

## MINI-REVIEW

# β-Adrenergic Receptors : New Target in Breast Cancer

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### Abstract

**Background:** Preclinical studies have demonstrated that β-adrenergic receptor antagonists could improve the prognosis of breast cancer. However, the conclusions of clinical and pharmacoepidemiological studies have been inconsistent. This review was conducted to re-assess the relationship between beta-adrenoceptor blockers and breast cancer prognosis. **Materials and Methods:** The literature was searched from PubMed, EMBASE and Web of Nature (Thompson Reuters) databases through using key terms, such as breast cancer and beta-adrenoceptor blockers. **Results:** Ten publications met the inclusion criteria. Six suggested that receiving beta-adrenoceptor blockers reduced the risk of breast cancer-specific mortality, and three of them had statistical significance (hazard ratio (HR)=0.42; 95% CI=0.18-0.97; *p*=0.042). Two studies reported that risk of recurrence and distant metastasis (DM) were both significantly reduced. One study demonstrated that the risk of relapse-free survival (RFS) was raised significantly with beta-blockers (BBS) (HR= 0.30; 95% CI=0.10-0.87; *p*=0.027). One reported longer disease-free interval (Log Rank (LR)=6.658; *p*=0.011) in BBS users, but there was no significant association between overall survival (OS) and BBS (HR= 0.35; 95% CI=0.12–1.0; *p*=0.05) in five studies. **Conclusions:** Through careful consideration, it is suggested that beta-adrenoceptor blockers use may be associated with improved prognosis in breast cancer patients. Nevertheless, larger size studies are needed to further explore the relationship between beta-blocker drug use and breast cancer prognosis.

**Keywords:** Beta-adrenoceptor blockers - breast cancer - prognosis - systematic review

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### Introduction

Breast cancer is the most common cancer in women in whole world (WHO, 2014). Although treatment of breast cancer has been in progress, global breast cancer mortality is still increasing annually (WHO, 2014). Therefore, new therapeutic options are needed. Recent studies had showed that β-Adrenergic signaling had an influence up on biological processes involved in the development of the carcinoma (Sood et al., 2006; Thaker et al., 2006; Chakroborty et al., 2009; Anil et al., 2010; Shahzad et al., 2010; Akbar and Alsharidah, 2014) by influencing tumor cells and the microenvironment of tumor cells (Entschladen et al., 2004; Antoni et al., 2006; Armaiz-Pena et al., 2008; Prema et al., 2008; Susan et al., 2010), including but not limited to the cancers of pancreas (Drell et al., 2003), breast (Barron et al., 2012; Diaz et al., 2012), ovary (Masu et al., 2001; Sood et al., 2006), colon (Masur et al., 2001), prostate (Grytli et al., 2013; Grytli et al., 2014). These effects can be removed by BBS (Masur et al., 2001; Drell et al., 2003; Zhang et al., 2010).

Beta-adrenergic system is comprised of catecholamines (Tang et al., 2013), and beta-adrenergic receptor is composed of three subtypes, β1, β2 and β3 (Yamazaki et

al., 2014). In preclinical studies, researchers had observed the expression of beta-adrenergic receptors in a few breast cancer cell lines and human breast cancer tissue samples (Madden et al., 2011; Park et al., 2011; Powe et al., 2011). Beta-adrenergic receptor signaling had been demonstrated to accelerate angiogenesis through increasing the expression of vascular endothelial growth factor (VEGF) (Lutgendorf et al., 2003; Thaker et al., 2006; Yang et al., 2006; Zhang et al., 2010) and interleukin-6 (IL-6) (Thaker et al., 2006; Sloan et al., 2010), promote breast cancer growth (Cakir et al., 2002; Thaker et al., 2006; Shi et al., 2011), recurrence and metastasis (Benish et al., 2008; Avraham et al., 2010; Sloan et al., 2010) and reduce apoptosis of cancer cells (Sasthy et al., 2007; Zhang et al., 2009; Sood et al., 2010; Set al., 2011). These effects can be suppressed by BBS (Masur et al., 2001; Drell et al., 2003; Lang et al., 2004; Palm et al., 2006; Landen et al., 2007; Zhang et al., 2010). However, some researchers demonstrated that β2-adrenergic receptor stimulation could significantly suppress the malignant transformation of cancers, cancer cell growth and proliferation by cutting of the Raf-1/Mek-1/Erk1/2 pathway (Carie and Sebti, 2007; Perez et al., 2012). In clinical studies, part of authors observed breast cancers' prognosis could be drastically

