II receptor antagonist, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Azoulay *et al.* 2012 (33)
Objectives	"…to determine whether angiotensin receptor blockers are associated with an overall increased risk of the four most common cancers, namely, lung, colorectal, breast and prostate cancers…". Primary objective = these cancers combined. Secondary objective = these cancers individually.
Methods	
Study design	Retrospective cohort design, from which a nested case-control study was performed.
Setting	United Kingdom. Study period from 1 January 1995 through 31 December 2010.
Participants	**Cohort** formed from patients prescribed an AHT from 1 January 1995 through 31 December 2008. Need to have ≥ 2 years of health records from date of cohort entry, if this was not the case, date moved forward to first prescription preceded by at least 2 years of database records Follow-up from entry into cohort through to first diagnosis of cancer, death from any course, end of registration with general practice at entry, or the 31 December 2010, whichever arrived first. **Cases** patients diagnosed with study cancer. Date of diagnosis assigned as 'index date'. **Controls** (up to 10: 1 case): randomly selected, matched base of age (via year of birth), sex, calendar year of cohort entry, prevalent user status (prescription of AHT during 2-year period prior to cohort entry), and duration of follow-up. **Excluded** if history of any of the four study cancers prior to entry into cohort, or if AHT use started within year of 'index date' (to account for latency).
Variables	**Outcome(s):** Primary outcome: all four cancers combined. Secondary outcome: four cancers (lung, colorectal, prostate, breast) individually. **Exposure(s):** prescription of an AHT. Grouped into ever use of mutually exclusive groups: 1) ARBs; 2) ACEIs; 3) CCBs; 4) other antihypertensives and; 5) beta-blockers/diuretics [ref]. **Pre-specified potential confounder(s):** excessive alcohol use, smoking status, BMI, HTN, CHF, CHD, diabetes, previous cancer (other than non-melanoma skin cancer or those under study), ever use of aspirin, other NSAIDs or statins. For breast cancer-specific analysis, further adjustment for oophorectomy, use of HRT and prior use of oral contraceptives. **Pre-specified potential effect modifier(s):** not specifically mentioned.
Data sources/measurement	Used UK General Practice Research Database (GPRD) for outcome, exposure and

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	covariate data. Covariate data measured at any time from at least 2 years prior to cohort entry, up until 1 year prior to index date).
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Conditional logistic regression with adjustment for excessive alcohol use, BMI, smoking, diabetes, previous cancer, ever use of aspirin, statins, or NSAIDs, oophorectomy, use of HRT, and prior use of oral contraceptives.
Results	
Number of participants	Total cohort: 1,165,781: 41,059 cases matched to 410,167 controls. Ever use of CCBs versus diuretics +/- beta-blockers [ref]: Cases: 2,070 Controls: 21,160
Description of study group (age, gender, other demographic data provided)	Mean age at cohort entry 63.4 years (SD 14.6), and 72.4 years for both cases and controls are index date. Cases and controls were followed for a mean of 5.5 (SD 3.3 years), 53% of cases and controls were male. Smoking 56.7% for cases, 49% for controls.49.4% of cases and 48.5% of controls taking a CCB (+/- other antihypertensive(s)).
Outcome(s) overall	Of 41,059 cases, 11,312 (27.5%) had breast cancer.
Main results	aRR 0.98 (95% CI 0.92 – 1.04).
Other analyses	Nil relevant
Discussion	
Limitations (author reported)	1) Relying on prescription data may not link directly with compliance, therefore misclassification bias toward the null possible. 2) Lack of information in GPRD regarding occupational exposures, race, and family history. 3) Could not assess for confounding secondary to differing levels of hypertension control.
Interpretation	No specific commentary regarding association between CCB and breast cancer,
Generalisability	Not mentioned specifically, though assembly of a ~ 1.2 million person cohort is cited as a strength of the study.
Funding	Grants from the Canadian Institutes of Health Research, Boehringer-Ingelheim, and the Canadian Foundation for Innovation.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, ARB = angiotensin II receptor blocker, aRR = adjusted relative-risk, BMI = body mass index, CCB = calcium channel blocker, CHD = coronary heart disease, CHF = congestive cardiac failure, CI = confidence interval, HRT = hormone replacement therapy, HTN = hypertension, IHD = ischaemic heart disease, NSAID = non-steroidal anti-inflammatory drug, SD = standard deviation.

Author(s) and year of publication (Reference number on manuscript)	Bergman *et al.* 2014 (34)
Objectives	To replicate the study by Li *et al.* (2013, ref 43) by using population registries with high coverage.
Methods	
Study design	Case-control study
Setting	Sweden Study period 1 January 2006 through 31 December 2011.
Participants	**Cases:** women receiving a diagnosis of breast cancer for the first time in 2011. **Controls (1: 5 controls):** sourced from the Swedish Population Registry, matched by age, could not have malignant or benign breast tumour or breast cancer *in situ* before 2011.
Variables	**Outcome(s):** new diagnosis of breast cancer. **Exposure(s):** use of CCBs between 1 January 2006 and 31 December 2011. Defined as >3 prescriptions during a year. **Potential confounder(s):** age, educational level, location of residence, and history of cancer at sites other than the breast. **Potential effect modifier(s):**
Data sources/ measurement	Swedish Cancer Register for outcome, Swedish Population Registry, National Registry on Prescription Drugs for exposure.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Logistic regression adjusted for above listed confounders. Dose-duration analysis performed.
Results	
Number of participants	19,766 total: 3,461 cases; 17,363 controls. <u>Continuous use of CCBs over 5 years:</u> 148 cases; 719 controls. <u>No continuous use of CCBs [ref]:</u> 3,314 cases; 15,765 controls.
Description of study group	Age range 55 to 74 years.
Outcome(s) overall	
Main results	aOR1.1 (95% CI 0.9-1.3)
Other analyses	For use in 2010 only: aOR 0.9 (95% CI 0.7-1.3) For use in 2009-10: aOR 1.1 (95% CI 0.8-1.5) For use in 2008-10: aOR 1.0 (95% CI 0.7-1.5) For use in 2007-10: aOR 1.1 (95% CI 0.8-1.6)
Discussion	

Limitations (author reported)	None reported
Interpretation	5 years of exposure to CCBs did not increase the odds of developing breast cancer. However, as the Li *et al.* (2013, ref 43) paper showed that long-term use (≥10 years) was associated with breast cancer, plan for continue surveillance.
Generalisability	Not discussed.
Funding	No specific funding mentioned, undertaken by staff of the National Board of Health and Welfare in Sweden, Stockholm, Sweden.

Abbreviations: aOR = adjusted odds ratio CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Chang *et al.* 2016 (35)
Objectives	"…to investigate the association of long-term use of antihypertensive agents with incident breast cancer among women aged 55 years or older…"
Methods	
Study design	Nested case-control study.
Setting	Taiwan Study period 1 January 2001 through 31 December 2011.
Participants	**Cohorts** Women aged 55 to 100 years in 2001, without any prescription for ACEIs or ARBs, alpha-blockers, beta-blockers, CCBs or other antihypertensive agent, or a diagnosis of incident cancer before study commencement. Separate cohorts included women prescribed ACEIs, ARBs, beta-blockers, CCBs and diuretics) and having a diagnosis of hypertension were also assembled. **Cases:** first diagnosis of breast cancer. The date of first breast cancer diagnosis was defined as the index date. **Controls:** For original cohort, from each case identified up to 4 age (5-year grouping) follow-up duration matched controls were selected from the cohort. For separate cohorts prescribed AHTs, from each case up to 4 age-matched (1-year grouping) and follow-up duration controls were identified for each cohort. **Excluded:** women not receiving a continuous insurance coverage in 2000.
Variables	**Outcome(s):** first diagnosis of breast cancer **Exposure(s):** prescription of ACEIs or ARB, dihydropyridine CCB (non-dihydropyridine were excluded), or beta-blockers prior to breast cancer occurrence. **Potential confounder(s):** other medical conditions (e.g. diabetes, hypertension), other medicines (e.g. diuretics, insulin), and socioeconomic status. **Potential effect modifier(s):** Nil specified.
Data sources/measurement	Outcome sourced for Taiwan's National Cancer Registry. Exposure from Taiwan's National Health Insurance (approximately 99% population coverage), specifically from the outpatient pharmacy prescription database, Insurance database also used to collect covariate medical, prescription, and diagnostic data.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Conditional logistic regression, for each cohort CCB use relative to non-use [ref]. Adjustment for study drugs and with potential covariates added into model stepwise and retained if p<0.1 for model entry and >0.05 for removal. Stratification by duration of use: current, recent (from drug discontinuation to cancer diagnosis < 6 months) and past use (if ≥ 6 months had passed), and use for: ≤ 2 years, > 2-4 years, >4-6 years, > 8 years. In final model adjustment for: study drugs (ACEIs/ARBs, beta-blockers, dihydropyridine

	CCBs) socioeconomic status, diabetes mellitus, ischaemic heart disease, myocardial infarction, heart failure, cerebrovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, depression, Charlson's index, diuretics, human insulin, statin, fibrates, aspirin, HRT, number of lipid measurements, number of mammography, number of outpatient visits, number of hospitalisations, length of hospital admissions more than 7 days.
Results	
Number of participants	Original cohort = 794,533. Cohort taking AHTs = 178,412. Cohort with hypertension diagnosis = 114,971.
Description of study group	Overall, mean age 62.70 for both cases and controls, median follow-up of 9.9 years, 16.8% of cohort died and 0.19% were lost to follow-up.
Outcome(s) overall	For overall cohort: Any CCB use: 3,529 cases and 10,909 controls. No use of CCBs [ref]: 5,868 cases and 26,679 controls. For cohort taking an AHT: Any CCB use: 1,260 cases and 4,534 controls. No use of CCBs [ref]: 816 cases and 3,770. For cohort with diagnosis of hypertension: Any CCB use: 950 cases and 3,595 controls. No use of CCBs [ref]: 356 cases and 1,629 controls.
Main results	For overall cohort: adjusted OR (aOR) for any use versus no use [ref]: 1.39 (95% CI 1.14 – 1.69). For cohort taking an AHT: aOR for any use versus no use [ref]: 1.21 (95% CI 0.88 – 1.67). For cohort with diagnosis of hypertension: aOR for any use versus no use [ref]: 1.71 (95% CI 0.99 – 2.95).

Other analyses	CCB use by duration relative to non-user (including no medication user):
	  ≤2 years (cases 2,906 control 8,662) aOR 1.28 (95% CI 1.05-1.57)
	  >2-4 years (cases 369 control 1,379) aOR 1.37 (95% CI 1.05-1.79)
	  >4-6 years (cases 174 control 599) aOR 1.43 (95% CI 1.02-2.01)
	  >6-8 years (cases 67 control 228) aOR 1.39 (95% CI 0.84-2.29)
	  >8 years (cases 13 control 41) aOR 1.38 (95% CI 0.48-4.01)
	
	Duration-response analysis shows no association for cohort with AHT use or diagnosis of hypertension.

Discussion	
Limitations (author reported)	Possible residual confounding for covariates not considered in the model (especially smoking), small cases numbers for 8-10 years of use may have limited power of study for

	this subgroup, non-dihydropyridine CCBs, diuretics, aldosterone receptor antagonists not included due to limited time scale of use in Taiwan, different comorbidity patterns might affect results (e.g. beta-blockers use in heart failure) and no formal competing risks analysis.
Interpretation	"…our study results did not suggest a causal relationship between long-term use of any AHT (dihydropyridine CCBs and others) and the risk of breast cancer". The authors attribute risk in the larger cohort to confounding by indication. "…physicians should not sacrifice the long-term cardiovascular benefits of AHTs just for fear of uncertain breast cancer risk…".
Generalisability	Not discussed.
Funding	Not mentioned.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, AHTs = antihypertensive drugs, ARBs = angiotensin II receptor blockers, CCB = calcium channel blockers, CI = confidence interval, OR = odds ratio.

Author(s) and year of publication (Reference number on manuscript)	Davis & Mirick 2007 (36)
Objectives	"To investigate whether the use of commonly prescribed medications, primarily antihypertensives and antidepressants, is associated with an increased risk of cancer"
Methods	
Study design	Case-control study (re-analysis of cases/controls from a study conducted 5 years previous).
Setting	Seattle, Metropolitan Area. Study interviews, March 2000 through December 2001. Cases originally diagnosed with breast cancer between November 1992 and March 1995.
Participants	**Cases** were women aged 20-74 at time of diagnosis; date of diagnosed defined as the 'index date'. **Controls** originally identified by random-digit dialling and frequency-matched to cases by 5-year age groups.
Variables	**Outcome(s):** newly diagnosed breast cancer, with sub-analysis including localised breast cancer only. **Exposure(s):** taking CCBs (antidepressants, NSAIDS and beta-blockers also assessed in the study). If participants recalled taking a medication, they were asked about "regular use" defined as use 4 days/week for > 6 months in the 10 years prior to diagnosis, duration of regular use (e.g. < 5 years versus 5-10 years), and recency of regular use (e.g. 2 years since diagnosis). **Potential confounder(s):** parity, age at first pregnancy, mother/sister breast cancer, early double oophorectomy, combined oral contraceptive use, ever upper-gastrointestinal series, ever smoker, mother/sister breast cancer < 45 years, alcohol intake (if premenopausal), HRT (if postmenopausal). **Potential effect modifier(s):** none mentioned
Data collection/measurement	Questionnaire sent out one week prior to telephone interview. Cases asked about exposure/covariate information from 10 years prior to their diagnosis, controls from 10 years prior to corresponding index date.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Logistic regression conditional on 5-year age strata and adjusted for confounders listed above.
Results	
Number of participants	In original study: 813 of eligible cases agreed to participate (of 1,039, 78%), for this study 600 (74% of those agreeing before, 58% of those eligible initially agreed to participate, 89% of the original cohort still alive). In original study: 793 (of 1,053, 75%) of controls agreed to participate. For this study 600 (76% of those agreeing before, 57% of original, 85% of the original study cohort still

	alive). CCB ever users: 38 cases; 36 controls. CCB never users [ref]: 509 cases; 560 controls.
Description of study group	Assume age range 25 through 83 years of age, though age range not specifically reported. Of 597 (of 600) cases reported on, 71% had localised disease, 28% had regional, 0.5% had distant disease).
Outcome(s) overall	7% of cases were ever users of CCBs; 6% of controls were ever regular users of CCBs.
Main results	Ever use of CCBs versus never use: aOR 1.4 (95% CI 0.9-2.4).
Other analyses	CCB use <5 years (relative to never use): aOR 1.7 (95% CI 0.9-3.0) CCB use 5-10 years (relative to never use): aOR 1.0 (95% CI 0.4-2.3) Use > 2 years prior to diagnosis (relative to never use): aOR 2.1 (95% CI 0.7-6.6) Use within 2 years of diagnosis (relative to never use): aOR 1.3 (95% CI 0.8-2.3) **For localised disease only** Ever use of CCBs (relative to never use) aOR 1.7 (95% CI 1.0-2.8) CCB use <5 years (relative to never user): aOR 2.0 (95% CI 1.1-3.8) CCB use 5-10 years (relative to never use) aOR 1.0 (95% CI 0.4-2.6) Use > 2 years prior to diagnosis (relative to never use): aOR 1.7 (95% CI 0.5-6.2) Use within 2 years of diagnosis (relative to never use): aOR 1.3 (95% CI 0.9-2.9)
Discussion	
Limitations (author reported)	1) Because participants contacted 5-8 years after initial study and asked about their medication use 10 years before diagnosis, recall necessary for 5 to 18 years in the past. 2) Small numbers recalling medication use in each class. 3) Limited to cases that survived for ≥ 5 years, therefore bias introduced by some having died in the interim and potential for different patterns of medication use.
Interpretation	"In conclusion, the results of this population-based study supports previous findings that

	calcium channel blocker use may be associated with a modest increase in breast cancer risk…".
Generalisability	No mention of generalisability.
Funding	Grant from the National Cancer Institute (R01 CA81614).

Abbreviations: aOR = adjusted odds ratio, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, NSAID = non-steroidal anti-inflammatory drug.

Author(s) and year of publication (Reference number on manuscript)	Devore *et al.* 2015 (37)
Objectives	"…to evaluate whether antihypertensive medication use, including long-term use, is associated with breast cancer incidence in women".
Methods	
Study design	Cohort study, follow up to previous study by Michels *et al.* (ref, 55)
Setting	United States Study period, assessment of outcome from 1 June 1988 through 1 June 2012 for Nurses' Health Study (NHS) cohort, from 1 June 1989 through 1 June 2011 for NHS.
Participants	NHS cohort female nurses aged 30 to 55 years enrolled in 1976, NHS II female nurses aged between 25 and 42 enrolled in 1989. Follow-up from baseline to end of follow-up period, diagnosis of breast cancer, death, loss to follow-up, whichever occurred first. Cohort members' eligible if returning questionnaires. Participants with incident breast cancer, other cancer types (excluding non-melanoma skin cancer) or who did not report height at baseline, were all excluded.
Variables	**Outcome(s):** Incident breast cancer. **Exposure(s):** AHT use, CCBs one of the classes analysed. **Potential confounder(s):** BMI, height, combined oral contraceptive use, menopausal status, HRT for postmenopausal women, age at first birth, age at menarche, history of breast cancer, benign breast disease, ethanol intake, physical activity, smoking history, shift work history, aspirin use, and concomitant use of other AHTs. **Potential effect modifier(s):** None specifically mentioned.
Data collection/measurement	Data collection via biennial questionnaire asking about health conditions, medications and lifestyle factors. Death registries checked at each questionnaire cycle to assess if non-responders have died. **Outcome** data via self-report on biennial questionnaire, ideally confirmed by examining medical records, phone conversation or with written confirmation. Death via national death index. **Exposure** to CCBs assessed in 1988, 1994, and then every two-years thereafter for NHS, from 2001 onwards for NHS II. If data not collected in a questionnaire round, responses from previous questionnaire carried forward. For NHS II, data imputed back to 1989 based on responses in 2001. **Covariate data** collected at baseline and updated at each questionnaire cycle, missing indicators used where data were missing.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Cox proportional hazards adjusting for confounders above except for aspirin and concomitant AHT use, as these did not made a difference to generated HRs. Initially, all eligible cohort members included, then only including women with diagnosis of hypertension, then based on consistency of use, finally stratifying model by oestrogen-receptor status.

Results	
Number of participants	In NHS 95,501 women eligible; in NHS II 115,140 women eligible.
Description of study group	Results state that demographic data similar for most demographic characteristics for current versus past/never users of AHTs, however current users tended to be older, have higher BMI, lower physical activity levels and less regular use of aspirin.
Outcome(s) overall	Overall 10,012 cases of breast cancer (6,718 in NHS; 3,294 in NHS II). **NHS cohort:** Current CCB use: 640 events/144,242 PYs Never/past CCB use [ref]: 6,077 events/1,634,906 PYs **NHS II cohort** Current CCB use: 87 events/47,431 PYs Never/past CCB use [ref]: 3,025 events/ 1,925,448 PYs
Main results	Results are for multi-variable adjusted model. Current CCB use versus never/past use [ref] **NHS cohort:** aHR 1.07 (95% CI 0.99-1.17) **NHS II cohort:** aHR 0.97 (95% CI 0.78-1.20) Analysis restricted to women with hypertension only, current CCB use versus never/past use [ref] **NHS cohort:** aHR 1.10 (95% CI 1.00-1.20) **NHS II cohort:** aHR 0.99 (95% CI 0.76-1.30) For consistent CCB use, incosistent CCB use, both versus never use [ref] **NHS cohort:** Inconsistent use – aHR 0.95 (95% CI 0.87 – 1.04) aHR 1.10 (95% CI 1.00-1.20) Consistent use – aHR 1.06 (95% CI 0.97 – 1.16) **NHS II cohort:** Inconsistent use – aHR 0.75 (95% CI 0.56 – 1.01) Consistent use –aHR 0.92 (95% CI 0.69 – 1.24) Duration response analysis (consistent use for 2-4, 6-8, 10-14, ≥16 years): 95% CI for aHRs all cross the unity value of HR = 1, exact values not reported here, see Table 4 in the Devore *et al.* study (ref, 30).
Other analyses	CCB current use versus never/past users stratified for oestrogen-receptor status **NHS**

	Oestrogen receptor-negative
	aHR 1.36 (95% CI 1.09 – 1.70)
	Oestrogen receptor-positive
	Not reported
	NHS II
	Oestrogen receptor-negative
	aHR 1.20 (95% CI 0.75 – 1.93)
	Oestrogen receptor-positive
	Not reported
Discussion	
Limitations (author reported)	1) Observational study, thus risk of confounders not accounted for. However, many potential confounders included in multi-variable analysis. 2) Self-report for exposure, thus risk of misclassification. 3) Self-report information carried forward between questionnaires (as some classes not asked about every time), thus risk of misclassification. 4) Classes of AHT not considered at sub-class level.
Interpretation	Interpretation of non-association between CCB and breast cancer, though cases where a positive association was found should be investigated further.
Generalisability	Not commented on in the paper.
Funding	National Cancer Institute funds NHS and NHS II. LRW received partial support from a NIH training grant.

