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The Risk of Antihypertensive Drug among Breast Cancer Patient: A Systematic Review and Meta-analysis

Sinta Wiranata[1], Ida Ayu Widya Anjani[1], Putri Ayu Wulandari[1], Anak Agung Bagus Putra Indrakusuma[1], I Gede Krisna Arim Sadeva[1], Ayu Dilia Febriani Wisnawa[1], Jonny Karunia Fajar[2], I Putu Yuda Prabawa[3], Putu Anda Tusta Adiputra[4], I Wayan Sudarsa[4], Anak Agung Wiradewi Lestari[3], Desak Made Wihandani[5], I Gede Putu Supadmanaba[5]

[1]Medical Student, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia; [2]Department of Internal Medicine, Brawijaya Internal Medicine Research Center, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, Indonesia; [3]Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Bali, Indonesia; [4]Department of Surgery, Division of Surgical Oncology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Bali, Indonesia; [5]Department of Biochemistry, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia

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***Correspondence:** Desak Made Wihandani, Department of Biochemistry, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, 80113, Indonesia. Email: dmwihandani@unud.ac.id
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Abstract

BACKGROUNDS: Breast cancer or breast carcinoma is the most common type of malignancy in women globally. According to the previous studies that indicate the usage of antihypertensive drugs may become a risk factor of cancer (beta-blockers [BBs], calcium channel blockers [CCBs], and diuretics). Both angiotensin-converting enzymes inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), on the other hand, have been associated to an increased or decreased risk of breast cancer.

AIM: To compare each type of antihypertensive medicines as a risk factor for breast cancer, we did a systematic review and meta-analysis of current evidence.

METHODS: We utilized the terms “antihypertensive”, “anti-hypertensive”, “anti-hypertensive medications”, “breast cancer”, “risk”, “case control”, and “cohort” in PubMed, ScienceDirect, and Google Scholar databases.

RESULTS: Our data calculation found that the risk of antihypertensive drugs was significantly different in overall analysis (odds ratio [OR] = 0.59, 95% confidence interval [CI] = 0.42–0.83, p = 0.003). Five studies with 39.503 breast cancer patients and 372.037 controls were included in the ARBs user sub-group. Our results found significant different of antihypertensive drugs among breast cancer patient (OR = 1.47, 95% CI = 1.02–2.11 p = 0.04). Our data calculation also confirmed no significant different in antihypertensive drugs among breast cancer patient (OR = 1.07, 95% CI = 0.99–1.16, p = 0.09) in diuretics user, (OR = 1.08, 95% CI = 0.99–1.18, p = 0.08) in CCBs user, (OR = 1.11, 95% CI = 0.98–1.26, p = 0.09) in BBs user, and (OR = 1.27, 95% CI = 0.64–2.50, p = 0.50) in ACEIs user.

CONCLUSIONS: Although, the finding reveal that antihypertensive drugs (diuretics, CCBs, BBs, and ACEIs) in overall are significant for the risk of breast cancer and also found that ARBs have a low potential in the risk of breast cancer.

Introduction

Hypertension is one of the world’s most common diseases [1], [2]. It has a high prevalence, impacting 9.4 billion people worldwide [3], [4], resulting in millions of deaths and a one-billion-person morbidity [5]. Antihypertensive agent is the most common intervention or treatment for this disease that commonly prescribed by doctor to help avoid adverse effects of hypertension such as stroke, insufficient heart, coronary heart disease, and other cardiovascular disease. The total finished prescriptions achieved in 2010 as many as 6782 million in United States of America (USA) alone [6].

The antihypertensive drug is classified or divided into some groups. The groups have some unique mechanisms and pathway that related to the specific receptor and ligan in suppressing hypertension condition (a variety of pathophysiological issues). The most used pharmacological groups used are diuretics, beta-blockers (BBs), angiotensin-converting enzymes (ACEs) inhibitors (ACEIs), calcium channel blockers (CCBs), and angiotensin II receptor blocker (ARB). Some other agents, such as renin inhibitors, centrally acting medications, alpha-adrenergic receptor blockers, and direct acting vasodilators are the additional hypertension drugs that are widely utilized for short-term treatment [7].