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improved by receiving BBS (Powe et al., 2010; Barron et al., 2011; Ganz et al., 2011; Melhem et al., 2011; Shah et al., 2011; Botteri et al., 2013; Holmes et al., 2013). Nevertheless some investigators suggested there was no significant relationship between beta-blocker users and non users in the risk of breast cancers' prognosis (Sendur et al., 2012; Holmes et al., 2013). Above all, the result is inconsistent. To make certain whether beta blockers affect the prognosis of breast cancer patients, a systematic review of their relationship is performed.

## Materials and Methods

### Criteria for inclusion in this review

The following inclusion criteria should be met in these candidate studies: (1) the study design was interventional; (2) the breast cancer patients should be confirmed the pathological type; (3) the usage of Beta-adrenoceptor blockers were evaluated; (4) clinical studies used a control group excluding animal and cell line studies; (5) clinical outcomes should be provided, such as survival, disease-free survival (DFS), tumor recurrence and metastasis. Divergences of the reviewers' inclusions were settled by discussion. Additional studies were identified by a hand search of the references cited in the original studies.

### Search methods for identification of studies

Related literatures are searched from the Pub-Med, EMBASE and Web of nature databases through using terms for breast carcinoma/cancer/tumor and beta-adrenoceptor blockers/beta blockers/beta-adrenoceptor antagonists. The overall search was based on humans and clinic, without restriction on language or region. Furthermore, to extend the search, we also used the "related articles" section. Data retrieval included all eligible studies and their references were thoroughly investigated. These literatures which printed before October 1st, 2014 were in the scope of our screening.

### Data extraction

As listed below, these data was extracted for each study: first author's name, publication year, patients' original country, number of patients investigated including comparison group and experimental group, exposure ascertainment, category of drug use (never/ever use), outcome confirmation, overall risk measurement, adjustments of confounders. The potential biases of all included articles were evaluated. Information was extracted from all eligible studies by two of the authors (Xuesong Chen, Ting Wang). Discrepancies between the authors were settled by consultation to reach a consensus.

## Results

### Eligible studies

There were 2119 potentially relevant studies through electronic search. After checking the title and abstract and screening full text articles when needed, a total of 10 articles were eligible for inclusion criteria as showed in the Figure 1. The main characteristics of these eligible articles are outlined in Table 1. All of the articles were

retrospective cohort studies built on the hospital. Five of the studies were located in Europe (Powe et al., 2010; Barron et al., 2011; Shah et al., 2011; Botteri et al., 2013; Cardwell et al., 2013), four in North America (Ganz et al., 2011; Melhem et al., 2011; Holmes et al., 2013; 2013), and one in Asia (Turkey) (Sendur et al., 2012). A total of 19,999 patients were included in the eligible studies, with study sizes ranging from 466 to 9817. It was variable in terms of beta-adrenoceptor blockers type and the average length of follow up. There were selective and no-selective selective and no-selective beta-adrenoceptor blockers. The average length of follow up ranged from 1.3 years to 10.5 years (Table 1).

### Data analysis

Six studies evaluated the effect of non-selective beta blockers use among breast cancer patients (Ganz et al., 2011; Melhem et al., 2011; Botteri et al., 2013; Cardwell et al., 2013; Holmes et al., 2013; 2013). Four studies assessed the effect of selective and non-selective beta blockers uses (Powe et al., 2010; Barron et al., 2011; Shah et al., 2011; Sendur et al., 2012). One retrospective cohort study provided information on the median daily dose of beta-adrenoceptor blockers (80mg) usage (Barron et al., 2011). Nine studies evaluated the association of Beta-adrenoceptor blockers usage versus non-use. Two studies' authors assigned participants into one combined treatment group (BBS and aspirin; BBS and ACEI), a single treatment group (BBS) or a control group (no BBS) (Ganz et al., 2011; Holmes et al., 2013). And Holmes MD et al. (2013) analyzed the association between breast cancer mortality and the use of beta blockers, the combined use of ACEIs and/or aspirin. Ganz et al. (2011) examined the association between BBS Users and BBS combined with angiotensin converting enzyme inhibitors (ACEI) users and breast cancer recurrence, breast cancer specific mortality, and overall mortality. Five studies assessed OS (Ganz et al., 2011; Shah et al., 2011; Melhem et al., 2011; Sendur et al., 2012; Holmes S et al., 2013). Six studies (Powe et al., 2010; Barron et al., 2011; Ganz et al., 2011; Botteri et al., 2013; Holmes et al., 2013; Cardwell et al., 2013) assessed cancer-specific mortality. And two of them assessed overall mortality (Ganz et al., 2011; Botteri et al., 2013). One study assessed RFS (Melhem et al., 2011). Three studies additionally examined tumor