Abbreviations: aHR = adjusted hazard ratio, AHT = antihypertensive drug, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy.

Author(s) and year of publication (Reference number on manuscript)	Fitzpatrick *et al.* 1997 (38)
Objectives	To investigate the epidemiologic association between calcium channel blockers and breast carcinoma risk.
Methods	
Study design	Cohort study
Setting	Selected counties in North Carolina, California, Maryland, Pennsylvania and, later, comprising African American participants (geographical locations not specified), United States. Study period 1989/90 through December 1994 for original cohort; 1992/93 through December 1994 for African American cohort.
Participants	For this analysis, women 65 – 100 years included. Excluded if history of breast cancer or congestive heart failure at entry, if institutionalised, unable to provide informed consent, wheelchair bound, under hospice care, or receiving radiation or chemotherapy for cancer. Never users followed up from entry to censor date, users from start date (of CCB) to censor date. Censor at cancer hospitalisation, death or last contact with study. Unexposed becoming exposed could be accounted for in analysis.
Variables	**Outcome(s):** incident breast cancer requiring hospitalisation. **Exposure(s):** CCB use, regardless of other drug use, duration of use or discontinuation during follow-up **Potential confounder(s):** age, race (African-American or other), smoking, alcohol intake, education, income, functional status, and self-reported diabetes, BMI. **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** data collected by via hospital medical records, thus non-hospitalised case data not included in this analysis. Event data to end of 1994 received by 20 May 1996 included in the analysis. **Exposure data** via interviewer-administered questionnaire, aided by transcribing details of drug (separated into verapamil, diltiazem, nifedipine, non-nifedipine dihydropyridine, all separated into immediate- or sustained-release), dose etc. from labels on boxes/bottles of AHTs. **Covariate data** collected via interviewer-administered questionnaire.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Cox proportional hazards used to calculate HRs. PYs began with a lag of 1 year after starting CCBs to allow for latency. Also modelled with 0, 6, 12 and 24-month lag period. Model adjusted for age, race (African-American or other), parity, and age at menopause, self-reported diabetes. Main comparison of any CCB use to no CCB use, also CCB use to other AHT use. Groups not mutually exclusive. Sub-analysis for only users of HRT.
Results	

Number of participants	3,198 women included in the analysis. Mean 5 years follow-up for original, and 2 years for African American cohort. Any CCB use: 20 events/759 cohort members/1600 PYs No CCB use: 55 events/2439 cohort members/10,784 PYs
Description of study group	Mean age for CCB users of 72.9 years; 72.9 years for other AHTs and 71.9 years for non-AHT users. Amongst CCB users, 33.4% were African American, relative to 19.7% of other AHT-users and 10.8% of no AHT users. Initially predominantly immediate-release CCBs, though this increased over the study period (1,191 PYs of immediate-release, versus 1,128 PYs of sustained-release CCBs for the study overall).
Outcome(s) overall	75 cases of incident breast cancer.
Main results	CCB use versus no use [ref] aHR: 2.57 (95% CI 1.47-4.49)
Other analyses	CCB use versus other AHT use [ref] aHR 2.91 (95% CI 1.41-6.00) CCB use at less than modal dose versus no CCB use [ref] aHR 2.29 (95% CI .56 – 9.39) CCB use at modal dose versus no CCB use [ref] aHR 1.53 (95% CI 0.7 -3.37) CCB use at great than nodal dose versus no CCB use [ref] aHR 4.42 (95% CI 1.37 – 14.27) CCB & oestrogen use versus no use of CCB or oestrogen [ref] aHR 4.48 (95% CI 1.58 – 12.75) Other values in this additional analysis not reported here, see table 6 in study by Fitzpatrick *et al.* (ref, 35).
Discussion	
Limitations (author reported)	1) previous drug use prior to study not considered 2) small number of incident cancer cases 3) no amlodipine, nifedipine associated with excess mortality in other studies
Interpretation	Positive association between CCB and breast cancer use found in this study warrants further investigation. Biologically plausible link, evidence of dose-dependence and accounting for confounding by investigation considered in this study. However, low number of cases means results should be interpreted with caution and more research is needed.
Generalisability	Not commented upon.
Funding	Supported "in part" via contracts from the National Heart, Lung and Blood Institute.

Abbreviations: aHR = adjusted hazard ratio, AHT = antihypertensive drug, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, PY = person-year.

Author(s) and year of publication (Reference number on manuscript)	Fryzek *et al.* 2006 (39)
Objectives	To determine the relation between use of CCBs and ACEIs and cancer in general, updating a previous study by Olsen *et al.* (ref, 56) and Sorensen *et al.* (ref, 49).
Methods	
Study design	Cohort study
Setting	North Jutland, Denmark Study period from 1 January 1989 through 31 December 2002.
Participants	Population used to form cohort were women residents of the county aged ≥50, but < 67 years as at 1 January 1989. Excluded if cancer diagnosis prior to start of follow-up, excepting for non-melanoma skin cancer. Follow-up from date of second prescription of AHT, age of 50 years, 1 January 1990, whichever occurred later. Follow-up ended on first of the following events: age of 67, death, emigration from the country, date of diagnosis for breast cancer, or 31 December 2002.
Variables	**Outcome(s):** breast cancer incidence. **Exposure(s):** ≥ 2 prescriptions for an AHT during the study period. 1989 data used to assign exposure status, follow-up commenced from 1990. **Potential confounder(s):** age, postmenopausal HRT use, NSAID use, number of live births, age at first birth. **Potential effect modifier(s):**
Data collection/measurement	Used linked population-based databases (Central Population Register, Danish Cancer Registry and Pharmaco-Epidemiologic Prescription Database of North Jutland).
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Log-linear Poisson regression adjusting for confounders listed above, and by calendar period (1990-1995 or 1996 to 2002). All covariates except for live births and age at first birth were able to change during the follow-up period. Duration-response and cumulative-dose-response (inferred from number of prescriptions) analyses conducted. Sub-analysis also by subclass of CCB (dihydropyridine versus non-dihydropyridine). Assume that use of AHTs and classes/sub-classes of AHT is relative to non-use of an AHT.
Results	
Number of participants	49,950 women in the cohort, 19,284 classified as exposed to an AHT medication, leading to 109,985 person-years of follow-up, average follow-up of 5.7 years (range 0 to 13 years).
Description of study group (age, gender, other demographic data provided)	Mean age at entry of 52 (range, 50 – 67); 76% in 50 – 54 year category. Of AHT users, 23% used a CCB (+/- other AHTs).
Outcome(s) overall	264 cases of incident breast cancer among women 'exposed' to AHTs during study period (PYs = 109,985), number for unexposed not reported.
Main results	Ever use of CCBs versus never use of AHTs [ref] aRR 0.80 (95% CI 0.59 -1.09)

	Exclusive use of CCBs versus never use of AHTs [ref]
	aRR 1.19 (95% CI 0.87 – 1.65)
	Based on number of prescription (for ever users):
	2 – 4 (61 cases of breast cancer): aRR 0.74 (95% CI 0.38 – 1.43)
	5 – 9 (40 cases) : aRR 0.85 (95% CI 0.44 – 1.64)
	10 – 19 (163 cases): aRR 0.81 (95% CI 0.55 – 1.2)
	Based on years of follow-up:
	<1 (23 cases): aRR 0.41 (95% CI 0.13 – 1.29)
	1-4 years (104 cases): aRR 0.84 (95% CI 0.54 – 1.29)
	5+ years (137 cases): aRR 0.89 (95% CI 0.57 -1.38)
Other analyses (e.g. sub-analyses of subpopulations, sensitivity analyses)	Ever use of dihydropyridines (n = 8493): aRR 0.85 (95% CI 0.60 - 1.20) Ever use of non-dihydropyridines (n = 1,113): aRR 0.72 (95% CI 0.42 – 1.23) No clear duration-response or cumulative dose-response (inferred from number of prescriptions) shown, see table 4 on paper by Fryzek *et al.* (ref, 36). The authors state that subgroup analyses with women taking HRT (as performed in the Fitzpatrick *et al.* study (ref, 35) did not support the positive association find in the other study.
Discussion	
Limitations (author reported)	1) lack of history before 1989 2) no information on BMI, age at menarche, alcohol use, physical activity 3) Length of follow-up may limit findings, plan to continue monitoring cohort.
Interpretation	"… this study offers no support for a relationship between any class of AHT and breast cancer risk"
Generalisability	Not mentioned specifically, but mention women in general in conclusion.
Funding	International Epidemiology Institute, Rockville, Maryland; the Ingeborg and Leo Dannins Foundation for Scientific Research; the Western Danish Research Forum for Health Sciences.

Abbreviations: AHT = antihypertensive drug, aRR = adjusted relative risk, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, NSAID = non-steroidal anti-inflammatory drug, PY = person-year.

Author(s) and year of publication (Reference number on manuscript)	Gonzalez-Perez *et al.* 2004 (40)
Objectives	To investigate the association between the risk of breast cancer and use of captopril and other antihypertensive medication.
Methods	
Study design	Nested case-control study.
Setting	United Kingdom Study period January 1995 through December 2001.
Participants (eligibility criteria, source of cases/controls (if applicable), define as matched/unmatched (if applicable)).	Women aged 30 – 79 years between January 1995 and December 2001, enrolled from the first day within study of period of having at least 1-year enrolment with the GP and 1 year since first computer-generated prescription. Cohort members with a code for cancer prior to starting date and those >70 years of age at start date and who had no data recorded during followed up time were excluded. Follow-up from start date through to recorded breast cancer, age of 80 years, death or the end of December 2001, whichever occurred first. **Cases** selected from the cohort, with the date of diagnosis defined as the 'index date'. For each cohort member, a random date during the study period generated, if this date fell within the period contributing person-time for that cohort member, this person was eligible to be a control. **Controls** frequency-matched by age (1-year interval), and calendar year.
Variables	**Outcome(s):** incident breast cancer **Exposure(s):** prescription of an AHT, defined as current or past use. **Potential confounder(s):** information collected on history of hypertension, diabetes, ischaemic heart disease, cerebrovascular disease, previous breast lump/biopsy ($\geq$ 1 year before index date), alcohol intake, BMI, HRT use also ascertained. **Potential effect modifier(s):** nil mentioned.
Data collection/measurement	This study used the UK General Practice Research Database (GPRD). **Outcome** identified through coding on the UK GPRD, with confirmation on these members patient profile. **Exposure and covariate data** from the UK GPRD alone.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Unconditional logistic regression used to generate odds ratio, assumed to be a valid estimate of the rate ratio, for use of AHTs and individual classes (including CCB) stratified by duration of use, relative to no use. Adjustment for: age, calendar year, hypertension, BMI, alcohol intake, smoking status, HRT

	use, prior breast lump/biopsy, and differing lengths of use of other AHTs. Duration-response analysis also conducted
Results	
Number of participants	Cohort comprised 734, 899 women. Of these, 4,005 codes for breast cancer, 297 of which could not be confirmed or were prevalent cases. 3,708 incident breast cancer cases included in this analysis. This was compared to 20,000 controls.
Description of study group	No age/demographic data provided besides that in eligibility criteria. Amongst cases, 10.1% had current or past use of CCB; this value was 10.8% amongst controls (respectively, 29% and 28% had a prescription for any AHT within 1 year of index date). (current)CCB use < 1 year: 63 cases; 377 controls CCB use 1 – 3 years: 66 cases; 419 controls CCB use > 3 years: 128 cases; 703 controls Past use (used ended >1 prior to index date): 118 cases; 657 controls No use [ref]: 3,333 cases; 17,844 controls
Outcome(s) overall	Overall incidence of breast cancer of 156 per 100,000 person-years, increasing incidence until 60 and then plateau thereafter.
Main results	(current) CCB use < 1 year versus no use [ref] aOR 0.8 (95% CI 0.6 – 1.1) CCB use 1 – 3 years versus no use [ref] aOR 0.8 (95% CI 0.6 – 1.1) CCB use > 3 years versus no use [ref]): aOR 1.0 (95% CI 0.8 – 1.2) Past CCB use versus no use [ref] aOR 0.9 (95% CI 0.8 – 1.2)
Other analyses (e.g. sub-analyses of subpopulations, sensitivity analyses)	Assume relative to no use. Nifedipine versus no use [ref] Current short (< 2 years), 36 cases, 216 controls aOR 0.9 (95% CI 0.6 – 1.3) Current long (> 2 years), 87 cases, 459 controls, aOR 1.1 (95% CI 0.8 – 1.4) Amlodipine versus no use [ref] Current short, 42 cases, 286 controls, aOR 0.7 (95% CI 0.5 – 1.0)

	Current long, 28 cases, 160 controls, aOR 1.0 (95% CI 0.7 – 1.5)
	Diltiazem versus no use [ref]
	Short duration, 20 cases, 137 controls, aOR 0.8 (95% CI 0.5 – 1.3)
	Long duration, 19 cases, 134 controls, aOR 0.7 (95% CI 0.4 – 1.2)
Discussion	
Limitations (author reported)	1) Unable to account for age at menarche, family history, age at first child or germ line mutation. Though noted that this seems unlikely to change the null results.
Interpretation	"…we did not find any association between antihypertensives and the risk of cancer".
Generalisability	No mention of generalisability.
Funding	No funding source mentioned.

Abbreviations: AHT = antihypertensive drug, aOR = adjusted odds ratio, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, GP = general practitioner, HRT = hormone replacement therapy.

Author(s) and year of publication (Reference number on manuscript)	Grimaldi-Bensouda *et al.* 2016 (41)
Objectives	"The primary objective … was to investigate the potential association between CCB use and risk for all types of cancer. The secondary objectives were to investigate the association between CCB and colon, breast and prostate cancers".
Methods	
Study design	Cohort study
Setting	United Kingdom Study period 1 January 1996 through 31 December 2009.
Participants	Age 18 to 79 years, visiting GP ≥1 time(s) during study period, with > 2 years primary care and > 1 year(s) prescription history. Patients with cancer event at any time prior to index date excluded.
Variables	**Outcome(s):** Development of cancer (all types) and breast, colon or prostate cancer (separately), developed 6 months after index date (this was date of first CCB use (CCB cohort), date of first AHT (AHT cohort) or date of first CCB use for matched CCB user (matched non-CCB cohort). **Exposure(s):** CCB defined as ≥ 1 prescription during study period. For breast cancer these were compared to an AHT cohort (subset of non-CCB cohort formed by assigning 4 age-and sex-matched to each CCB user within study period, who had used ≥ 1 non-CCB AHT during study period). **Potential confounder(s):** age, sex (both matching variables), alcohol consumption, diabetes, hypertension, arrhythmia, angina, or heart failure, statins, aspirin at or within 1 year of baseline, smoking status, BMI. **Potential effect modifier(s):** Nil specified.
Data collection/measurement	Used data from the Clinical Practice Research Datalink and National Cancer Registration System for **outcome, exposure and covariate data.**
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Conditional logistic cox-regression modelling including women cohort members only, to estimate HRs adjusting for age at index date, smoking status, BMI, alcohol consumption, diabetes, hypertension, arrhythmia, angina, heart failure, or use of statins or aspirin. 'CCB cohort' compared to 'AHT cohort'.
Results	
Number of participants	865,647 in total: 150,750 in CCB group; 557,931 in non-CCB group; 156,966 in other AHT group (ref for breast cancer-specific analysis). Women only: CCB cohort 75,794; and AHT cohort 84,697 [Ref].
Description of study group	Mean age for CCB cohort 61.5 years (SD 11.5) and for AHT cohort 51.4 years (SD 15.4), 50% male in CCB versus 46% in AHT cohort, 73.6% in CCB with hypertension at baseline versus 29.1% in AHT (though this was adjusted for in analysis), higher proportion obese in CCB group

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	versus AHT (28% versus 21%, respectively).
Outcome(s) overall	CCB use (women only): crude rate 3.05/1,000 PYs (1,397 cases of breast cancer for 457,417 PYs of follow-up). Other AHT use (women only) [ref]: crude rate 2.32/1,000 PYs (1,194 cases of breast cancer for 514,400 PYs of follow-up).
Main results	aHR 0.95 (95% CI 0.87-1.04).
Other analyses (e.g. sub-analyses of subpopulations, sensitivity analyses)	Nil relevant
Discussion	
Limitations (author reported)	• Younger age for the AHT cohort mentioned, though this was adjusted for in the analysis. • Results do not apply directly to populations not covered by the UK Clinical Practice Research Datalink.
Interpretation	"This…study provides strong evidence that CCB use is not associated with an increased risk of cancer…The analyses yielded results across all types of cancer…It is likely different results obtained from different countries are due to methodological rather than biological issues". **Note that conclusions for cancer generally, no specific conclusions for breast cancer specifically other than mention of results across all types of cancer.**
Generalisability	"The results of this study do not apply directly to populations not included in the CPRD network of physicians". However the authors note it is likely to be generalisable to the British population.
Funding	Innovative Medicine Initiative Joint Undertaking.

Abbreviations: aHR = adjusted hazard ratio, AHT = antihypertensive drug, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, NSAID = non-steroidal anti-inflammatory drug, PY = person-year, SD = standard deviation.