The use of antihypertensive drug may cause some side effects, both short- and long-term. Drowsiness, headache, edema or swelling, urine incontinence, tachycardia, sedation, dry mouth sensation, reduced renal perfusion, mild-moderate diarrhea, and bronchospasm are the most prevalent

side effects [8]. Antihypertensive medicine use may also be a risk factor for cancer, according to a recent study, however the exact mechanism that causes carcinogenic consequences is unknown [9]. Another type of cancer also found to have a link with the usage of antihypertensive drug is breast cancer [10].

Breast cancer or breast carcinoma is the most common type of malignancy in women globally. It is also known to be the second leading cancer in the number of deaths among women annually. More than 250,000 women with invasive breast cancer in the USA are diagnosed each year [11]. Breast cancer also led to the deaths of 520 men and 42,170 women in a recent study in the United States [12]. Patients' median survival from first relapse was 17 months, indicating that it is a life-threatening disease [13].

The link between antihypertensive drug use and the risk of breast cancer has piqued researchers' interest since 1990. Recent findings on the relation between antihypertensive drug use and the risk of breast cancer have been contradictory. BBs, CCBs, and diuretics have been associated to an increased risk of breast cancer in several studies [1], [2], [3], [4]. Meanwhile, taking an ACE inhibitor or an ARB has been linked to a higher or lower risk of breast cancer [14], [15].

Based on this, there are differences in results that do not produce generalized information. That is the opportunity to get answers to these differences. This is the first review so far to our knowledge that addresses the risk of antihypertensive medicines specific to breast cancer. As a response, to compare each type of antihypertensive medicines as a risk factor for breast cancer, we did a systematic review and meta-analysis of current evidence.

Methods

Literature search

PubMed, ScienceDirect, and Google Scholar were several databases combed for articles up through the last November 2020. The formula search employed Boolean "AND" or "OR" with "antihypertensive", "anti-hypertensive", "antihypertensive drugs", "breast cancer", "risk", "case control", and "cohort" keywords.

Selection of the studies

Studies included must meet the following criteria such as: (1) The result reported association of antihypertensive drugs use linked to the incidence of breast cancer patients; (2) the research calculated and announced on the relative risk of breast cancer using variable such as the odds ratio (OR 95%); (3) cross-sectional, cohort, and case-control study design; and (4) English-language studies. The study selection, quality evaluation, and data extraction were all done independently by three reviewers. The issue between the three reviewers was settled by consensus among the fourth and fifth reviewers. This study was designed using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline guidelines [16].

Measurement of the studies quality

Newcastle Ottawa Scale was used to measure the quality of studies. This instrument has three components: Patient selection (four points), group comparability (one point), and exposure determination (one point) (three points). Measurement in the selection components includes: Proper case definition, case representativeness, control group selection, and definition. Measurement in the comparability components includes: Research controls for the most and extra factor. Measurement in the exposure domain includes: Exposure determination, method of cases and controls determination, and rate of non-response. The overall score varied from 0 (worst) to 8 (best). The overall quality was rated as good (final score ≥7), moderate (final score ≥5 until <7), or poor (final score ≤4).

Extraction of the studies data

Using the predefined procedure, three reviewers retrieved the baseline characteristics, exposures, and outcomes of included studies independently. The initial name of author, publication year, design of research, the country, and the amount of people that participated (group of case and control) were all gathered. The length of each drug's therapy (diuretics, CCB, BB, ACEI, and ARB) was also retrieved. We e-mail the associated author when studies did not provide enough information to extract the data; however, we were unable to obtain further data using this technique since the associated author did not have the data information to begin with. We eliminated these studies from further quantitative analysis because we were unable to get the necessary data after trying to contact the associated authors.