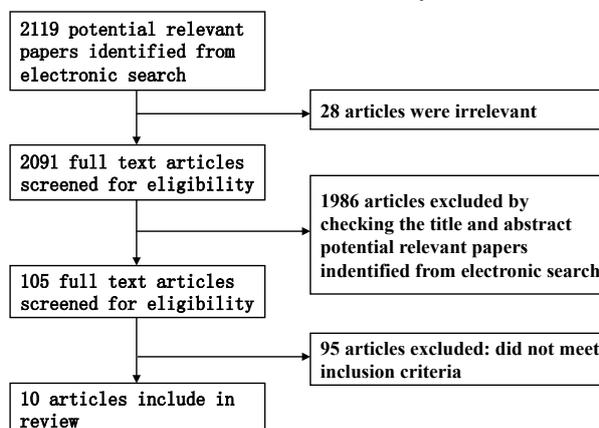


Figure 1. The Flow Chart of Study Selection and Exclusion

recurrence as an outcome (Powe et al., 2010; Ganz et al., 2011; Botteri et al., 2013). One study assessed disease free interval (Powe et al., 2010). Two studies discussed distant metastasis (DM) (Powe et al., 2010; Botteri et al., 2013). One study assessed DFS (Sendur et al., 2012). One study observed pathologic complete response (PCR) rates (Melhem et al., 2011).

*Risk of adjustments assessment*

Adjustments of these eligible studies were not all the same, which were showed in Table 1. Eight of these studies adjusted for age (Powe et al., 2010; Barron et al.,

2011; Ganz et al., 2011; Melhem et al., 2011; Sendur et al., 2012; Botteri et al., 2013; Holmes et al., 2013; Holmes et al., 2013). Seven of the eight studies, moreover, adjusted for stage of cancer simultaneously (Powe et al., 2010; Barron et al., 2011; Ganz et al., 2011; Melhem et al., 2011; Botteri et al., 2013; Holmes et al., 2013; Holmes S et al., 2013). There were three articles all adjusted for diabetes diagnosis, body mass index (BMI) and hormone receptor status (Ganz et al., 2011; Melhem et al., 2011; Cardwell et al., 2013). Four studies are adjusted for adjuvant treatment (Ganz et al., 2011; Botteri et al., 2013; Cardwell et al., 2013; Holmes et al., 2013). Two studies

**Table 1. Characteristics of the Studies**

Author (year)	Institution and country	Study period	Study design	Follow-up length	Statistical approach	Adjustments											
						A	B	C	D	E	F	G	H	I			
Barron et al, 2011	National Cancer registry Ireland (Ireland)	2001-2006	Population-based retrospective cohort	5years	Conditional logistic Regression, Kaplan-Meier plots and Multivariable Cox proportional hazards models	*	*										*
Ganz et al, 2011	Kaiser Permanente Northern California Cancer Registry and Utah Cancer Registry (USA)	1997-2010	Population-based retrospective cohort	8.2 years	Pearson chi-square , Kruskal-Wallis (K-W) tests and Cox proportional hazards model	*	*	*	*	*	*	*	*	*	*	*	*
Melhem et al., 2011	University of Texas MD Anderson Cancer Center (USA)	1995-2007	Hospital-based retrospective cohort	5.3 years	x2 test and Fisher's exact test	*	*		*	*	*	*	*	*	*	*	*
Botteri et al., 2013	the European Institute of Oncology in Milan (Italy)	1997-2008	Population-based retrospective cohort	3.0 years	Chi square test, Fisher exact test, Gray test and Multivariable Cox proportional hazards models	*	*	*									*
Powe et al., 2010	Nottingham City Hospital (Britain)	1987-1994	Hospital-based retrospective cohort	1.3 years	Kaplan-Meier plots test, Chi square , Fishers exact test and Multivariate Cox regression analysis	*											*
Sendur et al., 2012	Ankara Numune Education and Research Hospital (Turkey)	1998-2010	Hospital-based retrospective cohort	ns	ns												
Holmes MD et al., 2013	United States nurses (USA)	1985-2005	Population-based retrospective cohort	10.5years	Cox proportional hazards regression and multivariable models	*	*	*		*	*				*	*	*
Holmes S et al., 2013	Manitoba Cancer Registry (Canada)	2004-2008	Population-based retrospective cohort	6 years	Cox regression analysis and Kaplan-Meier survival curves	*	*										*