Author(s) and year of publication (Reference number on manuscript)	Hole *et al.* 1998 (55)
Objectives	"To measure the rates of incident and fatal cancer in hypertensive patients taking calcium antagonists and to compare these with rates in three control groups".
Methods	
Study design	Retrospective cohort study
Setting	Scotland Study period 1 January 1980 through 31 December 1995
Participants	Patients attending the Glasgow Blood Pressure Clinic during the study period. Follow-up from date of first prescription for an AHT, through to diagnosis of cancer, death or 31 December 1995, whichever comes first. Patients receiving no treatment or known to have cancer before first prescription were excluded.
Variables	**Outcome(s):** incident cancer (breast cancer included as one of 30 cancer sites). **Exposure(s):** first prescription for a CCB or other AHT. **Potential confounder(s):** age, sex, smoking status and year of observation. **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** from Scotland Cancer Registry, with co-author assigning outcome blinded to exposure. West of Scotland Cancer Registry used to assess the expected breast cancer incidence. **Exposure data** from blood pressure clinic prescription records, with co-authors blinded to outcome status. **Covariate** data also collected from blood pressure clinic records.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Ratio of relative risks calculated by comparing observed: expected cases for CCB users, to the observed: expected cases for non-CCB users. Expected case numbers adjusted for confounders listed above.
Results	
Number of participants	5,207 in study population (assessing the risk of all incident cancer), 2,297 prescribed a CCB, 2,910 prescribed another AHT. CCB group 14 observed cases (23%, of 62 amongst women); 12.86 expected No CCB group 17 observed cases (16%, of 109 amongst women); 22.67 expected cases
Description of study group (age, gender, other demographic data provided)	For study overall: mean age of women 57.4 years for those on CCBs; 48.3 years for those not. Proportion women aged above 70 years 13.4% for CCB group; 6.4% for no CCB group. Average follow-up 5 years for CCB group; 7.8 year for non CCB group.
Outcome(s) overall	

Main results	Calcium antagonist: non-calcium antagonist ratio of relative risks = 1.45. Difference no noted as significant with p<0.05.
Other analyses (e.g. sub-analyses of subpopulations, sensitivity analyses)	Nil relevant
Discussion	
Limitations (author reported)	1) Risk of ascertainment bias, reduced by using same method of cancer certification throughout, by avoiding new searches beyond standard identification, keeping assessors blinded to exposure/outcome (depending on what they were assessing). 2) Selection bias due to confounding by indication.
Interpretation	No evidence for an increase of cancer among patients taking calcium antagonists. No interpretation of breast cancer result.
Generalisability	No specific mention.
Funding	A.F.L supported by grants from the British Heart Foundation and Tenovus-Scotland.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Jick *et al.* 1997 (56)
Objectives	To study a large group of hypertensive patients to investigate the relation between calcium channel blockers and cancer.
Methods	
Study design	Nested case-control study
Setting	United Kingdom Study period based on outcome in 1995.
Participants	**Cohort,** Hypertensive patients who were current users of beta-blockers alone, ACEIs alone or CCBs alone (all +/- diuretics) and had at least four years of continuous medical history were eligible. Patients with history of cancer before 1995 (except for non-melanoma skin cancer) were excluded. **Cases** had a first-time cancer diagnosis in 1995. Date of diagnosis considered 'index date'. **Controls (up to 4: 1 cases)** sourced from cohort members, matched to cases by age (within 5 years), sex and GP surgery attended.
Variables	**Outcome(s):** incident cancer diagnosed in 1995 (except non-melanoma skin cancer) **Exposure(s):** exposure to CCB, ACEI, or beta-blocker (all +/- diuretic, but mutually exclusive of the other classes in the study) in the year prior to index date. **Potential confounder(s):** duration of hypertension, BMI, concurrent diuretic use, smoker status. **Potential effect modifier(s):** not mentioned
Data collection/measurement	This study used data from the UK General Practice Research Database (GPRD). **Outcome** data planned to be confirmed via questionnaire to GP/assessment of medical records. However, the 32% where questionnaires were not returned were included in the analysis as relative risks were similar to when they were excluded. **Exposure data** information also collected about duration of exposure, daily dose (at, lower, or higher than mode), and whether taken once, twice or three times per day.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Conditional logistic regression comparing CCB (+/- diuretics) use to beta-blocker use, adjusting for potential confounders listed above. No duration-response analysis conducted for breast cancer specifically.
Results	
Number of participants	For total study, 464 cases, with 18 excluded = 446 cases included, matched to 1,750 controls. Only 68% of those returned questionnaires, but as mentioned above, cases where a questionnaire was not returned were included in the analysis. <u>For Any cancer:</u> CCB, but not beta-blocker/ACEI: 178 cases; 573 controls

	Beta-blocker, but not CCB/ACEI [ref]: 183 cases; 755 controls CCB use (+/- diuretics) 80 cases; number of controls not reported Beta-blocker use (+/- diuretics) Number of cases or controls not reported.
Description of study group	Mean age for study overall of 71.6 years for cases; 71.3 years for controls. 79% of cases and 76% of controls had duration of hypertension ≥ 4 years.
Outcome(s) overall	For study overall (assessing cancer risk overall, not only breast cancer risk) 40% of cases were taking a CCB (+/- diuretic); relative to 33% of controls.
Main results	CCB use versus beta-blocker use (both +/- diuretic) [ref]: aRR 1.32 (95% CI 0.72 – 2.41)
Other analyses	Nil relevant to review.
Discussion	
Limitations (author reported)	1) Only had access to records for up to 7 years before diagnosis, therefore longer-term effect cannot be ruled out.
Interpretation	"We found not evidence of a material increase in the risk of any cancer casually associated with use of calcium-channel blockers relative to the use of beta-blockers".
Generalisability	Not discussed.
Funding	Bayer AG. Boston Collaborative Drug Surveillance Program supported by grants from: Astra AB, Berlex Laboratories, Bayer AG, Boots Healthcare International, Glaxo Wellcome Inc, Ciba-Geigy Corporation, Hoechst AG, RW Johnson Pharmaceutical Research Institute, Merck Research Laboratories, N V Orgenan, and Pfizer Inc.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, aRR = adjusted relative risk, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Lam *et al.* 2014 (42) **conference abstract and poster presentation**
Objectives	To confirm of refute the results of Li *et al.* (43) showing a positive association between CCB use and the development of breast cancer.
Methods	
Study design	Prospective cohort study
Setting	United States
Participants	Females, aged 50-70, with no history of breast cancer, categorised as 'General patients' (GPs) and coronary angiography (CV) patients. Participants prescribed CCBs matched with those not prescribed CCBs (1:1) based on age, race, tobacco, alcohol, body mass index, hypertension and follow-up time.
Variables	**Outcome(s):** incident breast cancer. Secondary outcomes of incident diabetes, coronary and renal disease. **Exposure(s):** Prescription of a CCB. **Potential confounder(s):**; **Potential effect modifier(s):** history of other cancers, family history of breast cancer.
Data collection/measurement	**Outcome, exposure and covariate** data extracted from Intermountain Healthcare databases
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Multivariable cox proportional hazards regression used, adjusted for effect modifiers (above). **Unclear if adjustment for matching criteria covariates.**
Results	
Number of participants	**From conference abstract:** 3,718 in total: 2,612 general patients and 1,106 CV patients.
Description of study group	**From poster presentation:** disease burden generally higher amongst CCB versus non-CCB group. Mortality also relatively higher amongst CCB group.
Outcome(s) overall	**From conference abstract**: Breast cancer predominantly developed in < 5 year of follow-up (64% of cases) – though maximum follow-up and cancer rate overall not specified.
Main results	**From conference abstract:** CCB prescription versus no CCB prescription [ref] **GP group:** aHR of 1.58 (95% 1.10-2.26) **CV group:** aHR 0.51 (95% CI 0.27-0.97) **From poster presentation:** CCB prescription versus no CCB prescription [ref] **GP group:**

	aHR 1.71 (95% CI 1.20 – 2.44) **CV group:** aHR 0.68 (95% CI 0.37 – 1.25)
Other analyses (e.g. sub-analyses of subpopulations, sensitivity analyses)	Consistent associations for both cohorts for several secondary outcomes (incident diabetes, coronary and renal disease) between the two groups (data not reported here). **From poster presentation:** Dihydropyridine CCB prescription versus (presumably) no CCB prescription [ref] **GP group:** aHR of 1.78 (95% 1.17 – 2.69) Non-dihydropyridine CCB prescription versus (presumably) no CCB prescription [ref] **GP group:** aHR of 1.5 (95% 0.86 – 2.63)
Discussion	
Limitations (author reported)	None detailed.
Interpretation	"Modest association" between CCB use and incident breast cancer observed in the general patient group, not reproduced in the CV patient group. These authors interpret the positive association as likely to represent uncorrected confounding (e.g. prescriber bias or drug interactions) and recommend further analysis through randomised controlled trials.
Generalisability	Not mentioned.
Funding	None mentioned.

Abbreviations: aHR = adjusted hazard ratio, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Largent *et al.* 2010 (43)
Objectives	"…to elucidate the association between hypertension, antihypertensive medication use, and breast cancer…".
Methods	
Study design	Prospective cohort study
Setting	California, United States Study period 2000 through 31 December 2006.
Participants	**Cohort:** women from California Teachers Study cohort, completing baseline survey in 1995/96, survey included questions on CCB from 2000/01. **Excluded:** >85 years at baseline, unknown history of hypertension or AHT use, incident breast cancer prior to filling in CCB-inclusive survey, unknown history of breast cancer, moved out of California, or who did not complete the AHT section of the questionnaire in that year. Follow-up from date of 2000/01 surveys, incident breast cancer, death, moving away from California, or 31 December 2006.
Variables	**Outcome(s):** incident invasive breast cancer, **Exposure(s):** AHT use (thiazide diuretics, CCB, ACEI and other antihypertensive) for ≥ 2 months **Potential confounder(s):** race, family history of breast cancer, age at first full-term pregnancy and number of full-term pregnancies, hormone therapy and menopausal status, lifetime physical activity, diabetes, BMI, smoking history, alcohol use, hysterectomy, breastfeeding, and percentage of calories from fat. **Potential effect modifier(s):** none mentioned.
Data collection/measurement	**Outcome data via** identified through linked-data with California Cancer Registry. **Exposure data** via 2000/01 self-administered questionnaire. **Covariate data via** baseline, self-administered, questionnaire.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Multivariable Cox-proportional hazards with person-years accumulated based on age in days, adjusted by confounders above and stratified by age at baseline (single age in years). CCB use relative to no CCB use (including those not using an AHT).
Results	
Number of participants	73,742 included in analysis relevant to this review (of 114, 549 eligible cohort members at baseline for the general analysis relating to AHT use and breast cancer risk). CCB regular use within 2 years 84 events/24,593 PYs No regular CCB use [ref] 1,630 events/448,175 PYs

Description of study group	Mean age at baseline of 52.8 years overall, 50.9 years for women without hypertension, and 62.2 years for women with hypertension. However, the CCB-relevant analysis began follow-up ~ 5 years beyond this. A history of high blood pressure reported by 16.8% of women.
Outcome(s) overall	For follow-up period relevant to this review, 1,714 invasive breast cancer diagnoses included.
Main results	CCB regular use within 2 years versus no regular use [ref]: aRR 1.05 (95% CI 0.84 – 1.31)
Other analyses	Nil relevant
Discussion	
Limitations (author reported)	1) Limited information on whether hypertension was controlled by drugs. 2) Limitation relating to collection of information at beginning of follow-up only.
Interpretation	No specific interpretation of CCB result. Overall comment based on total cohort with respect to AHT use: increased risk of invasive breast cancer was observed for long-term ($\geq$5 years) antihypertensive use. The authors mention the challenge of isolating the association with AHTs relative to any association with hypertension itself.
Generalisability	No specific mention.
Funding	NIH supported.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aRR = adjusted relative risk BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Leung *et al.* 2015 (44)
Objectives	"To address the conflicting evidence from previous studies…to evaluate the risk of breast cancer associated with long-term use of antihypertensives in hypertensive women."
Methods	
Study design	Case-control study.
Setting	Taiwan Study period 1 January 1998 and 31 December 2011.
Participants	Cases and controls selected from cohort formed of people with hypertension, taking AHTs for > 6 months continuously during study period. Follow-up from date of diagnosis of hypertension during study period, until death, or 31 December 2011, whichever came first. **Cases** defined those with incident breast cancer ((ICD-9 CM codes 174.xx and 175.xx) during study period. Index date defined as date of breast cancer diagnosis. **Controls** (4:1 cases) from cohort with no diagnosis of breast cancer, matched for age (5-year categories), index data, and year of hypertension diagnosis. **Excluded:** Patients with history of breast cancer prior to prescription of AHT, or without continuous enrolment in National Health Insurance Program excluded.
Variables	**Outcome(s):** first diagnosis of breast cancer, **Exposure(s):** treatment with AHTs (beta-blocker, CCB, ACEI, ARB) for > 6 months during study period **Potential confounder(s):** age, "comorbidities" at cancer diagnosis, measured in the year prior to cancer diagnosis, statins, HRT Rx. **Potential effect modifier(s):** none mentioned.
Data collection/measurement	The National Health Insurance Research Database and Catastrophic Illness Patient Database used to assign **outcome, exposure and covariate variables.**
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Logistic regression used to estimate crude and adjusted ORs, unclear exactly what adjusted for in main CCB versus no CCB use analysis. Duration – and cumulative dose-response analyses conducted. Additional analysis undertaken changing to AHT prescription at least 6-9 months before the index date.
Results	
Number of participants	6,463 hypertensive women with breast cancer, 18,987 randomly selected controls.
Description of study group	Mean age for controls, 61.9 (SD 10.7); 61.9 (SD 10.9) for controls. 52.8% of cases; 48.9% controls ever-users of CCBs. Use of HRT cases 15.7% and controls 12.4%. Use of Statin cases 11.4% and controls 6.8%. Diabetes cases 27.3% and controls 25.3%.
Outcome(s) overall	CCB users:

	3,411 cases; 9,290 controls
	No CCB use [ref]:
	3,052 cases; 9,697 controls
Main results	CCB ever use versus no CCB use:
	aOR 1.09 (95% CI 1.03 – 1.16)
	Duration-response analysis versus no use [ref]:
	≤1 year: aOR* 1.05 (95% CI 0.94 – 1.16)
	1-2 years: aOR* 1.08 (95% CI 0.98 – 1.19)
	2 – 3 years: aOR* 1.09 (95% CI 0.98 – 1.22)
	>3 years: aOR* 1.11 (95% CI 1.03 – 1.19)
	Test for trend, p = 0.006
	Cumulative daily defined dose (quartiles defined in paper), versus no use [ref]:
	<Q1: aOR*1.05 (95% CI 0.96 – 1.15)
	Q1-Q2: aOR* 1.07 (95% CI 0.98 – 1.18)
	Q2-Q3: aOR*1.06 (95% CI 0.97 – 1.17)
	>=Q4: aOR* 1.16 (95% CI 1.06 – 1.28)
	*Adjusted for peripheral vascular disease, diabetes mellitus, medicines use (including HRT, statin, beta-blocker and ACEI):
Other analyses	Changing date of AHT by 6 – 9 months described as not changing the result.
Discussion	
Limitations (author reported)	1) Database contained only de-identified records
	2) Only information on frequency and classes of prescribed medications, did not provide clinical laboratory data/clinic information
	3) No information on risk factors: physical activity, alcohol consumption, smoking, body mass index, socioeconomic status, and diet. Could confound association.
Interpretation	"…the long-term use of CCBs [or beta-1 selective blockers] is likely to be associated with breast cancer risk".
Generalisability	Not mentioned.
Funding	"No funding or sponsorship was received for this study or publication of this article".

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aOR = adjusted odds ratio, ARB = angiotensin II receptor blocker, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, ICD = international classification of disease.

Author(s) and year of publication (Reference number on manuscript)	Li *et al.* 2003 (45)
Objectives	"To explore whether use of CCBs and other classes of antihypertensive medications are associated with breast carcinoma incidence…in older women."
Methods	
Study design	Case-control study
Setting	Seattle-Puget Sound Metropolitan Area, United States Study period for outcomes occurring 1 April 1997 through 31 May 1999.
Participants	**Elibility:** women aged 65 – 79 years in these counties appearing on a list of social security recipients provided by the Centers for Medicare and Medicaid Services. **Cases:** eligible women diagnosed with invasive breast cancer between 1 April 1997 and 31 May 1999, having no previous history of *in situ* or invasive breast carcinoma. The 'reference date' for cases was the date of diagnosis. **Controls** were matched on age, selected via the Social Security register and resided in the same three counties cases were identified from. For reference dates for controls were chosen to match an expected distribution of reference dates for cases. **Excluded:** If a history of breast cancer recorded any time other than between April 1, 1997 and May 31, 1999.
Variables	**Outcome(s):** invasive breast cancer, **Exposure(s):** exposure to AHT (beta-blocker, CCB, ACEI and diuretics) ≥ 6 months. **Potential confounder(s):** race, income, marital status, education, age at menarche, parity, age at first birth, age at menopause, duration of combined oral contraceptive use, ever use of HRT, first-degree relative history of breast carcinoma, smoking status, average daily alcohol intake, BMI. **Potential effect modifier(s):** nil mentioned.
Data collection/measurement	**Outcome date** identified through the Cancer Surveillance system, a population-based tumour registry. **Exposure and covariate data** collected via participant interview. Recall enhanced by 'life events calendar' and pictures of different AHT medication.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Unconditional logistic regression, adjusted for age only, as other potential confounders did not change effect estimate by >10% when added one-by-one to the model. Cases/controls categorised as 'never users', 'users', 'former users' and/or 'current users'. CCB user versus never AHT user. Sub-analysis restricting to only AHT users, CCB use versus non-use.
Results	
Number of participants	975 (of 1,210, 80.6%) of eligible cases were interviewed; 1,007 (of 1,365, 73.8%) on eligible controls were interviewed.

Description of study group	- Greater proportion of non-white in control group. - Cases were somewhat more likely than controls to have an - early age at menarche, - to be older at the time of their first birth, - to have undergone a hysterectomy without a bilateral oophorectomy, - to have a first-degree family history of breast carcinoma, - to be ever users of HRT, - to have a history of hypertension, - to be current or former smokers, - to have higher levels of alcohol consumption, and - to have a higher BMI. Other demographic and reproductive characteristics were similar
Outcome(s) overall	Ever use of CCB: 149 (15.3%) of cases; 141 (14%) of controls. Never use of AHT [ref]: 446 (45.7%) cases; 490 (48.7%) controls. <u>Among those used antihypertensive:</u> Never used CCBs: 363 cases (out of 512); 348 controls (out of 489);
Main results	<u>Ever use of CCB versus no use of AHTs [ref]</u> aOR 1.2 (95% CI 0.9 – 1.5). <u>Duration-response analysis versus no use of AHTs [ref]:</u> 6 months – 5 years: aOR 1.2 (95% CI 0.8 – 1.7) 5-15 years – aOR 1.2 (95% CI 0.8 – 1.8) 15 years: aOR 0.6 (95% CI 0.3 – 1.3) Former use: aOR 2.1 (95% CI 1.0 – 4.5) Current use: aOR 1.1 (95% CI 0.8 – 1.5) <u>Sub-class analysis versus no use of AHTs [ref]:</u> Immediate – release: aOR 1.4 (95% CI 1.0 – 2.1) Sustained – release aOR 1.0 (95% CI 0.7 – 1.4) IR- non-DHPs, positive association with ever-use: aOR 1.6 (95% CI 1.1 – 2.5), however not higher for long-use, lower for former versus current users.
Other analyses	**Restriction only to ever users of AHTs:** <u>Ever use of CCBs versus no use of CCBs [ref]</u> OR 1.0 (95% CI 0.8 – 1.3) <u>Duration-response analysis, versus no use of CCBs [ref]</u> 6 months – 5 years: OR 1.0 (95% CI 0.7 – 1.5) >5 years: OR 0.9 (95% CI 0.6 – 1.3).

Discussion	
Limitations (author reported)	1) Only able to interview 80.6% of eligible cases and 73.8% of eligible controls, therefore there may be some selection bias. 2) Recall of patients relied upon to collect information. 3) Limited to women 65-79 years, may affect generalisability of results. 4) Large number of comparisons performed; therefore associations may be the result of chance. 5) More cases than controls reported a history of hypertension.
Interpretation	"…considering the available evidence, the finding of others and our own results indicating that IR CCBs may be associated with breast carcinoma incidence should be interpreted with caution".
Generalisability	Restricted to women 65-79 years, therefore results may not be applicable to younger women.
Funding	Supported by the National Cancer Institute.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aOR = adjusted odds ratio, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy.