Data analysis

The adjusted estimates of the risk of antihypertensive medication use between breast cancer patients were the study's primary outcome. The best-adjusted OR with 95% confidence interval (CI) was utilized. The Q-test was used to measure heterogeneity with a significance set at $p < 0.10$. The Egger test was used to measure publication bias, with significance set at $p < 0.05$.

Results

Literature search

During the initial search 1239 studies were identified. The reference review included three additional articles [3], [17], [18] Three hundred and thirty-one articles are suitable for review following examination of the titles and abstracts. For restricted access, there are 189 sections excluded and nine duplicate items removed. One hundred and forty-two full text sections have been eligible for access. Thirteen papers were obtained in the qualitative synthesis. Thirteen articles are suited for quantitative summarization (meta-analysis). This literature search process is based on a modified PRISMA flow chart (Figure 1).

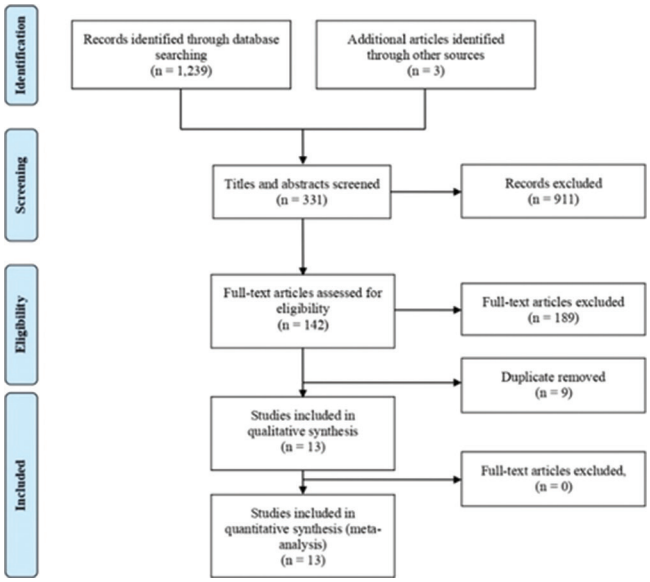

Figure 1: PRISMA flow diagram (modified)

Study characteristics

Table 1 provides an overview of the details from the 14 studies included. All studies were published in English. Two were prospective cohort studies and 11 were case–control studies. Six studies in the U.S., five in Europe, and two in Taiwan were conducted. The sample scales ranged from 654 to 747,085, with 885,590 participants and 352 to 149,417 cases of breast cancer, with a total of 185,626. Of these studies, eight had diuretic, CCB and BB results, seven were provided for ACEIs and five were provided for ARBs. Evaluations of the drug use between studies have not been consistent; reviews of prescription and questionnaires have been most used.

Data synthesis

A total of 13 studies [2], [3], [4], [6], [15], [17], [18], [19], [20], [21], [22], [23], [24], consisting 185,626 patients with breast cancer and 699,964 control sample were included in our study. Of those, the correlation between AHT (diuretics, CCB, BB, ACEIs, or ARBs) use and the risk of breast cancer was identified in five studies only [3], [4], [6], [21], [23]. A further eight studies failed to clarify the risk [2], [15], [17] [18, [19], [20], [22], [24]. Our calculation showed (Figure 2a) that the risk of antihypertensive drug was significantly different in overall analysis (OR = 0.59, 95% CI = 0.42–0.83, p = 0.003). Moreover, in ARBs user sub-group, we included five studies [2], [6], [15], [19], [21] consisting of 39.503 breast cancer patients and 372,037 control sample. Our results found (Figure 2f) that significant different of antihypertensive drug among breast cancer patient was observed (OR = 1.47, 95% CI = 1.02–2.11 p = 0.04). Our pooled data (Figure 2b-e) confirmed that the antihypertensive drug in the other drug subgroup did not differ in any significant way in breast cancer patients