Author	Database	Year	Population-based retrospective cohort	Follow-up	Model	A	B	C	D	E	F	G	H	I	Others
Shah et al., 2011	DIN-LINK database (Britain)	1997-2007	Population-based retrospective cohort	10 years	Cox proportional hazard model	*									
Cardwell et al., 2013	National Cancer Data Repository, Clinical Practice Research Datalink and Office of National Statistics death registration data (Britain)	1998-2007	Population-based retrospective cohort	6 years	Conditional logistic regression Cox proportional hazards model	*	*	*	*	*	*				*

\*adjusted confounders A age, B stage, C adjuvant treatment, D hormone receptor status, E diabetes, F body mass index, G hypertension, H menopausal status, I others. ns: not stated

adjusted for hypertension (Ganz et al., 2011; Melhem et al., 2011). Variable adjustments may be having an effect on the above-mentioned studies. However, they were not necessary for a review.

## Reported results

### Survival

It's presented in Table 2 of the risk estimates for survival. Barron et al. (2011) found women taking propranolol at the time of diagnosis (n=70) had an 81% lower risk of breast cancer-specific mortality (HR=0.19; 95% CI=0.06-0.60). However, they observed no association with breast cancer-specific mortality between atenolol and matched nonuser, 26.8%v26.0% (HR=1.08; 95% CI=0.84-1.40). After excluding patients with stage IV breast tumors, Propranolol users continued to enjoy a significantly lower risk of breast cancer-specific mortality, compared with matched nonusers (HR=0.20; 95% CI: 0.04 to 0.94). But atenolol users did not (HR=1.16; 95% CI=0.84 to 1.61). Powe et al. (2010) observed that the risk of breast cancer-specific mortality and metastasis reduced 71% (HR=0.291; 95% CI=0.119-0.715;  $p=0.007$ ) and 57% (HR=0.430; 95% CI=0.200-0.926;  $p=0.031$ ), respectively, after 10 years. Botteri et al. (2013) discussed the association BBS in triple-negative breast cancer (TNBC) patients. The population of breast cancer related death was 6 (8.1%) and 141 (19.4%), individually in beta-blocker users and non-users, with a corresponding adjusted HR=0.42 (95% CI=0.18-0.97;  $p=0.042$ ). At univariate analysis, Botteri et al. (2013) observed a suggestion of increased risk of death from causes other than BC in beta-blocker users compared to non-users, but there was no significant difference. Cardwell et al. (2013) investigated little evidence of an association between beta-blocker use and breast cancer-specific mortality (odds ratio=0.97; 95% CI=0.83, 1.13). Ganz et al. (2011) reported that beta-blocker users. ACEI users and beta-blocker combined with ACEI users had no statistically significant associated with cause-specific mortality. There was no reduction in overall mortality (HR= 1.04; 95% CI=0.72-1.51) in eta-blocker users and (HR= 1.94; 95% CI=1.22, 3.10;  $p=0.01$ ) in

ACEI users. However, beta blocker combined with ACEI had a higher risk of overall mortality. Powe et al. (2010) showed that beta-blocker treated patients' breast cancer had longer disease free interval (LR=6.658.  $P=0.011$ ) and longer breast cancer specific survival (LR=6.479;  $p=0.011$ ) compared to non treated breast cancer patients in Kaplan-Meier modelling with log rank testing. Modeled simultaneously or individually, the association between the risk of breast cancer death and beta-blocker users was non-significant. Melhem et al. (2011) reported that  $\beta$ -Blocker use had no significant association with OS among women with ER-positive breast cancer, TNBC, and all breast cancer. Kaplan-Meier estimates of OS showed that the risk of beta-blocker users was significantly improved ( $p=0.03$ ) in patients with TNBC on beta blockers when compared to TNBC not taking beta blockers. Beta-blocker users with ER-positive breast cancer had no significant effects on OS ( $P=0.65$ ). Sendur et al. (2012) observed no statistical significance in 5-year OS rates between metoprolol users and nonusers (metoprolol 96.8%, nonusers 92.9%;  $p=0.28$ ). Holmes et al. (2013) BBS had no effect on survival for breast cancers (HR= 1.10; 95% CI=0.92-1.32;  $p=.305$ ). In a population-based retrospective cohort study, Shah et al. (2011) didn't found significant difference in OS (HR=1.09; 95% CI=0.80-1.49) between patients with  $\beta$ -blocker (n=434) and patients with other antihypertensive medications (n=554). Holmes et al. (2013) observed no significant association with beta blockers and survival.