Author(s) and year of publication (Reference number on manuscript)	Li *et al.* 2013 (46)
Objectives	"To evaluate associations between use of various classes of antihypertensive medications and risk of invasive ductal and invasive lobular breast cancers amongst post-menopausal women".
Methods	
Study design	Case-control study
Setting	Greater Seattle Metropolitan Area, United States. Study period for outcome between 1 January 2000 and 31 December 2008.
Participants	**Eligibility criteria:** women aged 55 to 74 years diagnosed as having a primary invasive breast cancer between January 2000 and December 2008 identified through the Cancer Surveillance System (CSS), the population-based tumour registry that serves western Washington state. **Cases** eligible women with invasive lobular (ILC, ICD codes 8520, 8522, 8524), and a sample of ~ 25% with invasive ductal breast cancer (IDC, ICD code 8500) were eligible for selection as cases. IDC patients frequency matched by 5-year age group to ILC patients. Reference year defined as year of diagnosis. **Controls (1:1:1 ratio)** identified through random digit dialling on those with Landlines, from eligible counties (~1.2% of those eligible did not have a landline). Controls frequency matched for 5-year age group to ILC case patients, county, reference year. Reference year defined by expected distribution for controls based on reference years for cases. **Excluded:** Women for whom there was no information regarding antihypertensive medication or alcohol use were excluded from the analysis, as were women without a landline telephone.
Variables	**Outcome(s):** ILC or IDC forms of breast cancer **Exposure(s):** use of AHT, including diuretic, beta-blocker, CCB, ACEI, ATRA, and combination AHTs **Potential confounder(s):** age, race/ethnicity, education level, income, alcohol use, smoking status, HRT use, first-degree family history of breast cancer, parity, age at first birth, hypertension, hypercholesterolaemia, heart disease, BMI, recent mammography, other commonly used medications (lipid-lowering agents, NSAIDs, diabetes, hyperlipidaemia, depression) **Potential effect modifier(s):** nil mentioned.
Data collection/measurement	**Outcome** assigned via Cancer Surveillance System and confirmed via review of pathology reports **Exposure and covariate** information collected via an interviewer-administered questionnaire, medication information transcribed from pill bottles where available and visual aids also used to enhance recall.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with	Polytomous logistic regression used adjusting for age (5-year categories), reference year, county, race/ethnicity, and recency of alcohol use. Potential confounders other than recency of alcohol use did not change effect estimate by >10% when added to the model individually Women who

missing data.	had never used any type of AHT medication were the primary reference category. Analysis also conducted separating into 'current users', 'former users', and 'short-term users'. Analysis restricted to only users of AHTs conducted. Subclass (short, long-acting, dihydropyridine, non-dihydropyridine), duration-response and analysis stratifying by oestrogen-receptor type (positive or negative) also conducted.
Results	
Number of participants	Total cohort : 2495 eligible cases identified, 1984 (80%) were interviewed, and 1313 eligible controls identified, 902 (69%) were interviewed, Included in analysis: 891 controls (of 1,313 eligible, 68%), 905 IDC and 1,055 ILC cases (together, of 2,495, 79%). Cohort with hypertension: 360 controls, 353 IDC, 416 ILC cases.
Description of study group	Similar age distributions, income, history of hypertension (44%), heart disease and hypercholesterolaemia. ILC less likely to be African American, more likely to be college graduates, less likely to be obese, relative to IDC and controls. IDC and ILC patients more likely to have first-degree relative history of breast cancer, to use alcohol, to smoker, relative to controls. Use of HRT highest for ILC, lowest for controls.

Outcome(s) overall	CCB use amongst full cohort:
	 For IDC: CCB current use: Cases 94 and Controls 74
	           Non-user [Ref]: Cases 477 and Controls 456
	 For ILC: CCB User: Cases 102 and Controls 74
	           Non-user [Ref]: Cases 556 and Controls 456
	 CCB use (any duration) among Cohort with hypertension
	 For IDC: CCB current use: Cases 85 and Controls 70
	           Non-user [Ref]: Cases 268 and Controls 290
	 For ILC: CCB User: Cases 91 and Controls 70
	           Non-user [Ref]: Cases 325 and Controls 290

Main results	CCB use versus never use of AHTs [ref] Current use: IDC aOR 1.3 (95% CI 0.9 – 1.8) ILC: aOR 1.3 (95% CI 0.9 – 1.8) < 5 year use: IDC (36 cases; 35 controls): aOR 0.9 (95% CI 0.6 – 1.5) ILC(34 cases; 35 controls): aOR 0.8 (95% CI 0.5 – 1.3) 5-9.9 year: IDC (28 cases; 35 control) aOR 1.2 (95% CI 0.7 – 2.2), ILC (43 cases; 35 controls) aOR 1.3 (95% CI 0.8 – 2.4) ≥ 10 year: IDC (27 cases; 12 controls) aOR 2.4 (95% CI 1.2 – 4.9),

	ILC (31 cases: 12 controls) aOR 2.6 (95% CI 1.3 – 5.3). Test for trend, p = 0.01. Association with long-term use ≥ 10 years unaffected by oestrogen-receptor status: oestrogen receptor-positive breast cancer **invasive ductal** aOR 2.3 (95% CI 1.1 – 4.8) **invasive lobular** aOR 2.6 (95% CI 1.3 – 5.2), oestrogen receptor-negative **invasive ductal** aOR 3.1 (1.1 – 8.8), **invasive lobular** not reported. Sub-class analysis of CCBs on table 4 of paper. <ins>For ≥ 10 year of long-acting CCB versus never use of AHT [ref]:</ins> IDC (case/controls numbers not reported) aOR 2.7 (95% CI 1.2 – 5.7) ILC (cases/controls numbers not reported) aOR 2.5 (95% CI 1.2 – 5.5)
Other analyses	<ins>CCB use versus use of other AHTs (but not CCBs) [ref]</ins> Current use: IDC aOR 1.4 (95% CI 0.9 – 2.0) ILC aOR 1.2 (95% CI 0.8 – 1.6) Use < 5 year IDC (32 cases; 33 controls) aOR 1 (95% CI 0.6 – 1.8) ILC (31 cases; 33 controls) aOR 0.8 (95% CI 0.5 – 1.4) Use 5-9.9 years: IDC (23 cases; 22 controls) aOR 1.2 (95% CI 0.7 – 2.3) ILC (29 cases; 22 controls) aOR 1.2 (95% CI 0.7 – 2.1) Use ≥10 years: IDC (25 cases; 11 controls) aOR 2.6 (95% CI 1.2 – 5.4) ILC (26 cases; 11 controls) aOR 2.2 (95% CI 1.0 – 4.5)
<ins>Discussion</ins>	
Limitations (author reported)	1) Risk of recall bias. 2) Selection bias, lower response of controls versus cases. 80% of eligible cases interviewed; 69% of eligible controls.
Interpretation	Long-term use of CCBs may be associated with an increased risk of breast cancer.
Generalisability	Two factors increase generalisability: 1) population-based design; 2) high response rates amongst cases and controls.
<ins>Funding</ins>	This study was funded by the National Cancer Institute (R01-CA105041) and the US Department of Defense (W81XWH-05-1-0482).

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aOR = adjusted odds ratio, ATRA = angiotensin II receptor antagonist, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, ICD = international classification of disease, NSAID = non-steroidal anti-inflammatory drug.

Author(s) and year of publication (Reference number on manuscript)	Lindholm *et al.* 2001 (57) *
Objectives	"…to analyse the frequency of cancer in elderly patients who participate in the 'Swedish Trial in Old Patients with Hypertension 2'"
Methods	
Study design	Randomised, controlled trial.
Setting	Sweden. Recruitment from 1 September 1992 through 31 December 1998. Mean follow-up of 5.0 years, median of 5.3 years.
Participants	**Eligible:** Patients with hypertension, defined as systolic BP $\geq$ 180 mmHg and/or diastolic $\geq$ 105mmHg, randomly assigned to beta-blocker/diuretic, ACEI (lisinopril or enalapril), or a CCB (felodipine 2.5mg or 5mg, or isradipine 2.5mg or 5mg daily). Within group allocation was non-random. Participants seen twice a year throughout study follow-up and existing AHT prior to trial would be continued. Follow-up from enrolment to: diagnosis of a 3rd cancer, death, or end of study period, whichever occurred first **Exclusions:** contraindication to any of the study drugs, a requirement for any of the study drugs, orthostatic hypotension, participation in another study, severe of incapacitating illness or unwillingness to participate.
Variables	**Outcome(s):** cancer incidence (excepting basal cell carcinoma) **Exposure(s):** randomly assigned treatment with AHTs (beta-blocker/diuretic, ACEI or CCB). **Potential confounder(s):** age, demographic characteristics and pre-morbid conditions. **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** assigned via Swedish Cancer Registry, which is populated by clinical and pathology/cytology reports. **Exposure** assigned at randomisation, within group allocation was non-random. **Covariate data** collected at baseline.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Standardised incidence ratios (SIR) using person-years, with 5-year age group, sex and calendar-year specific incidence data for the whole of Sweden used as a reference. CIs calculated based on a Poisson distribution. Cumulative frequency function to show occurrence of new cancer. Log-rank test used to calculate hazard of first cancer after randomised, with adjustment for death and end of follow-up.
Results	
Number of participants	No loss to follow-up for this trial. 6,614 patients enrolled in this trial, 2,196 in the CCB arm.
Description of study group	Mean age (overall) 76 years (range 70-84 years) at baseline, 48 in CCB group (2.2%) had a history of breast cancer. 192 (8.7%) had a history of any cancer. For CCB group, mean age 75.9 years, 34% male.

	SIR overall of 0.98 (95% CI 0.76 – 1.25).
Outcome(s) overall	Breast cancer frequency overall was 67 (19.5% of total 344 incident cancer amongst women in the study). Frequency of breast cancer in CCB group (women only) of 19 (observed): 22.54 (expected).
Main results	SIR for patients in CCB group of 0.84 (95% CI 0.51 – 1.32). Note outcome "essentially the same" when re-analysed excluding patients with a history of cancer diagnosis.
Other analyses	Nil relevant.
Discussion	
Limitations (author reported)	1) No adjustment for risk factors: obesity, smoking, previous smoking, alcohol, or protective factors like participating in a clinical trial, residence in rural areas etc. 2) No information of any pre-existing AHTs prior to enrolment. Some patients taking multiple AHTs (follows from inclusion criteria); this was not adjusted for. 3) Median follow-up relatively short at 5.3 years, cancer has long latency.
Interpretation	"We saw no significant deviation from the expected number from any cancer type". No specific interpretation of breast cancer result.
Generalisability	No discussion in the paper.
Funding	The study was supported by grants from Astra (AstraZeneca), Merck Sharp and Dohme, Sandoz (Novartis) and Zeneca (AstraZeneca).

* STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement used for RCT to be consistent with other study data, though typically RCTs will report against the CONsolidated Standards of Reporting Trials (CONSORT) Statement.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Meier *et al.* 2000 (47)
Objectives	"To explore further whether long-term use of ACE inhibitors, CCBs or beta-blockers may be associated with a decreased or increased risk of breast cancer…"
Methods	
Study design	Case-control study
Setting	United Kingdom Study period for outcome 1 January 1992 through 30 September 1997.
Participants	**Eligibility:** women $\geq$ 50 years old at index date with a drug prescription history in the database of $\geq$ 3 years. **Cases** a first-time diagnosis of incident breast cancer during study period (index date is date of diagnosis). **Controls** (4:1 case) selected for each definite and probable breast cancer case, matched by age, physician practice, calendar date (index date for case), and number of years of medical history in the database. **Excluded:** malignancy, excepting non-melanoma skin cancer prior to breast cancer diagnosis were excluded.
Variables	**Outcome(s):** incident breast cancer. **Exposure(s):** AHT medication, classified as CCBs only, ACEIs only, beta-blockers only, mixed users (all +/-diuretics). **Potential confounder(s):** smoking status, BMI, history of alcohol abuse, previous hysterectomy, history of benign breast disease. **Potential effect modifier(s):**
Data collection/measurement	**Outcome, exposure and covariate data** via the UK General Practice Research Database (GPRD). Breast cancer diagnoses classified as: <u>confirmed</u> (undergoing mastectomy, radiotherapy and/or chemotherapy with detailed clinical records) and <u>probable</u> (hospitalised at first-time diagnosis and who had some information was recoded (e.g. new tamoxifen) but the patient record lacked further evidence of final confirmation of the diagnosis, were counted as cases. When assessing outcome, exposure information was suppressed.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Conditional logistic regression modelling adjusting for smoking status and BMI. CCB use relative to no use of AHT (except for diuretic). Users separated into current and past users. Duration-response, subclass analyses, as well as analysis if HRT used concurrently were conducted.
Results	
Number of participants	3,706 case and 14,155 controls.
Description of study group	• Mean duration of medical history of 5.3 years (range of 3 – 14 years: 50 - 59 years: 32%, 60 -69 years: 26%, 70 years or older: 42%).

	• >75% had >5 years of follow-up.
Outcome(s) overall	No antihypertensive, except Thiazide [Ref]: 2567 cases and 9745 controls CCB use any duration: 190 cases and 735 controls CCB use ≥5yrs: 53 cases and 226 controls
Main results	CCB use versus no use of CCBs/beta-blockers or ACEIs [ref] aOR 1.0 (95% CI 0.8 – 1.1) Duration of CCB use versus no use of CCBs/beta-blockers or ACEIs [ref] 1-2 years (79 cases, 293 controls) aOR 1.0 (95% CI 0.8 – 1.3) 3-5 years (19 cases, 75 controls) aOR 1.0 (95% CI 0.6 – 1.6) ≥5 years (53 cases, 226 controls) aOR 0.9 (95% CI 0.7 – 1.2) Unknown (39 cases, 141 controls) aOR 0.7 (95% CI 0.7 – 1.5)
Other analyses	Sub-class analysis relative to use of neither CCBs, beta-blockers or ACEIs [ref]: Nifedipine aOR: all 95% CI cross unity value of 1. Other DHPs: all 95% CI cross unity value of 1. Diltiazem HCl: all 95% CI cross unity value of 1. Verapamil HCl: all 95% CI cross unity value of 1. Mixed CCB use: all 95% CI cross unity value of 1. Use of CCBs and oestrogen replacement for ≥ 3 years (5 cases; 27 controls) aOR 0.8 (95% CI 0.3 – 2.0).
Discussion	
Limitations (author reported)	1) cannot extrapolate data to long-term use 2) Unable to control for factors such as ethnic origin, socioeconomic status, physical activity or diet (as not recorded in the database).
Interpretation	This analysis does not provide evidence for an association between CCBs and breast cancer.
Generalisability	No specific mention of generalisability, though the authors note that there are a large numbers of cases in this study.
Funding	The present study was not directly funded. Study supported in part by Cooperative Agreement FD-U-00140501 from the U.S. Food and Drugs Administration. The Boston Collaborative Drug Surveillance Program is supported by Astra, Sodertalje, Berlex Laboratories, Glaxo Wellcome, Roche, Novartis, RW Johnson Pharmaceutical Research Instititute, Medeva PLC.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aOR = adjusted odds ratio, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy.

Author(s) and year of publication (Reference number on manuscript)	Michels *et al.* 1998 (58)
Objectives	To investigate whether self-reported use of CCB, beta-blockers, or ACE-I; relative to the use of diuretics, was associated with incidence of or mortality from cancer.
Methods	
Study design	Prospective cohort study.
Setting	United States Study period 1988 through 1 May 1994.
Participants	**Cohort** formed from the Nurses' Health Study participants which was initiated in 1976 and includes 121,701 female registered U.S. nurses aged 30 –55 years at the time of entry. For the current analysis, follow-up was started from 1988 after return of a questionnaire on medication from the participant through to May 1, 1994, or the diagnosis of cancer or death, whichever occurred first. **Excluded:** Participants who were reported use of both CCB and ACE-I. Women were also excluded from the analysis if their year of birth, smoking status in 1988, menopausal status in 1988, or weight or height was unknown, or if their date of death was prior to 1988 or not yet known.
Variables	**Outcome(s):** cancer incidence and mortality. Mortality results not reported here. **Exposure(s):** thiazide diuretics, beta-blockers, calcium channel blockers, ACEIs, or any combination – assessed only in 1988. **Potential confounder(s):** age, weight, height, cholesterol level, systolic and diastolic blood pressure, smoking, amount of current smoking, alcohol intake, regular physical activity, menopausal status, HRT use of >=5 years, aspirin >=5 days per month, diabetes, cancer, stroke, myocardial infarction, CABG, PTCA, angina pectoris, hypertension in or prior to 1988. **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** self-reported via 2-yearly questionnaire and these women were contacted for study physicians to view hospital records, blinded to exposure information. **Exposure** assigned via responses in 1998 questionnaire without further updating. **Covariate** data collected via 2-yearly questionnaire, updated during study period.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Relative risks calculated for CCB users compared to no CCB use using pooled logistic regression. CCB use relative to non-use, adjusting for age, multiple drug use, self-reported weight, height, smoking status and mean number smoked daily for women who smoked in 1988, alcohol intake in 1988, physical activity, menopausal status in 1988, postmenopausal HRT, cholesterol level, systolic and diastolic blood pressure in 1988, aspirin intake, diabetes, history of stroke, MI, CABG, PTCA, angina, hypertension in or prior to 1988,family history

	of breast carcinoma, history of benign breast disease, age at menarche, parity, age at first birth, and age at menopause.
Results	
Number of participants	18,635 in the study population, 684 died, 502 (2.7%) lost to follow-up. 2,361 on CCB; 16,274 not on a CCB. 107,256 person-years of data.
Description of study group	Mean age for CCB group 58 years; 56.8 years for non-CCB group. Women prescribed CCBs more likely to have a history of diabetes, pulmonary disease, ischaemic heart disease, angina pectoris, or CABG. Women reporting use of other cardiovascular medications were more likely to be hypertensive (38.9% versus 70.6%).
Outcome(s) overall	852 were newly diagnosed with cancer between 1988 and 1994, and 335 died of cancer during this follow-up period. Breast cancer incidence: Non-user of AHT [Ref]: 304 (out of total 730 cancer incident among non-user) CCB user: 51 (out of total 122 cancer incident among CCB user)
Main results	CCB use versus no CCB use [ref]: aRR 1.07 (95% CI 0.78 – 1.48) [Non-user 82,524 PYs (Ref); CCB user 11,807 PYs]
Other analyses	Nil relevant.
Discussion	
Limitations (author reported)	1) Self-reported medication use, however population consisted of health professionals, which may offset information bias resulting from this. 2) No information on duration of use, or if use began in or before 1988. 3) Could not ascertain what proportion of women was diagnosed with cancer prior to taking any medications. 4) No dose information, could not study at a sub-class level.
Interpretation	"…these prospective data suggest a major association between the use of calcium-channel blockers or the short-acting formulation and cancer incidence or cancer mortality is unlikely." "Further follow-up is needed to rule out late effects of calcium channel blockers on cancer risk".
Generalisability	Not discussed.
Funding	Supported by research grant CA 40356 from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, aRR = adjusted relative risk, AHT = antihypertensive drug, CABG = coronary artery bypass graft, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, MI= myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, PYs = person-years

Author(s) and year of publication (Reference number on manuscript)	Olsen *et al.* 1997 (59)
Objectives	"…to examine the incidence of cancer in a population-based cohort of approximately 18,000 users in a well-defined region of Denmark".
Methods	
Study design	Cohort study.
Setting	North Jutland, Denmark. Study period 1 January 1991 through 31 December 1993. Mean follow-up time 1.8 years (range 0 to 3).
Participants	Cohort members received a prescription for a CCB during the study period. Follow-up from date of prescription through to emigration, death, or 31 December 1993. **Excluded:** malignancy diagnosis (except non-melanoma skin cancer) prior to breast cancer diagnosis. **Excluded:** unable to find on prescription database or death before or on the day of CCB prescription.
Variables	**Outcome(s):** cancer, excluding non-melanoma skin cancer **Exposure(s):** a prescription for a CCB **Potential confounder(s):** none mentioned **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** assigned via Danish Cancer Registry. **Exposure** assigned via the Pharmaco-epidemiological prescription database.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Number of cases observed amongst cohort compared to that expected based on data from the Danish Cancer Registry. This was used to calculate standardised incidence ratios (SIR). County-specific incidence rates for all tumour categories, calculated according to sex and age (in 5-year groups), were applied to person-years of observation to obtain the number of cancers expected if the incidence rates the same as that for the general population of the county, following a Poisson distribution.
Results	
Number of participants (in total and per group) and number lost to follow-up (if applicable)	17,944 patients included in the study (overall assessing cancer risk, not only breast cancer). 17,911 included in the analysis (0.2% had died or could not be found on the prescription database).
Description of study group	Overall, 32% < 59 years of age; 28% 60 -69 years, 29% 70 – 79 years, 11% ≥ 80 years. Overall, 49% men, 27% on verapamil only, 41% DHPs only, 24% diltiazem only, 8% mixed use.
Outcome(s) overall	32 breast cancer cases observed: 40.3 were expected.
Main results	SIR 0.8 (95% CI 0.5 – 1.1).