Table 1: Study characteristics in our analysis

Author and Year	Antihypertensive Drug User		Country	Study Design	Main Results	Quality
	BC	N				
Meier *et al*. 2000	1139	17861	United Kingdom	Case control	The risk of developing breast cancer is affected by no association in the long-term use of ACE inhibitors or CCBs	Good
Li *et al*. 2003	975	1982	USA	Case control	Particular types of antihypertensive medications (immediate-release CCBs and certain diuretics) increase the risk of breast carcinoma among older women	Moderate
Gonzalez-Perez *et al*. 2004	3708	23708	United Kingdom	Cohort	Anti-hypertensive drugs and breast cancer risk are not associated. Captopril in the same line was not associated with a lower risk of breast cancer, though it cannot be safely ruled out a small reduction in risk for long-term use	Good
Largent *et al*. 2006	172	654	USA	Case control	Use of other blood pressure medications was not found to be associated with breast cancer risk. These results support a positive link among women aged 50–75 years between the treatment of hypertension, diuretic use, and breast cancer risk	Good
Davis and Mirick 2007	547	1247	USA	Case control	The use of calcium channel blockers (CCBs) associated a slightly increased risk of breast cancer, but no trend was associated with increasing duration or repetition of use.	Moderate
Coogan *et al*. 2008	5989	11493	USA	Case control	The use of diuretics does not increase breast cancer risk	Good
Hallas *et al*. 2012	19947	332623	Denmark	Case control	The association between ARB/ACEI use and cancer are weak	Good
Botteri *et al*. 2013	74	800	Italy	Cohort	A significantly decreased risk of recurrence, metastasis, and death related to BC was associated with the consumption of BB	Good
Li *et al*. 2013	1960	2851	USA	Case control	In particular, long-term use of calcium canal blockers is associated with the risk of breast cancer	Good
Leung *et al*. 2015	6463	25450	Taiwan	Case control	In the study was found beta-1 selective blocker and CCBs have association with breast cancer risk	Good
Chen *et al*. 2015	352	1013	USA	Case control	A second primary contralateral breast cancer risk was not associated with an antihypertensive class, including calcium channel obstruction agents, β blockers, ACE inhibitors, and diuretics	Moderate
Gómez-Acebo *et al*. 2016	1736	3631	Spanish	Case control	The long-term usage of CCBs was associated with certain types of breast cancer	Good
Chang *et al*. 2016	9397	46985	Taiwan	Case control	There were no significant association of using hypertension medication with the breast cancer risk	Moderate

BB: Beta-blockers, CCB: Calcium channel blockers, ACEI: Angiotensin-converting enzymes inhibitors, ARBs: Angiotensin II receptor blockers, BC: Breast cancer, n: Total sample.