### Disease Progression

Results for BBS use and disease progression are outlined in Table 2. Botteri et al. (2013) reported that the 5-year cumulative incidence of breast cancer related events (local recurrence, regional recurrence, distant metastases, death from breast cancer) for beta-blocker users and for non-users was 13.6 % and 27.9 % (Gray test  $P=0.015$ ), individually. The risk of breast cancer related events was statistically significant for multivariable analysis (HR=0.52; 95% CI=0.28-0.97;  $p=0.041$ ) between beta-blocker users and non-users. The incidence of distant metastases was statistically significant decline

**Table 2. The Relationship Between Beta-adrenoceptor Blockers and Breast Cancer Events**

Author (year)	Disease stage	Exposure	Study population	No. of BBS	No. of controls	Research objectives	No. of cases	HR
Barron et al., 2012	I-IV, X	BBS: P, Aa	5333	P70 A525	4738	BCSD	P: 4 no: 20	P:HR:0.19;95% CI:0.06-0.60 A:HR:1.08;95% CI:0.84-1.40
Ganz et al., 2011	I-IIIa	BBS/ other AH	1779	204	1372	BCSD	User: 17 no: 130	HR:0.76;95% CI:0.44-1.33;P:0.34
						All cause mortality	User: 30 no: 221	HR:1.04;95% CI:0.74-1.51;P:0.83
						recurrence	User: 34 no: 216	HR:0.86;95% CI:0.57-1.32; P : 0.49
Melhem et al., 2011	I-III	BBS/ other AH	1413	102	1311	OS	User: 18 no: 335	HRd:0.64, 95% CI:0.38-1.07;P: 0.09 HRe:0.35, 95% CI:0.12-1.00;P : 0.05
						RFS	User: 17 no: 387	HRd:0.52, 95% CI:0.31-0.88;P:0.015 HRe:0.30, 95% CI:0.10-0.87;P:0.027
Botteri et al., 2013	I-IVb	BBS/ other AH	800	74	726	BCSD	User: 6 no: 141	HR:0.42, 95% CI:0.18-0.97;P: 0.042
						Breast cancer related events	User: 11 no: 199	HR: 0.52; 95 % CI:0.28-0.97;p:0.041
						DM	User: 3 no: 110	HR:0.32, 95% CI:0.12-0.90;P: 0.031
Powe et al., 2010	I-II	BBS/ other AH	466	43	374	BCSD	ns	HRf:0.291;95% CI:0.119-0.715, p:0.007
						specific survival	ns	LR:6.479, p:0.011
						Disease free interval	ns	LR:6.658, p:0.011
						DM	User: 5 NH: 102	HRf:0.430;95% CI:0.200-0.926, p:0.031 x2g:4.852, p:0.028
							Other AH: 15	x2:7.264 p:0.026
recurrence	ns							
Sendur et al., 2012	I-III	BBS (meto-prolol)	544	88	456	OS	ns	User:96.8%, no:92.9% P:0.28
						DFS	ns	User:98.3%, no:90.4% P:0.13
Holmes MD et al., 2013	I-III	BBS/ other AH	4661	770	3891	BCSD	User: 45 no: 247	HR:0.76, 95% CI:0.54-1.05
Holmes S et al., 2013	I-IV	BBS/ other AH	4019	531	2310	Survival	ns	HR: 1.10, 95% CI: 0.92-1.32
Shah et al., 2011	ns	BBS/ other AH	984	434	554	OS	ns	HR:1.09;95% CI: 0.80-1.49
Cardwell et al., 2013	I-IV	BBS	9817	1378	5754	BCSD	User: 182 no: 677	HR: 1.24, 95% CI:0.81, 1.88

ns: not stated AH: antihypertensive therapy DM: distant metastases; NH: Non hypertensive breast cancer patients RFS: relapse-free survival DFS: disease-free survival BCSD: breast cancer specific death a P: propranolol A: atenolol ; b: Patients with metastatic disease at diagnosis were excluded; c: Pre-diagnostic beta-blocker use in 2 years prior to breast cancer diagnosis; d: all breast cancer patients; e: Triple-negative breast cancer patients; f: compared to Non -treated breast cancer patients; g: compared to patients receiving other AH