Other analyses (e.g. sub-analyses of subpopulations, sensitivity analyses)	Nil relevant.
Discussion	
Limitations (author reported)	1) Potential for people prescribed CCBs to be in poorer health, or for cancer to aggravate cardiovascular disease 2) Potential for bias through these individuals having more interaction with the health system 3) Follow-up period of only 3-years
Interpretation	No breast-cancer specific interpretation, but overall: "…our study…revealed no evidence of a tumour-promoting effect".
Generalisability	Not commented upon.
Funding	Danish Cancer Society and Danish National Research Foundation.

Abbreviations: CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Pahor *et al.* 1996 (60)
Objectives	"…to assess whether individuals taking calcium-channel blockers, for any indication were at higher risk for developing cancer than those not taking those drugs."
Methods	
Study design	Prospective cohort study
Setting	Selected countries in Massachusetts, Iowa, Connecticut, United States. Study period for outcome between 1988 through 31 December 1992. Mean of 3.7 years of follow-up.
Participants	**Eligible:** Based on the Established Populations for Epidemiologic Studies of the Elderly. Cohort aged $\geq$ 65 years at baseline in 1982, 80% of eligible population interviewed. Follow-up until reported cancer, death, or 31 December 1992, whichever happened first. **Excluded:** if could not link with Medicare (MEDPAR) file, reported cancer prior to study commencement, or taking cancer-associated medication (e.g. tamoxifen).
Variables	**Outcome(s):** first cancer event **Exposure(s):** patients taking CCBs in 2 weeks before baseline interview **Potential confounder(s):** age; sex; ethnic origin; coronary heart disease; heart failure; hypertension; stroke; diabetes; use of beta-blockers, ACEIs, diuretics, digoxin, nitrates, NSAIDs, aspirin, corticosteroids, oestrogens, coumarin, smoking, alcohol, physical disability, BMI, number of hospital visits. **Potential effect modifier(s):**
Data collection/measurement	**Outcome** assigned from 6-year follow-up questionnaire through 31 December 1992 by examining Medicare (MEDPAR) files (validated against a Cancer Registry in one study state). **Exposure** self-reported at baseline in 1982/83. Labels from bottles/boxes also used to transcribe information from prescription medication. **Covariate data** self-reported at baseline interview in 1982/83.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Kaplan Meier curves and cox-proportional hazards stratified by region, with CCB use relative to non-use, adjusted for age, sex, ethnic origin, heart failure, number of hospital admissions, cigarette smoking and alcohol intake, with assumption of proportionality assessed. Indicators for missing data used (e.g. 1.1% had data missing on cigarette smoking).
Results	
Number of participants	Of original >10,000 interviewed in 1982/83, 6,566 participants were still alive and interviewed in 1988 (baseline for this study). 298 excluded because could not link with health records. Total cohort for the current analysis 5052 patients: 451 CCB user and 4601 non-CCB user.
Description of study group	For study overall: Patients taking CCBs more likely to have CV disease, diabetes, to use CV drugs, to be disabled, to have lower diastolic BP and to be admitted to hospital. Other

	demographic data were similar. Mean age 79 for both groups.
Outcome(s) overall	31 breast cancer events reported (7.4% of total 420 incident cancer in this study).
Main results	Use of CCB any duration vs non-CCB [Ref]: aHR 1.65 (95% CI 0.49 – 5.55)
Other analyses	Note that for cancer overall in this study, an aHR of 1.72 (95% CI 1.27 – 2.34) was reported, with a positive dose-response (low, medium, high dose) – test for trend p = 0.0094.
Discussion	
Limitations (author reported)	1) Possibility of residual confounding 2) CCB users had higher hospitalisation rates; risk of selection bias through increased cancer detection. 3) Misclassification of exposure/outcome. Exposure only assessed at baseline, cancers not leading to hospitalisation/death missed. 4) Mainly short-acting CCBs used in this study. Long-acting CCBs might keep below a "harmful threshold".
Interpretation	Positive association found for cancer overall, further research should assess association. Overall, CCBs were associated with a general increased risk of cancer in the study population.
Generalisability	Potentially limited generalisibility to younger patients.
Funding	National Institute on Aging, M Pahor supported by University research grants from Italy.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, aHR = adjusted hazard ratio, AHT = antihypertensive drug, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, NSAID = non-steroidal anti-inflammatory drug.

Author(s) and year of publication (Reference number on manuscript)	Poole-Wilson *et al.* 2006 (48)
Objectives	To report the safety profile of nifedipine gastro-intestinal therapeutic system based on adverse effects reported in the ACTION trial.
Methods	
Study design	Randomised, double blind placebo-controlled trial
Setting	Nineteen countries, multi-centre trial. Mean follow-up 4.9 years.
Participants	**Inclusion:** Patients aged $\geq$ 35 years, stable symptomatic angina pectoris requiring treatment. Also needed a history of myocardial infarction, proven angiographic coronary artery disease, positive exercise test, or perfusion defect also needed, left ventricular ejection fraction $\geq$ 40%. **Exclusions:** heart failure, any major cardiovascular event or intervention in last 3 months, planned angiography or intervention, known intolerance to dihydropyridines, valvular, pulmonary disease, unstable insulin-dependent diabetes mellitus, any gastrointestinal condition prohibiting use of gastro-intestinal therapeutic system, any condition other than coronary artery disease limiting life expectancy, hypotension, uncontrolled hypertension, elevated creatinine or aminotransferase levels, women could only participate if no risk of pregnancy. **Follow-up** through the pre-defined end-date, patient refusal, clinical reason for stopping, or need for concomitant medication incompatible with study medication.
Variables	**Outcome(s):** multiple, site-specific cancer was one of them (in absence of pre-existing cancer, excepting non-melanoma skin cancers) **Exposure(s):** random assignment to nifedipine gastro-intestinal therapeutic system (GITs) 30mg, increasing to 60mg after 6 weeks, once daily or placebo **Potential confounder(s):** age, demographic characteristics, life-style and pre-morbid conditions. **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** confirmed via pathology report and **Exposure** assigned as part of the trial.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Incidence rate for an event by assigned treatment group was calculated as the number of patients with the event concerned divided by the total time 'at risk'. Hazard ratios (HRs) comparing nifedipine with placebo and their 95% confidence intervals (CIs) were obtained by Cox proportional-hazards analysis using treatment allocation as the only covariate. No adjustment made.
Results	
Number of participants	3,825 (of which site-specific cancer data for 3,655) in nifedipine group; 3,840 (of which site-specific cancer data for 3,654) in placebo group. Females: nifedipine groups 784 and placebo group 797.

Description of study group	Mean age 63 years for both, ~ 80% participants male.
Outcome(s) overall	Nifedipine GITS relative to placebo: 16 (15 female, 1 male) events versus 8 events (7 female, 1 male) respectively.
Main results	Hazard ratio of approximately 2.25 (based on rates reported in paper, 95% confidence intervals not reported, though cross unity value of 1).
Other analyses	Nil relevant.
Discussion	
Limitations (author reported)	None reported, though see interpretation below.
Interpretation	No specific interpretation regarding breast cancer risk. "The data on particular cancers is based on small numbers of cases and significant differences could represent chance findings".
Generalisability	Not discussed
Funding	Bayer Healthcare.

* STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement used for RCT to be consistent with other study data, though typically RCTs will report against the CONsolidated Standards of Reporting Trials (CONSORT) Statement.

Abbreviations: CCB = calcium channel blocker, CI = confidence interval, HR=hazard ratio

Author(s) and year of publication (Reference number on manuscript)	Raebel *et al.* (49) **conference abstract and conference poster.**
Objectives	Conference abstract: "To assess the relationships between CCB or ACEI use and risk of invasive breast cancer in postmenopausal women with <1 to 12 years CCB or ACEI use". Conference poster: "We estimated and compared risk of incident invasive breast carcinoma in a large cohort of postmenopausal women with hypertension who were new users of CCB or angiotensin converting enzyme inhibitors (ACEI)".
Methods	
Study design	Retrospective cohort study.
Setting	United States, 3 "Kaiser Permanente" (managed care consortium) regions. Study period 1997 to 30 April 2013
Participants	Women >55 years with hypertension and enrolled > 1 year prior to cohort entry, who were "new users" of CCBs or ACEIs. **Excluded:** <1 year follow-up, history of breast cancer
Variables	**Outcome(s):** Invasive lobular carcinoma or invasive ductal carcinoma of breast **Exposure(s):** CCB or ACEI use, who were followed up for > 1 year over study period (1997-2012) **Potential confounder(s):** Unclear if pre-specified. Time varying covariates were: other AHTs, age, BMI, hysterectomy, diabetes, alcohol, oestrogen, statins, mammography, and non-time varying were: region, race, education and cohort entry year. **Potential effect modifier(s):** none mentioned.
Data sources/measurement	The Kaiser Permanente data based appears to be the source for outcome, exposure and covariate data.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	For conference abstract: Association assessed for each year of follow-up for 12 years using a "life table approach" to obtain crude HRs and a discrete survival method to obtain HRs adjusted for covariates mentioned above. Reference group was <1 year of CCB or ACEI use. For poster presentation: Cox proportional hazard regression model used. CCB use relative to ACEI, adjusted for age, demographic characteristics and participating site.
Results	
Number of participants	Total cohort 165,807 women: CCB = 29,830 (18%); ACEI = 135,977 (82%)
Description of study group	Mean age of 68 and 67 years for CCB and ACEI users, respectively. Mean follow-4.7 years for CCB group, of which mean time on CCB was 2.6 years.
Outcome(s) overall	From poster: Breast cancer outcome: CCB = 572 (1.9%); ACEI = 2,688 (2.0%)

Main results	From conference abstract: For CCB use, with <1 year of CCB use as reference (unclear if ACEI users included in reference group), authors state that 95% CIs of the adjusted HRs cross the value of 1. Examples given in abstract of 9 years, adjusted HR = 1.09 (95% CI 0.6 – 2) and 12 years, adjusted HR = 0.88 (95% CI 0.28-2.78). **From poster presentation:** <u>Cox Regression Analysis</u> aHR 1.02 (95% CI 0.93-1.12) [Ref ACEI] <u>Discrete time survival mode</u> aHR 0.91 (95% CI 0.83-1.00) [Ref ACEI]
Other analyses	**From poster presentation:** <u>Analysis restricting to ≥ 2 years of ACEI/CCB use:</u> <u>Cox Regression Analysis</u> aHR 1.08 (95% CI 0.98-1.20) [Ref ACEI] <u>Discrete time survival mode</u> aHR 0.97 (95% CI 0.87-1.07)
Discussion	
Limitations (author reported)	None mentioned.
Interpretation	• Conference abstract: "Compared to <1 year use, for CCB use to 12 years, we found not statistically significant increase breast cancer risk". • **Poster presentation:** "No statistically significant increase in risk of invasive breast cancer among postmenopausal women with hypertension exposed to CCB compared ACEI."
Generalisability	Not discussed.
Funding	None mentioned.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, CCB = calcium channel blocker, CI = confidence interval, HR = hazard ratio.

Author(s) and year of publication (Reference number on manuscript)	Rosenberg *et al.* 1998 (61)
Objectives	"To assess whether calcium channel blocker use increases the risk of cancer overall and of specific cancers."
Methods	
Study design	Case-control study
Setting	Baltimore, New York and Philadelphia, United States. Study period 1983 through 1996
Participants	**Cohort:** Population was patients aged 40 – 69 years admitted to study hospitals from 1983 to 1996. **Cases** had a primary diagnosis of cancer within 1 year of admission for cancer overall and for site-specific cancers for which there were ≥ 20 cases. History of prior cancer (excepting non-melanoma skin cancer) or concurrent cancer was excluded. **Controls** selected from patients admitted for conditions judged not to be directly related to antihypertensive drugs. No matching criteria reported.
Variables	**Outcome(s):** primary cancer (overall) within 1 year of admission to hospital; site-specific cancers for which ≥20 cases were available **Exposure(s):** taking a CCB, ACEIs or beta-blocker ≥1 year prior to admission **Potential confounder(s):** age, interview year, BMI, annual visits to a physician 2 years before admission, race, years of education, breast cancer in a mother or sister, benign breast disease, age at menarche, age at first birth, parity, age at menopause, alcohol consumption, duration of COC use, duration of oestrogen supplementation. **Potential effect modifier(s):** none mentioned.
Data collection/measurement	**Outcome** via discharge summaries/pathology reports by researchers blinded to exposure status. **Exposure** assigned via interview, including drug, date started, duration, and frequency of use (but not dose). **Covariate** data via patient interview.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	For breast cancer, female cases compared to female controls. Unconditional logistic regression analysis comparing CCB use to non-CCB user, controlling for confounders listed above, age controlled for with 5-year categories. Duration-response analysis also conducted.
Results	
Number of participants	For study overall, 9,513 (of 9,642 available for the study) cases; 6,492 (or 8,826 available) controls available.
Description of study group	For study overall, mean age of cases 56 years; 41% male. Mean age of controls 52 years; 42% male. Mean duration of use of CCBs was 3.8 years amongst cases; 3.7 years amongst

	controls.
Outcome(s) overall	For cancer overall, amongst women, 215 cases used CCBs; 190 controls used CCBs.
	92 users of CCB developed breast cancer, relative to 190 controls (women only).
Main results	Use of CCB relative to never use [ref]
	aRR 1.1 (95% CI 0.8 – 1.4)
Other analyses	For use ≥5 years, beginning ≥1 year before admission:
	CCB use relative to never [ref] (amongst 27 cases, 53 controls, women only)
	aRR 1.1 (95% CI 0.7 – 1.8)
	Use of CCBs and oestrogen supplements relative to no use [ref]:
	16 cases; 32 controls, women only.
	aRR 1.1 (95% CI 0.6 – 2.0)
	Both restricting to use ≥5 years (RR, 0.8) and those using within 5 years of admission (RR, 1.5), both 95% CIs crossed unity.
Discussion	
Limitations (author reported)	1) Absence of information on dose, though no duration-response effect was found.
	2) Type of CCB (e.g. immediate- versus sustained-release) was not assessed.
	3) Restriction to <70 years, whereas other studies have included older cohorts.
Interpretation	"…the present results suggest that CCB use is unrelated to the overall risk of cancer or of specific cancers." No interpretation on breast cancer result specifically.
Generalisability	Not commented upon other than restriction to cohort < 70 years of age.
Funding	Funding by National Cancer Institute, additional support from the US FDA. Grant from Bayer AG and Knoll AG.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aRR = adjusted relative risk, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Sajadieh *et al.* 1998 (62) *
Objectives	"…to study the risk of cancer in relation to verapamil use".
Methods	
Study design	Prospective randomised double-blind, placebo-controlled trial.
Setting	Denmark Study period 1985 through 31 December 1993.
Participants	**Eligibility:** Multi-centre trial. Patients aged 76 years following acute myocardial infarction (MI), randomly assigned to verapamil 120mg three times daily or placebo in week 2 following acute MI. Follow-up from enrolment to December 1993. **Excluded if:** treatment with CCB, beta-blockers, uncontrolled congestive heart failure, sinoatrial block within last 3 days before randomisation, 2nd or 3rd degree atrioventricular block persisting after 3rd day of admission, hypotension or other severe disease, unwillingness to participate, or residence outside of the catchment area.
Variables	**Outcome(s):** primary outcome was mortality and major events, this study is a secondary analysis assessing the risk of cancer, overall and site-specific **Exposure(s):** treatment with verapamil 120mg three times daily or placebo **Potential confounder(s):** none mentioned **Potential effect modifier(s):** none mentioned
Data collection/measurement	**Outcome** assigned via Danish Cancer Registry. **Exposure** randomly assigned as part of the study.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	The observed cases were compared to expected values based on sex, age year (5-year group), and calendar-specific (5- year group) incidence rates from the Danish Cancer Registry based on person-years of observation. Observed compared to expected using life table analysis, 95% CI assuming Poisson distribution. Differences in rate ratios used to calculate standardised incidence ratios (SIRs).
Results	
Number of participants	897 in placebo; 878 in verapamil group. 10,474 person-years of follow-up. Female participants, 183 in placebo; 176 in verapamil treated group.
Description of study group	No significant differences in baseline characteristics. Mean duration of treatment 15 months.
Outcome(s) overall	Total cancer occurred 130 cases: 73 in the placebo-treated group (5,214 patient-years), and 57 in the verapamil-treated group (5,260 patient-years). Breast cancer occurred in women only, 3 cases in total: 1 placebo group; 2 verapamil group. Expected for both placebo and verapamil of 2.5 cases.
Main results	SIR, placebo group: 0.4 (95% CI 0.01–2.2) SIR, verapamil group: 0.4 (95% CI 0.1 – 2.9)

Other analyses	Nil relevant
Discussion	
Limitations (author reported)	1) Did not have information about duration of verapamil use at time of diagnosis. 2) No correction for smoking habits (62% current smokers) 3) Findings in patients with coronary heart disease may not be applicable to other patient groups.
Interpretation	"…no increased risks in any of the groups [of individual cancers], with only one exception [lung cancer]".
Generalisability	Findings in patients with coronary heart disease may not be applicable to other patient groups.
Funding	Funding information not reported on this paper.

*STROBE statement used for RCT to be consistent with other study data, though typically RCTs will report against the CONSORT Statement.

Abbreviations: CCB = calcium channel blocker, CI = confidence interval.