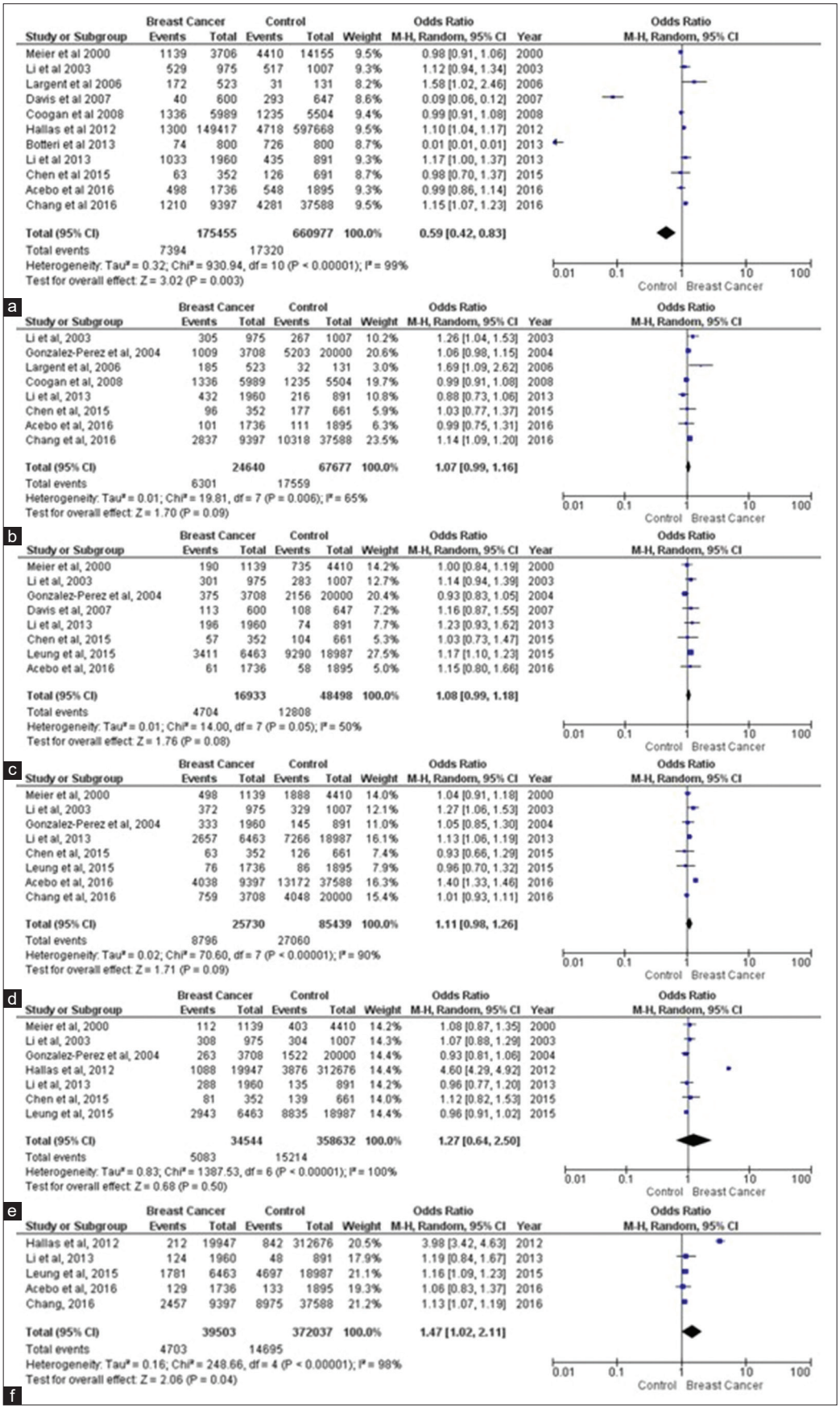

Figure 2: Forest plot of antihypertensive drug among breast cancer patient. (a) Overall analysis. (b) Diuretics user sub-group. (c) Calcium channel blockers user sub-group. (d) Beta-blockers user sub-group. (e) Angiotensin-converting enzymes inhibitors user sub-group. (f) Angiotensin II receptor blockers user sub-group

(OR = 1.07, 95% CI = 0.99–1.16, p = 0.09) in diuretics user, (OR = 1.08, 95% CI = 0.99–1.18, p = 0.08) in CCB user, (OR = 1.11, 95% CI = 0.98–1.26, p = 0.09) in BB user, and (OR = 1.27, 95% CI = 0.64–2.50, p = 0.50) in ACEIs user. Table 2 summarizes how the antihypertensive drug risk is correlated and the effect estimate is estimated in patients with breast cancer.

Heterogeneity and publication bias

The Q-Test was used to evaluate evidence of heterogeneity. Our analysis showed that overall analysis and a whole subgroup of drug user's demonstrated heterogeneity ($p < 0.10$). The random model of the effect was therefore used to determine the correlation and the estimate of effect. In addition, possible biases in the publication of the Egger test have been assessed. Our analysis showed that the BB subgroup and ACEI/ARB subgroup ($p < 0.05$) have identified a possible bias in publication. We found no publication bias in diuretics and CCB subgroups. Table 2 describes the summary of the heterogeneity of the study and its possible publication.