Author(s) and year of publication (Reference number on manuscript)	Saltzman *et al.* 2013 (50)
Objectives	A re-analysis of earlier cohort data (study by Fitzpatrick *et al.* ref 35) to assess the association between antihypertensive medication and breast cancer risk.
Methods	
Study design	Prospective cohort study.
Setting	Selected counties in North Carolina; California; Maryland; Pennsylvania and; later comprising African American participants (geographical locations not specified), United States. Study period 1989/90 through 31 December 2001 for original cohort; 1992/93 through 31 December 2001 for African American cohort.
Participants	Adults aged ≥65 years at recruitment. Exclusion if participants institutionalised, dependent on wheelchair, in hospice care, receiving radiation or chemotherapy, history of breast cancer or of heart failure. Follow-up from recruitment through to death, breast cancer diagnosis or end of 2001, whichever arrived first.
Variables	**Outcome(s):** breast cancer, invasive or *in situ*, **Exposure(s):** AHT use (CCB, Diuretics, beta-blockers, ACEI) **Potential confounder(s):** Race, smoking, history, education and income, BMI, use of oestrogen replacement therapy, diabetes, age, average weekly alcohol consumption, age at menopause, waist-hip ratio. **Potential effect modifier(s):**
Data collection/measurement	**Outcome** assigned by linkage to population-based cancer registries. **Exposure** assigned by details abstracted from AHT labels during annual interview. **Covariate data** during annual interview. Hypertension diagnosis classified by self-report, taking AHTs, having a resting systolic BP of ≥140mmHg, resting diastolic BP of ≥90mmHg.
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Cox proportional hazards used to assess association. AHT use treated as a time-varying exposure. "Exposed time" began when first reporting AHT use and continued until end of follow-up. Additional analysis to assess recency of use, with "exposed" considered use within previous 2 years for this analysis. Analyses also repeated amongst hypertensive women using AHTs to assess for bias by indication. Women could be included in groups for more than one class of AHT. CCB use relative to AHT non-user, adjusting for potential confounders included in the model only if changing association by >10%. **Age, average weekly alcohol consumption, age at menopause, waist-hip ratio were retained.** No evidence of effect modification found via likelihood ratio tests.
Results	
Number of participants	Total women cohort: 3201. Follow-up period of ~12 years. Non user of AHT medication = 1675 (~14,081 PYs), CCB user (ever) = 392 (~9,916 PYs)

	CCB use within past two years = 5,740 PYs
Description of study group	Higher proportion of women using AHTs were African American, had less high School education, less likely to have income >$25,000. Of non-users, higher proportion was smokers, reported consumption of 2 alcohol drinks per week. AHT users had higher waist – hip ratio, more likely to be hypertensive and have diabetes.
Outcome(s) overall	Ever user: Breast cancer during the follow-up period was 188 Non-user of AHT [Ref]: Breast cancer 69 (36.7% of total breast cancer incident) CCB user: Breast cancer 55 (29.3% of total breast cancer incident) Use in past 2 years: Breast cancer during the follow-up period was 143 Non-user of AHT [Ref]: Breast cancer 53 (37.1% of total breast cancer incident) CCB user: Breast cancer 40 (28% of total breast cancer incident)
Main results	For ever use analysis versus never AHT users [ref]: CCB (all types): aHR 1.1 (95% CI 0.7 – 1.6) CCBs (immediate-release), 24 cases: aHR 1.2 (95% CI 0.7 – 2.0) CCBs (sustained-release), 43 cases: aHR 1.1 (95% CI 0.7 – 1.6) Use in past 2 years versus never AHT use [ref]: CCB (all types), 40 cases: aHR 1.6 (95% CI 1.0 – 2.5) CCBs (immediate-release), 16 cases: aHR 2.4 (95% CI 1.3 – 4.5) CCBs (sustained-release), 28 cases: aHR 1.4 (95% CI 0.8 – 2.3)
Other analyses	No associations between AHT use and risk of any particular breast cancer subtype (data not presented in the paper). Amongst women with diagnosed hypertension or taking AHTs, aHR 1.8 (95% CI 0. 9 – 3.5) for recent use of immediate-release CCBs.
Discussion	
Limitations (author reported)	1) Data on exposure only during, but not before cohort follow-up. Therefore, could not accurately assess duration-response. 2) Limited statistical power to detect modest increase in relative risk. Due to relatively small sample size, the study had limited statistical power to identify more modest elevations in risk in the range of 20–50% and to conduct sub-analyses. 3) People moving outside of catchment areas would have had outcome data missed.
Interpretation	"Here, we observed that while there was some suggestion that calcium channel blockers increase breast cancer risk, this association appears to be confined to recent use of immediate-release formulations".
Generalisability	Not commented upon specifically.
Funding	Part support via a pilot grant Avon Foundation for Women.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, aHR = adjusted hazard ratio, AHT = antihypertensive drug, BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval, PYs = person-years.

Wright, C. and Moorin, R. and Chowdhury, E. and Stricker, B. and Reid, C. and Saunders, C. and Hughes, J. 2017. Calcium channel blockers and breast cancer incidence: An updated systematic review and meta-analy

Author(s) and year of publication (Reference number on manuscript)	Soldera *et al.* 2015 (51) **conference abstract and conference presentation**
Objectives	"…to determine whether the use of CCBs is associated with an increased risk of breast cancer overall, and to assess whether this risk varies with cumulative duration of use".
Methods	
Study design	Cohort study
Setting	United Kingdom. Study period to 31 December 2010.
Participants	Women newly treated with antihypertensive drugs between 1 January 1995 and 31 December 2009. **No exclusion criteria listed.**
Variables	**Outcome(s):** new diagnosis of breast cancer **Exposure(s):** Exposure to AHT (CCB, beta-blocker, diuretics, ARB or ACEI) **Potential confounder(s):** age, smoking status, body mass index, alcohol consumption, use of HRT or other prescription drugs. **Potential effect modifier(s):** not specified (though arguably some confounders are more likely effect modifiers).
Data collection/measurement	**Outcome, exposure, covariate** data collection via the UK Clinical Practice Research datalink
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Time-dependent cox proportional hazards used to estimate HRs adjusted for listed confounders. CCB use considered a time-varying variable, in relation to other AHT use. Exposure lagged by 1 year ("for latency considerations and to minimise reverse causality"). Secondary analysis to see if risk varied with duration of use.
Results	
Number of participants	273,152 women in total: 1,567,104 person-years of follow-up. CCB user 107,337 and Non-CCB user 165,815 [Ref]. No mention of any loss to follow-up.
Description of study group	Mean age (SD) for CCB users 62.6 (14.3) years; 58 (16.2) years for non-users.
Outcome(s) overall	4,520 newly diagnosed with breast cancer (incidence rate of 2.9/1,000 person-years). Breast cancer event: CCB user : 1518 Non-CCB user (other AHT) user: 3002 [Ref]
Main results	Incident rate for women using a CCB: 2.8/1,000 PY Incident rate for women using other AHTs: 3.1/1,000 PY <u>CCB versus other AHT [ref]</u> aHR 0.98 (95% CI 0.92-1.04) **Addition from conference presentation (same comparison):** aHR 0.96 (95% CI 0.90 to 1.03) [Conventional adjustment]

	aHR 0.97 (95% CI 0.89 to 1.05) [Time-varying adjustment]
Other analyses	CCB versus other AHT [ref] <5 years of use: HR 0.97 (95% 0.90-1.03) 5-10 years: HR 1.08 (95% CI 0.94-1.25) >10 years: HR 0.69 (95% CI 0.36-1.33) **Addition from conference presentation (same comparison):** CCB use by duration relative to Non-CCB user (p-trend = 0.25) < 5 years (1,302/ 431,598 PYs) aHR 0.96 (95% CI 0.90 to 1.03) 5 to 10 years (207/ 56,192 PYs) aHR 1.05 (95% CI 0.90 to 1.22) ≥ 10 years (9/ 3,978 PYs) aHR 0.61 (95% CI 0.32 to 1.20) Analysis done by CCB type (Short / long acting), all compatible with an aHR of 1.
Discussion	
Limitations (author reported)	**From conference presentation:** 1. Misclassification of exposure possible if noncompliance or treatment by specialist since prescriptions issued by general practitioners; 2. Possibility of residual confounding 3. Power for secondary analysis may not exclude an increased risk over 10 years of less than 20%.
Interpretation	"The results of this large population-based study indicate that the long-term use of CCBs is not associated with an increased risk of breast cancer".
Generalisability	Not specifically mentioned.
Funding	None mentioned.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, aHR = adjusted hazard ratio, ARB=angiotensin receptor blocker, CCB = calcium channel blocker, CI = confidence interval, HRT = hormone replacement therapy, PYs = person-years, SD = standard deviation.

Author(s) and year of publication (Reference number on manuscript)	Sorensen *et al.* 2000 (52)
Objectives	To investigate both cancer incidence and cancer mortality in an extension of a previous analysis of CCB users by Olsen *et al.* (ref 56).
Methods	
Study design	Cohort study
Setting	North Jutland, Denmark Study period 1 January 1989 through 31 December 1995.
Participants	Exposed to CCBs, as defined by receiving ≥ 2 prescriptions during study period.
Variables	**Outcome(s):** incident cancer cases and cancer deaths, excluding non-melanoma skin cancers excluded for analysis. Mortality also an outcome, though not reported here. **Exposure(s):** taking a CCB, defined as receiving ≥ 2 prescriptions during study period. **Potential confounder(s):** Nil **Potential effect modifier(s):**
Data collection/measurement	**Outcome** assigned via the Danish Cancer Registry. **Exposure** assigned via Pharmaco-epidemiological Prescription Database,
Statistical methods, methods for controlling for confounders/effect modifiers, methods for dealing with missing data.	Number of cancer cases observed amongst cohort CCBs compared to the expected number based on the Danish Cancer Registry, with standardised incidence ratios (SIRs) then calculated assuming a Poisson distribution is followed.
Results	
Number of participants	23,167 in cohort (73,193 person-years of follow-up); 11,726 women.
Description of study group	Mean age for women in study group 66.4 (SD 13.4) years; mean follow-up time of 3.2 years.
Outcome(s) overall	Breast cancer frequency during the follow-up period was 84 (18.5% of total 454 malignant cancer incident among women in this study). 86.7 cases expected.
Main results	SIR of 0.97 (95% CI 0.77 – 1.20)
Other analyses	
Discussion	
Limitations (author reported)	1) Inability to control for smoking and other confounders 2) Lack of information of CCB use before 1989 3) Lack of clinical detail regarding indications for use, limited duration of use and follow-up
Interpretation	Not specific interpretation for breast cancer. For cancer generally, the authors observe that "…our large, population-based study provides no evidence of an association between use of calcium channel blockers and an increase in cancer incidence or mortality."
Generalisability	Not commented upon.

Abbreviations: CCB = calcium channel blocker, CI = confidence interval, SD = standard deviation.

Appendix E. Risk of bias assessments for included studies. Reference on main paper in parentheses.

Assimes *et al.* 2008 (54)[*]

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Case groups had a diagnosis of cancer, whereas the control group did not. Otherwise, eligibility the same for both groups.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable	Study used linked data.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	No	Comparison group is appropriate, justification for thiazide diuretic group to reduce confounding by indication and justified by authors based on limited evidence of any association between thiazide diuretics and cancer.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Did not review study protocol, no obvious difference between methods and results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	No information given that assessors were blinded to exposure, though using Cancer Registry should reduce the risk of differential misclassification.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Use of linked data improves validity and reliability of measures used to assess eligibility. Exposure outcomes measured using prescriptions as a proxy for use, cited as a study limitation. Outcome measure used a Cancer Registry and comorbid data (though it is not possible to discern exactly what conditions were adjusted for), utilised doctors' files. Accuracy of registry not explicitly discussed but for sake of review considered as acceptable.
Q7. Was length of follow-up different across study groups?	Yes	14.7% of the thiazide diuretic (but not CCB), compared to 2.1% of CCB (but not thiazide diuretic) had total use > 7.5 years. The "current use" > 7.5 years was 5.8% and 1.1% for the groups

		respectively.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Not applicable	Study utilised linked data, no mention of any loss to follow-up.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Yes	The use of linked data reduces the likelihood of differential misclassification bias. Note relatively small outcome numbers for different exposure groups. Note that prescription database was offline for 18 months, which may have led to some non-differential misclassification.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls matched to cases based on entry to cohort, sex and age (+/- 3 years).
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Some, but not all, a priori confounders in the review protocol were adjusted for in statistical analysis, possible for residual confounding from confounders such as smoking, though probably less concern in this study given the null result.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, though small numbers in CCB exposure group cited as one study limitation.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.

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| Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate? | Indeterminable | Seem reasonable to non-statistician risk-assessor, no major inadequacies noted other than insufficient reporting of what comorbid conditions were adjusted for. Residual confounders (e.g. smoking) not adjusted for, survival analysis accounting for starting then stopping medication probably preferred, but not allowed by data collected. |

Abbreviation: CCB = calcium channel blocker.

Azoulay *et al.* 2012 (33)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Nested case-control analysis therefore inclusion as case needed a cancer diagnosis, controls selected from those registered on the UK GPRD.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable	Used linked data from the GPRD database.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	No	Use of beta-blockers/diuretics seems reasonable for this study and helps to account for confounding by indication.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	No obvious differences between methods and results reported, study protocol not reviewed if it exists.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No mention of blinding, though probably not an issue for this study.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Measured from GPRD information and thus any misclassification would be expected to be non-differential.
Q7. Was length of follow-up different across study groups?	No	Length of follow-up 5.5 years for both cases and controls.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Not applicable	No mention of loss to follow-up in the study, as this study used GP-linked data for a cohort on AHTs, would expect loss to follow-up to be non-differential.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.

Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	Residual confounders such as race would be useful, however, a large population-based study using linked-data and valid and reliable measures and so believable in the context of evidence available.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls matched to cases based on age, sex, year of entry to cohort, prescription of AHT in 2 years leading up to cohort entry and duration of follow-up (unsure if these were adjusted for in the analysis).
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Controls matched to cases as indicated in question 12. Controls matched to cases based Several confounders adjusted for in the analysis, some such as race omitted.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No mention of sample size calculation, though assembly of a 1.2 million-person cohort is cited as a strength of this study.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?		Seem reasonable to non-statistician risk-assessor and in line with many of the other studies in this literature. Inability to adjust for AHTs stopping after starting is limiting, though attempt to demonstrate dose-response is good.

Abbreviations: AHT = antihypertensive drug, GPRD = General Practitioner Research Database.

Bergman *et al.* 2014 (34)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Yes	Case-control study, therefore cases had diagnosis of cancer, controls chosen from population registry. Definition of outcome/exposure the same for both groups.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable	Study used linked data from registries rather than recruiting participants.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Choice of "no continuous use" as comparator does introduce possibility of confounding by indication.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	No protocol reviewed. This study aimed to replicate that of Li *et al.* (2013, ref 43), followed these methods using different database to Li and colleagues.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No mention of blinding, though use of cancer registry etc. reduces risk of differential misclassification bias.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Valid and reliable measures used, though accuracy of databases with regards to covariates such as level of education is not discussed.
Q7. Was length of follow-up different across study groups?	No	Similar distribution between cases and controls for follow-up in this study.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Not applicable	No mention of loss to follow-up from registries.

Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	Study limited by not accounting for confounders such as smoking, alcohol and for use non-continuous use as a reference group means that confounding by indication could be an issue.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls matched to cases based on age.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Age matching of controls to cases and adjusted for this in the statistical analysis. Potential confounders considered include age, education level, location of residence, and history of benign/malignant tumour at sites other than the breast. However, smoking, alcohol intake and other important confounders not adjusted for in the analysis.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. However, reasonably large population-based study.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Indeterminable	Seem reasonable to non-statistician risk-assessor, similar methods to other studies included in the literature.

Wright, C. and Moorin, R. and Chowdhury, E. and Stricker, B. and Reid, C. and Saunders, C. and Hughes, J. 2017. Calcium channel blockers and breast cancer incidence: An updated systematic review and meta-analy

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Chang *et al.* 2016 (35)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for three assembled cohorts and then a nested case control study within this.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Uses administrative databases and so no recruitment.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Cohort taking AHTs and with a diagnosis of hypertension are appropriate sources for comparator group of no CCB use. That he cohort with a diagnosis of hypertension was 35% smaller than that taking AHTs may indicate some incomplete diagnostic records, of AHTs used for non-hypertension indications (e.g. post myocardial infarction for angiotensin-converting enzyme inhibitors (ACEIs)). These other conditions were adjusted for in the multivariable analysis.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable.	Study protocol not reviewed. No deviation from protocol mentioned in the paper.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No blinding of assessors mentioned, administrative data use reduces risk of researcher misclassification of outcome +/- exposure.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Administrative database used has high (~99%) population coverage.

Q7. Was length of follow-up different across study groups?	No	One of the matching criteria for controls was duration of follow-up.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Not applicable	Small loss to follow-up on 1,482 (0.19% of 794,533) for largest cohort, no mention that this was differential. Smaller cohorts were a subset of the 794,533 cohort and so no reason to suspect large or differential loss to follow-up.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms of adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Yes	The collection of outcome, exposure and covariate data used appropriate sources, results seem credible in spite of study limitations.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Matching based on age and duration of follow-up from within assembled cohorts to select for controls.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Yes	Covariates other than study drugs of interest added stepwise in to model, the adjusted for variables are comprehensive, with the exception of smoking which is not included.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, but large population-based sample. Small cases numbers in longer duration of follow-up created wider confidence intervals for adjusted

		odds ratios for these groups.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable.	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Yes	Conditional logistic regression used, but model adjusts for a large number of potential confounders and the sub-cohorts assembled to adjust for confounding by indication is a strength of this study. However, the model doesn't include adjustment for age and duration of follow-up, both matching variables.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, CCB = calcium channel blocker.

Davis *et al.* 2007 (36)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Yes	Case-control study and thus cases had cancer, controls did not. Otherwise inclusion/exclusion criteria similar due to age matching of controls.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Indeterminable	Controls identified through random-digit dialling, recruitment of cases not described in this study.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Main limitation of this study is that the questions are about details so far in the past, comparator group probably not ideal as they may have less detailed medical records/recall compared to cases.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	Attempt to blind participant to exposure of interest, no mention of if assessors blinded to outcome/exposure.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	No	Questionnaire-based design introduces issues with recall of drug information prior to diagnosis of breast cancer (for cases) and corresponding index date (for controls). Unsure how initial outcome was assessed. Potential for misclassification bias which may be differential as patients with cancer might have better medical recall/records relative to controls. Authors attempted to offset this by sending questionnaire one week ahead of time, however unsure how much this would have

		helped.
Q7. Was length of follow-up different across study groups?	No	Same time had passed for cases and controls, those using CCBs and those not.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Partially	Authors note that death in cases group might be higher than for controls; this is indeed the case (17.1% of cases deceased; 4.2% of controls). Attempt to correct this by obtaining information on women having localised, regional or distant breast cancer, with the assumption that bias would be less for women with localised disease at diagnosis.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	The use of a questionnaire to collect information from 5 – 18 years in the past introduces significant recall issue and leads to a question of the reliability of the exposure data collected. This combined with relatively small cases numbers lead to some question over the association with ever use, (aOR of 1.4 though with 95% CI 0.9 – 1.4). Compared to literature using linked databases to obtain outcome/exposure information, this study design would seem of lower quality. An attempt is made to characterise a duration-response relationship, though none is seen.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g.	Partially	Controls frequency-matched to cases based on 5-year age groups.

through stratification, matching, propensity scores)?		
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?		Matching based on age, adjusted for in the analysis. Information on several important confounders was collected, though some (e.g. BMI) are omitted and questionnaire-based design might lead to differential or non-differential misclassification.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	Small numbers recalling medication use in each class cited as a study limitation; no sample size calculation provided in the paper.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Indeterminable	The use of conditional logistic regression is consistent with that of many studies in the literature, it would have been good to list adjusted for confounders on this paper rather than referencing a previous study.

Abbreviations: aOR = adjusted odds ratio, CCB = calcium channel blocker, CI = confidence interval.

Devore *et al.* 2015 (37)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for all entering the cohort study.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same for all entering the cohort study.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Having past/never use as comparator group for analysis introduces the risk of confounding by indication. The authors do address this by performing a secondary analysis restricting only to participants with hypertension.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol, if there is one, not reviewed.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	Not mentioned that assessors were blinded to exposure information. That all self-reported cases of breast cancer ended up being included in the analysis (due to an accuracy of self-report data > 98%), this lack of blinding is probably not an important study limitation.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	There were issues in this study with imputing data for CCBs and ACEIs backwards for the NHS II cohort and where it was assumed that AHT were continuing through years in which questionnaires did not capture this information. Outcome data seemed reasonable; the authors tested the accuracy of self-report prior to deciding that all self-report cases would be included in the analysis. Some potential issues for recall for both exposure

		and confounders – though one would expect this to be a non-differential bias.
Q7. Was length of follow-up different across study groups?	No	Length of follow-up was the same for both groups.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Not applicable	Follow-up quoted as >90% for each cohort, no mention of different loss to follow-up between CCB users and past/never users.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	The study is based on a large population-based cohort. The outcome data is quite well sourced and a strength of this study is accounting for many potential confounders, though the authors acknowledge a limitation of this observational study is that residual confounding may be present. The major limiting issue for this study is that exposure data was reasonably inconsistently collected, though given the comparator group is past/never use perhaps this would not affect results significantly. The choice of past/never use as the comparator group introduces the risk of confounding by indication. That a null result was found might decrease the importance of these limitations, another strength is that it follows from previous work with the same cohort (Michels *et al.* 1998).

Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	A lot of confounders were adjusted for in the analysis, a strength of this study. Restricting an analysis to only participants with hypertension helps to assess confounding by indication.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size, though this is a large population-based cohort study. Numbers were high compared to other studies.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable.	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Use of cox-proportional hazards seems more appropriate than other studies where logistic regression was used (though these were limited by the data available). No adjustment for multiple comparisons. NHS and NHS II data appropriately analysed separately.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, AHT = antihypertensive drug, CCB = calcium channel blocker, NHS = Nurses' Health Study.

Fitzpatrick *et al.* 1997 (38)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for both.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same for both
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	No	Compares to both non-CCB users and other AHT users, not sure whether non-mutually exclusive nature of the groups is an issue.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Protocol for study not reviewed.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	Not mentioned that assessors blinded to exposure data.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Use of bottle labels by interviewers improves the assignment of exposure data; outcome data would miss those cases not attending hospital. Data on other covariates collected by questionnaire, complemented with clinical data such as blood pressure measurement.
Q7. Was length of follow-up different across study groups?	No	No reason to think that length of follow-up was different.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Indeterminable	Number lost to follow-up not noted on the study, no mention of differential loss to follow-up.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse events that may be a consequence of the	No not relevant to this review	

intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Partially	This study reports a positive association between the use of CCBs and breast cancer. However, some associations reported have small case numbers, there is not a clear dose-response relationship shown. Immediate-release CCBs were more prevalent at the beginning of the cohort, compared to the end and these were not differentiated in the analysis from sustained-release formulations. As other studies also found that immediate-release CCBs, but not SR CCBs were associated with incident breast cancer, perhaps aggregating these together is not appropriate.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Most a prior confounders in this review adjusted for in the analysis. HRT use is considered in a separate stratified analysis, though with small outcome cases numbers.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, though small incident cancer numbers cited as a study limitation.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess	Partially	Not entirely clear how the covariates

the main harm or adverse effect outcomes inadequate?		eventually adjusted for in the final model are chosen, choice of Cox-proportional hazards seems consistent with techniques used in other studies and appropriate to the data.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker, HRT = hormone replacement therapy, SR = sustained-release.

Fryzek *et al.* 2006 (39)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for all groups
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable	Using population registries, recruitment not necessary.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to non-users of AHTs may introduce risk of confounding by indication.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No mention of blinding of assessor to exposure, though outcome data read from the Danish Cancer Registry, reducing the risk of misclassification bias.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Population-based registries used for this study. The Danish Cancer Registry's accuracy is commented upon with a reference, the prescription database and Central Population Registry are not explicitly commented on regarding their accuracy, though would expect any misclassification bias to be non-differential.
Q7. Was length of follow-up different across study groups?	No	Length of follow-up not mentioned as different between the two groups.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	No loss to follow-up mentioned, emigration numbers not reported so cannot assess if they were different between the groups.

Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	Some confounders are omitted. However, used of 3 linked populations registries, assessment of number of prescription-response and separation of dihydropyridine and non-DHP drugs are strengths of this study. It would have been interesting to see separation of immediate – and sustained-release formulation.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Information on BMI, age at menarche, alcohol use and physical activity was not available, ideally these would be adjusted for in an analysis in cases of uneven distribution between groups.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. However, this is a large, population-based study extending a previous cohort analysis.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable.	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes	No	Statistical methods seem appropriate to the data available; separation into immediate-

inadequate?		release and SR formulations would have been useful, acknowledging the risk of multiple comparisons leading to spurious results.

Abbreviations: AHT = antihypertensive drug, DHP = dihydropyridine.

Gonzalez-Perez *et al.* 2004 (40)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Yes	Nested case-control study, therefore cases had incident breast cancer, controls selected by matching to cases.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Compared to no CCB use, though with adjustment for other AHTs. Analyses also adjusted to hypertension.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	No mention of blinding of outcome assessors.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Used GPRD for outcome, exposure information and covariate data, thus if there is misclassification likely to be non-differential. Authors mention that several studies have been conducted reinforcing the completeness of the GPRD.
Q7. Was length of follow-up different across study groups?	No	
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	Loss to follow-up not mentioned as an issue.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse	No	Not relevant to this review.

events that may be a consequence of the intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Yes	Seems to be good ascertainment of outcome, exposure data, analysis of duration-response effect and disaggregation by different drugs within the CCB class, adjustment for the majority of important confounders including hypertension, to account for confounding by indication.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Frequency matching of cases to controls based on age and calendar year of entry.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Authors cite as a limitation unable to collect information on age at menarche, family history, and age at first child or germ line mutation.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample-size calculation. Large population-based study.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Changing from unexposed to exposed does not seem to have been accounted for, though whether this is likely to change the results seems unclear.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker, GPRD = General Practitioner Research Database.

Grimaldi-Bensouda *et al.* 2016 (43)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Uses linked data, no recruitment.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Comparison to users of other AHTs is appropriate to account for confounding by indication (note hypertension also adjusted for in the analysis).
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No mention of blinding of assessors in the abstract or conference presentation.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Indeterminable	Outcome and exposure variables from population-based registries, source of covariate data not clear but seems reasonable to assume these were sourced from the Clinical Practice Research Datalink.
Q7. Was length of follow-up different across study groups?	No	No mention of different length of follow-up.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	No mention of loss to follow-up, or differential loss to follow-up.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse	No	Not relevant to this review

events that may be a consequence of the intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Yes	Sourcing of data seems appropriate, comparator group probably appropriate, for cancer overall a duration-response analysis is provided, though not for breast cancer specifically.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Mentions that this is a "matched-cohort" study, by sex and age.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Use of HRT not adjusted for in analysis, other non a priori to this review confounders such as age at menarche, parity, also not adjusted for. However, adjustment for hypertension and several other medical conditions is appropriate.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, however this is a large population-based study.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Yes	Seem appropriate to data available, adjusted confounders decided based on previous findings as risk factors for cancer.

Abbreviation: AHT = antihypertensive drug.

Hole *et al.* 1998 (55)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	CCB group and non CCB group (but other AHTs) are both sourced from a Glasgow Hypertension Clinic, both compared to age and year of observation adjusted West of Scotland population-based registry data.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable.	Retrospective analysis and so no recruitment, just use of patient records.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Assuming that any increased cancer risk due to hypertension is evenly spread between the CCB and non-CCB group, then the comparison between the groups is reasonable. However, the selection of population-based controls may mean that any increase in observed cancers over expected is not only attributable to treatment and if, for example, the level of hypertension control is worse in the CCB, relative to the non-CCB group, then this could be an issue.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable.	Study protocol not reviewed, methods correlated with reported results.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	Co-author assigning outcome (incident cancer) blinded to exposure (CCB or non-CCB). Treatment classified by co-authors blinded to outcome status.
Q6. Were valid and reliable measures, implemented consistently across all study	Partially	Reliability of outcome measurement depends upon the reliability of coding in the database

participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?		used, the authors note that these data quality for inclusion in 'Cancer Incidence in Five Continents', "…the only accepted publication on the incidence of cancer". Authors comment that no further searches for cancer beyond registry amongst clinic patients were conducted, in an attempt to reduce differential misclassification. Exposure data sourced from the Glasgow Blood Pressure Clinic, no comment by the authors of the reliability of these records. Limited confounding data collected, age and year of observation, expect to be accurate.
Q7. Was length of follow-up different across study groups?	Yes	For CCB group average follow-up was 5 years, for non-CCB group it was 7.8 years.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Indeterminable	Unclear if loss to follow-up is differential for this study, no sensitivity analyses performed to assess impact if there was.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this study
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this study
Q11. Are the results believable taking study limitations into consideration?	Partially	For the portion relevant to this review, the case numbers are small and thus it is difficult to draw firm conclusions. The comparison of blood pressure clinic patients to population-based controls (with only limited adjustment) introduces issues of potential bias to the study.
Q12. Any attempt to balance the allocation	Partially	Adjustment for age important given difference

between the groups or match groups (e.g. through stratification, matching, propensity scores)?		in mean ages between the groups.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	No	Limited adjustment for confounding in this study.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable.	No sample size calculation for study overall. Small numbers of incident breast cancer in both the CCB (14 cases) and non-CCB groups (17 cases).
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	The comparison to population-based controls introduces issues that limit the study results and don't seem to be fully accounted for in the statistical analysis. Adjustment for multiple testing using the Bonferroni correction.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker.

Jick *et al.* 1997 (56)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Cases had a diagnosis of cancer; controls did not. Otherwise eligibility criteria similar.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Partially	Cases were contacted via questionnaire to confirm cancer diagnosis and those not confirming were excluded from the analysis, whereas controls were not contacted as part of the study (database records reviewed only). However, as only 68% of these questionnaires returned
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to beta-blocker group addresses confounding by indication (at least partially) those the veracity of the relative risk relies upon beta-blockers themselves having a low risk of breast cancer.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed. Change to include cases not returning a questionnaire to confirm diagnosis justified by relative risks being similar when they were included to when they were excluded.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	No information about blinding of assessors.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome, exposure and covariate data from population-based registries. Issue with questionnaire being used to confirm diagnosis addressed by removing this step in the analysis. However 18 people who did return questionnaires were excluded, thus some risk of selection bias introduced.
Q7. Was length of follow-up different across	Indeterminable	No mention of different length of follow-up

study groups?		between the groups.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	Registry-based study and thus expect limited loss to follow-up. However, no mention of high or differential loss to follow-up or sensitivity analysis to address this.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review
Q11. Are the results believable taking study limitations into consideration?	Yes	The use of linked databases to collect all outcome, exposure and covariate data. Thus any misclassification would be expected to be limited and non-differential. Small selection bias introduced by excluding some cases that returned a questionnaire probably does not markedly affect results.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls matched to cases based on age, sex and GP practice attended.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Yes	Matching of controls to cases (as above) and adjustment for smoking, BMI, duration of hypertension and diuretic use. However, confounders such as alcohol use not adjusted for. Confounding by indication addressed by having beta-blockers as a reference group, unless level of control of hypertension is different between these groups.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5%	Indeterminable	No sample size calculation, adjusted RR for breast cancer based on 80 incident cases.

or more between groups in at least one primary outcome measure?		
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Yes	Conditional logistic regression used, with all potential confounders being included in the final model. Stratification by duration of use and dose performed for cancer overall (not clear trend), though not for breast cancer specifically.

Abbreviations: BMI = body mass index, GP = general practitioner.

Lam *et al.* 2014 (42) * conference abstract and presentation *

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Cases had incident breast cancer; controls did not. Otherwise eligibility appears the same.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable	Population-based registry and patients thus not recruited.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Selection of matched controls not on a CCB introduces risk of confounding by indication. However, matching controls to cases based on hypertension reduces the importance of this.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable.	Study protocol not reviewed, methods appear to match results but note assessment based upon conference abstract and poster.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable.	No information provided.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Limited information on outcome, exposure, and covariate allocation – used registry-based information and thus would expect any misclassification to be non-differential (except in case of missing data/more detailed data e.g. for the CV group).
Q7. Was length of follow-up different across study groups?	Indeterminable	No information on any length of follow-up.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Indeterminable	Matching of controls to cases by follow-up time.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse	No	Not relevant to this review.

events that may be a consequence of the intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Partially	Issues with potential confounding by indication, selection of two different groups of patients makes for interesting comparison, though those undergoing coronary angiography are at particular risk of residual confounding. Attempt to replicate a previous study, not compelling evidence of an association.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Matching based on age, race, tobacco, alcohol, BMI and follow-up time.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Adjustment for history of other cancers, family history of breast cancer. Assume also adjustment to matching covariates, though this is not mentioned. Some confounders such as use of HRT not adjusted for.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, numbers of incident breast cancer not reported, just relative risks.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Yes	Use of cox-proportional hazards allows adjustment for length of exposure, adjustment for several confounders.

Abbreviation: CCB = calcium channel blocker.

Largent *et al.* 2010 (43)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for both groups.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same for both groups.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	"No regular use" comparator introduces risk of confounding by indication.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	No information on blinding provided.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome data verification adequate, authors quote 99% accuracy for the population-based registry used. Confounder data seems to be from baseline questionnaire (1995-96) rather than from 2001-01 where exposure data are sourced. Thus a risk those confounder characteristics have changed in the interim. Unclear if all of these data were collected in each subsequent survey. Self-report of exposure data also, risk of recall bias.
Q7. Was length of follow-up different across study groups?	Indeterminable	Not mentioned if length of follow-up was different for comparator groups.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Yes	Cox-proportional hazards analysis addresses any differential loss to follow-up.

Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	No relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	The collection of exposure and confounding data is less reliable than population-based databases, though self-report of exposure data does potentially reduce issues of prescription as a proxy for taking the drugs (a problem when using the prescription databases). The outcome allocation is reliable. Misclassification of exposure would likely be non-differential, though confounding variables may be more/less accurately reported by patients with hypertension relative to those without
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Yes	Age-stratified analysis adjusted for a large range of confounders. No adjustment for hypertension (or level of control) and comparator of 'no regular use' introduces risk of confounding by indication, though less important given null result.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. 84 breast cancer cases in the CCB group.

Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	No duration-response, dose-response analysis, but otherwise statistical methods are adequate.

Abbreviation: CCB = calcium channel blocker.

Leung *et al.* 2015 (44)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Cases had a diagnosis of incident breast cancer, controls did not. Otherwise eligibility criteria the same.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable.	Study utilised population-based databases.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Given participants were only hypertensive patients.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods match the reported results.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	No mention of blinding of assessors.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Outcome, exposure and confounding variables collected from a population-based database.
Q7. Was length of follow-up different across study groups?	Indeterminable	No mention of different loss to follow-up.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Indeterminable	No mention of differential or high loss to follow-up, not adjustment in sensitivity analysis.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse	No	Not relevant to this review

events that may be a consequence of the intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Partially	Main limitation is that the variables adjusted for in the analysis are not clarified in the study, residual confounders such as alcohol use, BMI may be important given that the bottom of the 95% CI for the adjusted analysis is close to unity. Dose-response analysis strengthens cases for a true association with these data.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls matched to cases based on age, index data and year of hypertension.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Residual confounding (e.g. by BMI, alcohol etc. as highlighted by the authors).
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. A large number of cases taking a CCB.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Model covariates unclear for the main analysis. Duration-response analysis is helpful, though more detailed data would allow correction for differential follow-up time.

Abbreviations: BMI = body mass index, CCB = calcium channel blocker, CI = confidence interval.

Li *et al.* 2003 (45)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Cases had incident breast cancer and controls did not. Otherwise selection criteria were the same.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Risk of confounding by indication, though sub-analysis restricting to "ever users" of AHTs in an attempt to explore this.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable.	Study protocol not reviewed.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No information provided on blinding of assessors.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome data linked to population-based registries. Exposure based on interview, with visual aids to enhance recall. Confounders also collected via interview. Note that 80.6% of eligible cases and 73.8% of controls were interviewed, introducing risk of selection bias.
Q7. Was length of follow-up different across study groups?	Indeterminable	No indication that length of follow-up was different.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Indeterminable	Note differences in response to take part in study, in Q6. No adjustment for this.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to review
Q10. Are any important harms or adverse	No	Not relevant to review

events that may be a consequence of the intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Partially	Issues with multiple comparisons, some potential selection bias, misclassification due to recall limitations etc. This study focussed mainly on IR CCBs, which are no longer commonly used. Age adjustment only could introduce issues, as collectively potential confounders may have had a marked impact (i.e. above the 10% mentioned by the co-authors for individual covariates) on the associations reported.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Matching of controls to cases based upon age and location.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	No	Omitted from analyses (other than age) as found to impact association by <10%, when added to model individually.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. 149 cases were "ever users" of a CCB.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Adjustment for potential confounders seems to be limited; age-adjustment only may not be sufficient for this analysis.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker.

Li *et al.* 2013 (46)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Cases have incident invasive ductal or invasive lobular breast cancer; controls do not.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Yes	Cases identified by population-based cancer registry, controls identified via random digit dialling.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Use of "never use" of an AHT as the reference group could introduce a risk of confounding by indication. However, this was explored in an additional analysis, with similar results to that seen with the original reference group.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, however, methods described match the results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No indication of blinding of assessors.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome data used population-based registries, with reclassification of type as necessary based upon review of pathology records. Exposure data relied on self-report by participant, introducing risk of recall bias. Tablet bottles/boxes and visual aids used to enhance recall. Potential confounder covariates collected by interview, thus again risk of recall bias.
Q7. Was length of follow-up different across study groups?	Indeterminable	No mention of different length of follow-up. Duration-response analysis would partly correct for any difference.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact	No	Differential response rate for this case-control study listed as a study limitation and may

assessed (through sensitivity analysis or other adjustment method)?		introduce some bias.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	Concern with adding potential confounders to model changing association by >10%, as combination of several confounders adjusted for in the model may have impacted results. Case numbers are relatively small (e.g. 27 ductal; 31 lobular) for the >=10 year sub-analysis.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls frequency matched for 5-year age group to ILC case patients, statistical analysis methods also mentions matching by county and by reference year.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Concerns noted in Q11 regarding parsimonious model used by authors in this study. Addition of further covariates may have affected the strength of the association reported.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. Total 94 ductal and 102 lobular cases amongst CCB ever users for this study.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess	Partially	Issues noted with adding each potential

the main harm or adverse effect outcomes inadequate?		confounder to model individually to see if relative risks alter by >10%, residual confounding may present an issue in this analysis. No corrections for multiple testing.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker.

Lindholm *et al.* 2001 (57)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for all groups.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same for all groups
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to general population to calculate SIR may make confounding by indication an issue.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	Double-blinded.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Use of cancer registry to assess endpoint reduces risk of non-differential misclassification.
Q7. Was length of follow-up different across study groups?	No	This is accounted for in the analysis.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	Loss to follow-up not assessed through sensitivity analysis, analysis is intention-to-treat. 77% of CCB group was still taking CCB as assigned after 4 years in the trial.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse	No	Not relevant to this review.

events that may be a consequence of the intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Yes	Though small case numbers and inability to adjust for potential confounders such as smoking may limit analysis. This is, for example, if the smoking prevalence is higher amongst the CCB group relative to the general Danish population. Latency is also a potential issue here given reasonably short length of follow-up.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Randomisation helps to reduce bias, though there are some potential issues in differences between trial participants and the general population that don't seem to have been adjusted for in these authors' analysis.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation provided. Only 19 observed breast cancer cases during the trial.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	It may have been useful to compare randomised groups to one another, rather than comparing to the general Danish population via SIRs.

Abbreviation: SIR = standardised incidence ratio.

Wright, C. and Moorin, R. and Chowdhury, E. and Stricker, B. and Reid, C. and Saunders, C. and Hughes, J. 2017. Calcium channel blockers and breast cancer incidence: An updated systematic review and meta-analy

Meier *et al.* 2000 (47)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Partially	Cases had incident breast cancer; controls did not. Otherwise eligibility criteria are the same.
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable.	Use of population-based registry (the UK GPRD).
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Selection of no AHT use as the reference group introduces the risk of confounding by indication.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods described correspond to results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No information on blinding, though use of population-based registry reduces risk of differential misclassification.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially.	Use of population-based registries to assess outcome, exposure, and potential confounders are reliable measures. Assumes that prescription is a proxy for use. 'Definite' and 'probable' cases included seems reasonable and tested via sample of probable cases for which confirmation was requested.
Q7. Was length of follow-up different across study groups?	No	Mean follow-up of 5.3 years, no mention of differential length of follow-up. More than 75% of case and control groups had follow-up > 5 years.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	Population-based registry and thus expect loss to follow-up to be low. No mention of differential/high loss to follow-up and no adjustment for this.

Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Yes	Outcome, exposure and confounding data are sourced from the same, and a reliable source. Exploration of the effect of several confounders (though not those such as socioeconomic status) available via the GPRD. 190 cases in the CCB group and exploration of duration-response and individual CCBs subclasses are strengths of this study. Limited by relatively short follow-up.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Yes	Controls matched by age, physician practice, calendar date (index date for case), and number of years of medical history in the database.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Exploration of the impact of several confounders on the association between CCBs and breast cancer explored, though only smoking and BMI included in final model. Authors report that adding further covariates to the model (in multivariate models, assume several added simultaneously to model) did not "materially change" association.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, 190 cases in the CCB group.

Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?		Seem adequate, though no correction for multiple testing.

Abbreviations: AHT = antihypertensive drug, BMI = body mass index, CCB = calcium channel blocker, GPRD = General Practitioner Research Database.

Michels *et al.* 1998 (58)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to women using 'other cardiovascular drugs' could introduce bias in women for each group having different patterns of morbidity, may be related to differential risk of cancer.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	Physicians confirming outcome blinded to exposure information.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome data self-reported with confirmation by physician. Exposure data self-reported in 1988 and not updated beyond this. The authors' report that 57% of those using CCBs in 1988 were still reported this use in 1994. Recall bias may be reduced by this cohort being made up of nurses, however, change in pattern of drug use or duration of use could not be adjusted for. In 1988 CCBs primarily immediate-release. Covariate data self-reported and updated 2-yearly via questionnaire.
Q7. Was length of follow-up different across study groups?	No	No reported difference in length of follow-up.

Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	No mention of differential/high loss to follow-up, no exploration through sensitivity analysis.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	Main issue with this study is that the exposure is assigned at baseline. Recall bias is also an issue given self-reporting of exposure data and potential confounders. Multiple confounders are adjusted for in this analysis. No exploration of dose- or duration-response and timeframe means that CCBs under study would be mainly immediate-release, rather than majority sustained-release in contemporary practice.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Multiple self-reported potential confounders adjusted for in the analysis, omission of some (e.g. socioeconomic status) but otherwise adequate (acknowledging potential drawbacks of self-reported data).
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5%	Indeterminable	No sample size calculation; 51 incident breast cancer cases amongst 11,807 person-years of

or more between groups in at least one primary outcome measure?		CCB use; 304 breast cancer cases amongst 82,524 non-CCB users.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable.	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Incorporation of person-years of follow-up helps to reduce the impact of loss to follow-up, adjustment for multiple confounders in the analysis. Main limitation in this study of assignment of exposure at baseline without review during study cannot be rectified through statistical analysis.

Abbreviations: CCB = calcium channel blocker.

Olsen *et al.* 1997 (59)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same
Q2. Does the strategy for recruiting participants into the study differ across groups?	Not applicable	Population-based database used for identifying participants.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Population-based comparator group introduces bias if people on a CCB are less well/ have more interaction with the health system (and therefore more opportunities for diagnosis of cancer). Age-adjustment probably doesn't address this adequately.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable.	Study protocol not reviewed. Methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	No mention of blinding of assessors, though assignment of outcome and exposure has low vulnerability to selection bias.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Use of population-based registries to assign outcome and exposure reduces risk of differential misclassification. No exploration of covariates in this study.
Q7. Was length of follow-up different across study groups?	No	No mention of different length of follow-up.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	Use of population-based registries makes risk of loss to follow-up low, not mentioned that there is high/differential loss to follow-up and no sensitivity analysis for this.

Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this study
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this study
Q11. Are the results believable taking study limitations into consideration?	Partially	Limitation of this study is risk of bias due to confounding, including confounding by indication.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Partially	SIRs calculated with expected case numbers adjusted for age and county.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	No	Limited adjustment for potential confounders in this analysis.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. 31 breast cancer cases included in this analysis.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Residual confounders not accounted for in this analysis. Null results makes this less of an issue, though could still affect the association.

Abbreviation: CCB = calcium channel blocker.

Pahor *et al.* 1996 (60)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to non-CCB users introduces the risk of confounding by indication; note that 81.7% of those taking CCBs had hypertension, relative to 90% in the CCB group.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, if it exists, methods described match the results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	No mention of blinding of assessors.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome data assigned by reviewing Medicare Provider files, the validity of this assessed by comparing to Iowa's Cancer Registry. Exposure data self-reported at baseline, interviewer aided by asking for tablet bottle/boxes. Covariate data, including self-report of comorbidities and measurement of clinical indicators such as blood pressure taken as baseline. Self-reported data susceptible to recall bias.
Q7. Was length of follow-up different across study groups?	No	No indication of differential loss to follow-up, average follow-up of 3.7 years.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other	Indeterminable	No reported high/differential loss to follow-up.

adjustment method)?		
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Partially	Issue with assignment of exposure and covariates at baseline being carried through on the Kaplan-Meier curves. Positive association for CCB and breast cancer crosses unity, but has low numbers. Timeframe of study means likely to be majority data for immediate-release CCB.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	Partially	Stratification by region in the analysis.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Stratification by region, age, ethnic origin, heart failure, number of hospital admissions, cigarette smoking, alcohol intake and oestrogen use. Residual confounders such as BMI, socioeconomic status not adjusted for in this analysis. No adjustment for level of blood pressure control in this majority hypertensive population.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?		No sample size calculation. There are 31 events amongst CCB and non-CCB users in this cohort, total cancers among CCB users in this study 47 (therefore estimated 4 cases of breast cancer among users in this study).
Q15. Are the statistical methods used to assess	Not applicable.	This review is assessing a harm/adverse effect

the primary benefit outcomes inadequate?		outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Seems adequate, though limited scope with small cases number for breast cancer analysis. Carrying forward exposure data through survival analysis could be problematic if people stop taking CCBs during the study.

Abbreviations: BMI = body mass index, CCB = calcium channel blocker.

Poole-Wilson *et al.* 2006 (48)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for both groups.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same for both groups.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Reasonable assuming sufficient equipoise with treatment at the time to justify a placebo control.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed. Methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	Double-blinded.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Examination of pathology reports seems reasonable assuming undertaken by a competent person. If assessors unblinded, potential risk of ascertainment bias.
Q7. Was length of follow-up different across study groups?	No	No evidence of different length of follow-up between groups.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Not applicable	Analysis appears to be intention-to-treat.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms or adverse events that may be a consequence of the	No	Not relevant to this review.

intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Yes	However, small case numbers reported.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	No	No correction for confounding.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable.	No sample size calculation provided in the reviewed paper.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Seem reasonable and correction for person-time in study to calculate hazard ratio is a strength. However, a 95% confidence interval would be useful.

Raebel *et al.* 2015 (49) *conference abstract and presentation *

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	No difference in selection criteria for compared groups, though which groups are compared is not entirely clear from the conference abstract.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	No recruitment, insurance database used.
Q3. Is the selection of the comparison group inappropriate, afar taking into account feasibility and ethical considerations?	Indeterminable	The authors indicate that the reference was <1-year use, though not clear if angiotensin-converting enzyme inhibitors (ACEI*s*) and calcium channel blockers (CCBs) part of cohort assessed separately (one would assume that there is some crossover, with some cohort members taking both agents). Based on the poster presentation, comparator is reference is users of ACEIs, this is an appropriate comparator.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not mentioned.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	Not mentioned in this conference abstract or presentation.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	The use of an insurance database for exposure, outcome and covariate data seems appropriate, though no information about this health information system accuracy is provided.

Q7. Was length of follow-up different across study groups?	Indeterminable	Unsure if reference group (<1 year of use) stopped taking CCBs or were followed up for less time on average than those taking CCBs for a longer period of time.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	Indeterminable	No mention of any loss to follow-up. Retrospective cohort assembled.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review.
Q10. Are any important harms of adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review.
Q11. Are the results believable taking study limitations into consideration?	Indeterminable.	Full study results were unable to be published in this conference abstract, full appraisal of data not possible.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	None mentioned.
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Smoking not adjusted for, assessing users of CCBs +/- ACEIs only likely reduces the risk of confounding by indication.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable.	No sample size calculation, though large cohort assembled of 165,807 women. Cases numbers of incident breast cancer not reported. Stratification by single years of follow-up may reduce the preciseness of

		hazard ratio point estimates.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable.	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Indeterminable.	This depends on whether follow-up time differed between groups. Questions around whether mortality was higher for reference group, unclear from reading conference abstract.

Rosenberg *et al.* 1998 (61)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	Yes	Cases had incident cancer, controls had conditions not judged to be related to antihypertensive drugs. This could introduce some bias between cases and controls. Controls are hospital-based.
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Both recruited on admission to study hospitals between 1983 and 1996.
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to never use could introduce confounding by indication. In a sub-analysis CCB use was compared to use of beta-blockers, but this was for cancer generally rather than breast cancer specifically.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed. Methods described match results reported. Sub-analysis with beta-blocker comparison doesn't seem to be a priori, however, not relevant to breast cancer outcome.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	Assessors allocating disease were blinded to exposure status.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Partially	Outcome, exposure and covariates obtained by interviewers on admission to hospital, risk of recall bias. Hospital-based cases/controls may limit generalisibilty of data to general population.
Q7. Was length of follow-up different across study groups?	No	No indication of differential length of follow-up
Q8. In cases of high loss to follow-up (or	No	Data collected at baseline therefore loss to

differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?		follow-up is not an issue.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review
Q11. Are the results believable taking study limitations into consideration?	Partially	Interview collection of data at baseline, and that these are people admitted to hospital are important limitations of this study. Blinding of outcome assessors to exposure is a strength.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	The most important missing confounder is smoking status.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. 92 breast cancer cases amongst CCB users.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	No	Statistical analysis seems adequate, though some confounding not accounted for, CCB considered as a class for breast cancer

		analysis, short latency period accounted for by requiring >=1 year before admission for AHT use.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker.

Sajadieh *et al.* 1999 (62)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same for both groups
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same for both groups
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Reasonable assuming sufficient equipoise for trial question to justify placebo.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	Double-blinded.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Use of cancer registry to assign outcome should reduce risk of misclassification, exposure assignment undertaken at random.
Q7. Was length of follow-up different across study groups?	No	No evidence of differential length of follow-up
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	Analysis appears to be intention-to-treat. N
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse events that may be a consequence of the	No	Not relevant to this review

intervention/exposure missing from the results?		
Q11. Are the results believable taking study limitations into consideration?	Yes	However, small patient numbers and use of thrice daily dosing verapamil limit relevance to contemporary practice.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	No	No confounders assessed for in analysis. Risk factors, medical conditions, age, sex, reported in the trial appear to be reasonably evenly spread between the groups.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculations, though note small case numbers reported.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Reporting of SIRs limits comparison between placebo and active groups. However, small case numbers probably means that this is unimportant to overall study interpretation as relevant to this review.

Saltzman *et al.* 2013 (50)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	For main analysis restriction to never use of AHTs, however sub analysis restricting to women diagnosed with hypertension.
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed, however methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Indeterminable	No information that interviewers are blinded to exposure/outcome (would not make sense that they are).
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?		Linked data are used to assign outcome via cancer registries. Exposure and covariates data are collected during interview, with measurement of blood pressure during interview. Assignment of hypertensive status by self-report, taking AHTs, or by clinical measurement.
Q7. Was length of follow-up different across study groups?	No	No indication of differential length of follow-up. Comment by authors that people moving outside catchment area would not be included amongst outcome data.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	No high/differential loss to follow-up reported or tested in sensitivity analysis.

Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review
Q11. Are the results believable taking study limitations into consideration?	Partially	Main result is for immediate-release CCBs, may have limited relevance to contemporary practice.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Multiple confounders added to model to see if estimate changed by >10%, excluded if not changing by >10% alone.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation, 55 cases amongst all CCB use.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Issue with adding individual covariates to model and assessing change (rather than together) which could mean residual confounding is retained in the model. No adjustment for multiple testing.

Abbreviations: AHT = antihypertensive drug, CCB = calcium channel blocker.

Soldera *et al.* 2015 (51) *conference abstract and presentation *

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Yes	Comparator of other AHTs helps to address confounding by indication improves comparability but may limit generalisability (though that latter probably doesn't matter).
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed. Limited methods and results due to conference abstract/presentation format, however methods described match results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	No	No indication, use of population-based registries makes this unimportant.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Use of population-based registries amongst AHT users is reliable and consistently used in this study.
Q7. Was length of follow-up different across study groups?	Indeterminable	No indication of differential length of follow-up
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other adjustment method)?	No	No indication of differential/high loss to follow-up or sensitivity analysis for this.
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review

Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review
Q11. Are the results believable taking study limitations into consideration?	Partially	Large, population-based study appears to adjust for several relevant confounders. Risk of residual confounding if comparator groups different in regards, for example, to socioeconomic status. Abstract/presentation format limits information available to critique.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	Partially	Some confounders, e.g. socioeconomic status/ethnicity omitted. However confounding by indication reduced by study design.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. However this is a large population-based study.
Q15. Are the statistical methods used to assess the primary benefit outcomes inadequate?	Not applicable	This review is assessing a harm/adverse effect outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Introduction of latency and hazard analysis is adequate and appropriate to these data.

Abbreviation: AHT = antihypertensive drug.

Sorensen *et al.* 2000 (52)

Question to assess the risk of bias	Assessment (yes, partially, no, indeterminable, not applicable)	Evidence/Comments
Q1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	No	Same
Q2. Does the strategy for recruiting participants into the study differ across groups?	No	Same
Q3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	Partially	Comparison to Danish General Population may not be appropriate if the characteristics of those taking CCBs differ from the general population (i.e. more hypertension, different distribution of cancer-related risk factors such as smoking).
Q4. Does the study fail to account for variations in the execution of the study from the proposed protocol?	Indeterminable	Study protocol not reviewed. Methods described correspond to results reported.
Q5. Was the outcome assessor not blinded to the intervention or exposure of participants?	Yes	Not highly relevant to this study design, no information of any blinding of assessors provided.
Q6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participants health benefits and harms, and confounding?	Yes	Use of population-based registries utilising linked data means that measures are reliable; any misclassification bias would be expected to be non-differential.
Q7. Was length of follow-up different across study groups?	Not applicable	Mean follow-up time for 3.2 years, assume that calculation of SIRs considered expected cancer incidence over this length of follow-up.
Q8. In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (through sensitivity analysis or other	Not applicable	See question 7.

adjustment method)?		
Q9. Are there important primary outcomes missing from the results?	No	Not relevant to this review
Q10. Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?	No	Not relevant to this review
Q11. Are the results believable taking study limitations into consideration?	Partially	Non-adjustment for potential confounders is an issue with this study design. Furthermore, incident cancer over the 3.2 years of follow-up were 84, so relatively small numbers to calculate SIR. This study was unable to assess exposure prior to 1989, and the study period means that immediate-release CCBs probably predominate. No dose/duration-response analysis, or breakdown of CCB class into subclasses.
Q12. Any attempt to balance the allocation between the groups or match groups (e.g. through stratification, matching, propensity scores)?	No	
Q13. Were the important confounding variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	No	SIR would adjust for age, though other confounders not accounted or in this analysis.
Q14. Is the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?	Indeterminable	No sample size calculation. This study had 84 cases of incident breast cancer amongst a cohort of 11,726 women.
Q15. Are the statistical methods used to assess	Not applicable	This review is assessing a harm/adverse effect

the primary benefit outcomes inadequate?		outcome rather than a benefit outcome.
Q16. Are the statistical methods used to assess the main harm or adverse effect outcomes inadequate?	Partially	Calculation of SIRs as a measure of relative effect leaves the possibility of differences between the cohort members taking CCBs and the general population (e.g. confounding by indication). This is less important given null result of this study.

Abbreviations: CCB = calcium channel blocker, SIR = standardised incidence ratio.

Appendix F Quality assessments

Table 1. Non-randomised studies with quality assessment using the Newcastle-Ottawa Scale.(1)

Study author(s) and year of publication (reference on manuscript)	Study design	Number of stars assigned			Total
		Selection	Comparability [1,2]	Exposure/Outcome[3]	
Assimes *et al.* 2008 (54)	Nested case-control	3	2	3	8
Azoulay *et al.* 2012 (33)	Nested case-control	3	2	3	8
Bergman *et al.* 2014 (34)	Case-control	3	1	3	7
Chang *et al.* 2016 (35)	Nested case-control	3	1 (2 for versus AHT part)	3	7 (8 for AHT part)
Davis & Mirick 2007 (36)	Case-control	4	1	1	7
Devore *et al.* 2015 (37)	Cohort	4	1	2	7
Fitzpatrick *et al.* 1997 (38)	Cohort	4	1	1	6
Fryzek *et al.* 2006 (39)	Cohort	4	1	3	8
González-Pérez 2004 *et al.* (40)	Nested case-control	4	1	3	8
Grimaldi-Bensouda 2016 *et al.* (41)	Cohort	4	2	3	9
Hole *et al.* 1998 (55)	Retrospective, cohort	3	1	3	8
Jick *et al.* 1997 (56)	Nested case-control	3	2	3	8
Lam *et al.* 2014 (42)	Prospective, cohort	4	1	2	7
Largent *et al.* 2010 (43)	Prospective, cohort	2	1	3	6
Leung *et al.* 2015 (44)	Case-control	3	2	3	8
Li *et al.* 2003 (45)	Case-control	4	1 (2 for versus AHT part)	2	7 (8 for AHT part)
Li *et al.* 2013 (46)	Case-control	4	1 (2 for to versus AHT part)	2	7(8 for AHT part)
Meier *et al.* 2000	Case-control	4	1	3	8
Michels *et al.* 1998 (58)	Prospective, cohort	2	1	3	6

Olsen *et al.* 1997 (59)	Cohort	4	1	2	7
Pahor *et al.* 1996 (60)	Prospective, cohort	4	1	2	7
Raebel *et al.* 2015 (49)	Retrospective, cohort	4	1 (2 for main analysis)	3	8 (9 for main analysis)
Rosenberg *et al.* 1998 (61)	Case-control	2	1	3	6
Saltzman *et al.* 2013 (50)	Prospective, cohort	4	1	3	8
Soldera *et al.* 2015 (51)	Cohort	4	2	3	9
Sorensen *et al.* 2000 (52)	Cohort	3	1	3	7

1= most important factor selected as hypertension/use of antihypertensive drugs, or an only hypertensive cohort (i.e. controlling for 'confounding by indication').

2. For adequate follow-up period criterion, this was set at study period of 5 years.

3 = exposure for case-control and outcome for cohort studies.

Table 2. Quality assessment of randomised controlled trials using the Gradings of Recommendations Assessment, Development and Evaluation criteria. (2)

Study author(s) and year of publication (reference on manuscript)	Study limitations (risk of bias)[1]	Inconsistency of results (if consistent this does not increase quality)	Indirectness of evidence	Imprecision	Reporting bias	Overall quality of evidence
Lindholm *et al.* 2001 (57)	Double blind, good allocation concealment, no loss to follow-up, no early cessation or relevant selective reporting.	Consistent as only one measure.	Direct	Imprecise, 95% confidence interval (CI) for standardised incidence ratio crosses unity value of 1.	No evidence of reporting bias.	Moderate
Poole-Wilson *et al.* 2006 (48)	Double blind, good allocation concealment, no differential loss to follow-up (some terminated early), no early cessation or relevant selective reporting.	Consistent as only one measure.	Direct	Imprecise, 95% CI for hazard ratio crosses unity value of 1.	No evidence of reporting bias.	Moderate
Sajadieh *et al.*	Double blind,	Consistent as only one	Direct	Imprecise,	No evidence of	Moderate

Study author(s) and year of publication (reference on manuscript)	Study limitations (risk of bias)[1]	Inconsistency of results (if consistent this does not increase quality)	Indirectness of evidence	Imprecision	Reporting bias	Overall quality of evidence
1999 (62)	good allocation concealment, no differential loss to follow-up (2 centres, 10% of total finished early, for administrative reasons), no early cessation or relevant selective reporting.	measure.		95% confidence interval (CI) for standardised incidence ratio crosses unity value of 1.	reporting bias.	

1. Lack of allocation concealment, lack of blinding, large loss to follow-up or early cessation of trial/selective reporting outcomes considered. Original trial methods were consulted where necessary.

References

1.   Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa, Canada: 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 5 May 2017].
2.   Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-6.

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