Discussion

Breast cancer is sometimes diagnosed with concurrent comorbidities, such as hypertension, heart disease, diabetes, and arthritis. This condition also correlates with their vulnerability related age. Thus, breast cancer patients' prediagnostic health status in middle and age groups may affect tumor prognosis and treatment decisions. Several studies established that age and comorbidity strongly influence therapeutic decisions and were associated with less aggressive cancer therapy and that older women were less likely to have extensive pretreatment [25]. Meanwhile, antihypertension drugs were known to influence the prognosis of breast cancer patients. In addition, studies about hypertension drugs-related breast cancer still have a lot of contradictory results. A study with 13 consisting of 185,626 breast cancer patients and 699,964 control samples shows that antihypertensive drugs (diuretics, CCB, BB, and ACEIs) are not significant for the risk of breast cancer. However, we found that ARBs have a weak potential in the risk of breast cancer. Our overall findings showed different results with a meta-analysis of randomized clinical trials of antihypertensive therapy that showed no increased cancer risk with the use of antihypertensive therapy [26]. In another study, there was no evidence about the association between CCB use and the increased risk of breast cancer, which is in line with some studies included in this meta-analysis [20], [22], [27] On the opposite side, another study found a significant relationship between long-term use of CCB with breast cancer and the differences might be because of the duration of CCB use in the samples [28]. About the BBs, the study before has the same result as our study that found BB is not associated with improved clinical outcomes in women with breast cancer [29]. However, another study found that BBs can reduce the risk of breast cancer recurrence [30].

Diuretic, as the treatment of hypertension, was also significantly associated with breast cancer risk [3]. Li *et al*. conducted a detailed study on antihypertensive medications and found thiazide and potassium-sparing diuretics, but not loop diuretics, to be associated with a modest increase in breast cancer risk postmenopausal women aged 65–79 years. In the present study, it cannot be ruled out that diuretic use was due to the underlying condition of hypertension, or vice versa [4]. CCBs have been used for so long as one of the hypertension drug categories. It was hypothesized to lead to the proliferation of the cells and tumor growth [31]. Li *et al*. study was established consistently with two previous meta-analyses in 2014, indicating no carcinogenic effect of CCB on breast cancer [27], [28] A comprehensive review showed that CCBs are

Table 2: Summary of risk factors of antihypertensive drugs among breast cancer patients

Risk Factor	Variable	NS	Model	Breast Cancer		Control		OR	95% CI	pH	pE	p
				TS	Value (%)	TS	Value (%)					
Diuretics		3										
	<5 years		Random	894	354 (39.60)	502	191 (38.04)	0.82	0.50–1.39	0.019	0.386	0.473
	≥5 years		Random	894	540 (60.40)	502	311 (61.96)	1.15	0.72–1.84	0.040	0.333	0.545
CCB		3										
	<5 years		Fixed	477	237 (49.69)	801	467 (58.30)	0.98	0.75–1.27	0.150	0.223	0.893
	≥5 years		Fixed	477	240 (50.31)	801	334 (41.70)	1.02	0.78–1.31	0.150	0.223	0.893
B-Blockers		4										
	<5 years		Fixed	932	444 (47.64)	1798	973 (54.11)	0.91	0.77–1.09	0.840	<0.0001	0.325
	≥5 years		Fixed	932	488 (52.36)	1798	825 (45.89)	1.09	0.92–1.30	0.840	<0.0001	0.325
ACEIs		3										
	<5 years		Fixed	513	281 (54.80)	630	377 (59.85)	1.18	0.91–1.54	0.304	0.102	0.202
	≥5 years		Fixed	513	232 (45.22)	630	253 (40.15)	0.84	0.64–1.09	0.304	0.102	0.202

Value was presented in n (%); NS: Number of studies, TS: Total sample, BC: Breast cancer, OR: Odds ratio, 95% CI, 95% confidence interval, pH: p heterogeneity, pE: p Egger.

associated with an enhancement of the risk of tumor development by reducing the levels of intracellular Ca^{2+} as a potential signal for cellular apoptosis [32]. Its basic assumption was directly contradicted with the several laboratories finding that demonstrating an elevation in cytoplasmic Ca is not required for either the activation of DNA endonucleases or apoptosis mechanism [33]. An apoptosis mechanism could be reproducibly initiated by a decrease in cytoplasmic Ca^{2+} levels [34]. Even though not well understood, it has been proposed that the low level of Ca^{2+} could avoid cation-mediated charge neutralization of DNA, thus resulting in apoptosis stimulation. Chelators of intracellular $Ca^{2+}$and the calmodulin inhibitor-7 have been shown that increased the apoptosis rate in neutrophils virtually. Cytoplasmic Ca^{2+} deficiency in the cells could be rescued from apoptotic cell death with the use of Ca^{2+} ionophores or Ca^{2+}channel agonists [35]. Lack of an apparent requirement for elevated Ca^{2+} levels in the cytoplasm during apoptosis suggests that cation sensitive DNA endonucleases activation may require only in deficient levels of Ca^{2+} or may not even be an essential process. This observation could help to rationalize why CCBs have inconsistent effects on apoptosis [36].

Most preclinical studies have shown that BBs inhibit multiple cellular pathways involved in breast cancer progression and tumor growth, including cell proliferation, angiogenesis, the metastatic process, and tumor immune responses [37], [38], [39], [40], [41]. *In vitro* studies reported that BBs have significantly decreased Ki-67 expression, phosphorylation of multiple mitogenic activated protein kinases, and cyclic adenosine monophosphate (cAMP) responsive element-binding protein (CREB). BBs also increased phosphorylation of protein kinase B (PKB), glycogen synthase kinase 3 (GSK3), and p53 expression [39], [40]. *In vivo* studies also reported the same outcomes related to BBs effect on breast cancer progression through inhibition or antagonism of the beta-adrenergic receptor (β-AR) signaling. β-AR is previously known to promote and increase breast tumor growth, breast cancer metastases, angiogenesis through VEGF, upregulation of both expression of macrophage-derived factors (COX2, MMP-9, and VEGF), and matrix metalloproteinase (MMP), especially MMP-2 [41], [42].

Some studies on the clinical phase also reported that BB consumption before diagnosis presented a significantly lower metastasis rate in breast cancer patients [42], [43]. On another side, only a few studies have reported associations between BBs and breast cancer [2], [19]. Thus, our findings are consistent with the most previous studies that found no significant difference of BB drug among breast cancer patients [42], [43]. However, we were unable to report the relationship between the use of particular types of BBs and breast cancer patients since most of the studies do not reported the subclass of BB drugs used in the cases. Only one case-control study in the USA that further classified BB drugs into short and long-acting BB and found that the OR of short-acting higher than long-acting BB used [4].

Conclusions

Hypertension being one of breast cancer comorbidity and influence their quality of life. Antihypertension drug weather prognosis or the risk of breast cancer remains the contradiction result. Regarding to our finding in 13 studies established statistical significant the association between antihypertension drug and breast cancer.

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Ethical Approval and Consent to Participate

Ethic approval and informed consent were not required in our study.

Limitations

Our meta-analysis had several limitations. Limit to enroll all eligible studies due to article access, difficulty in summarizing data due to difference data presentation data in several studies, we could not evaluate the others variable such as risk factors that might affect the intervention duration and outcome, differences in the classification of intervention durations mean that we may not have sufficient power to accurately estimate the risks associated with long-term drug use.

Authors Contributions

Idea/concept: SW. Design: SW and IAWA. Control/supervision: SW and JKF. Data collection/processing: ADFW, AABPI, and IGKAS. Extraction/Analysis/interpretation: PAW, AABPI, IGKAS, SW, and IPYP. Literature review: SW, JKF. Revision and proof

reading: DMW, IGPS, PATA, IWS, and AAWL. Writing the article: PAW, AABPI, IGKAS, SW, and IAWA. Critical review: all authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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