(HR=0.32; 95% CI=0.12-0.90; p=0.031) in favor of BBS. In the study by Powe et al. (2010), the authors reported a significant reduction in metastasis development ( $\chi^2=4.986$ ;

p=0.026). In addition, when analyzing the risk of distant metastases, they observed a significant difference between beta-blocker drugs users and other anti-hypertensive

medications users, 11.6% v 30.6% ( $\chi^2=4.852$ ;  $p=0.028$ ). In Kaplan-Meier modeling with log rank testing, hypertensive breast cancer patients therapeutically treated with BBS users owned significantly longer distant metastasis-free interval (Log rank (LR)=5.208;  $p=0.022$ ) compared to non-treated patients. At a multivariate Cox hazard model, the author demonstrated that the risk of developing DM decreased 57% (HR=0.430; CI=0.200-0.926;  $p=0.031$ ) in beta-blocker treated patients compared to non-treated breast cancer patients. Melhem et al. (2011) found that beta-blocker users achieved a markedly improved RFS among all breast cancer patients (HR=0.52; 95% CI=0.31-0.88;  $p=0.015$ ) and patients with TNBC (HR=0.30; 95% CI=0.10-0.87;  $p=0.027$ ). Beta-Blocker users, however, had no significant association with RFS among women with ER-positive breast cancer. In addition, When compared beta-blocker users to non-users by the Kaplan-Meier estimates of RFS, the RFS was markedly improved ( $p=0.02$ ) among patients with TNBC on BBS, but not among ER-positive breast cancer ( $P=0.4$ ). Sendur et al. (2012) didn't find statistical significance in DFS (metoprolol 98.3% V nonusers 90.4%,  $p=0.13$ ), when compare metoprolol users to nonusers. In the study of Powe et al. (2010), the authors reported a significant reduction in tumor recurrence between BBS users and non-hypertensive breast cancer patients ( $\chi^2=13.091$ ;  $p=0.001$ ), and between other anti-hypertensive medications patients and BBS users ( $\chi^2=7.264$ ;  $p=0.026$ ). Ganz et al. (2011) reported patients with  $\beta$ -blockers showed a non-significant 14% reduction (HR=0.86; 95% CI=0.57-1.32) in the risk of breast cancer recurrence (distant, loco-regional, or contralateral) compared to unexposed women (no BBS and ACEI). Melhem et al. (2011) found no significant 48% and 70% reduction in risk of breast cancer recurrence in beta users of TNBC and breast cancer, respectively. Botteri et al. (2013) also observed that the local and regional recurrence was no significant change between BBS users and non-users.

## Discussion

Although the relationship between beta-adrenoceptor blockers and breast-carcinoma events has been observed in previous studies, the conclusions were inconsistent and some were even controversial. So a systematic review was needed in order to investigate the further association. To the best of our knowledge, this is the first systematic review to investigate the association between Beta-adrenoceptor blockers and breast-carcinoma events. Ten retrospective cohort studies were identified. The majority of the eligible studies were from hospital. Most studies were in small size and had relatively short follow-up periods.

Three studies reported a significant reduction in the risk of breast cancer-specific mortality in beta-blocker users (Powe et al., 2010; Barron et al., 2011; Botteri et al., 2013). Furthermore, one of them observed a no significant improvement of the mortality from causes other than breast cancer in beta-blocker users (Botteri et al., 2013). Three studies demonstrated a suggestion of a reduced risk of breast cancer death associated with

beta-blocker drugs, but not reached statistical significance (Ganz et al., 2011; Cardwell et al., 2013; Holmes et al., 2013). In these researchers, Ganz et al. (2011), Cardwell et al. (2013) and Holmes et al. (2013) adjusted most of the adjustments. Thomas I. Barron, Powe et al. (2010) and Botteri et al. (2013) only adjusted others, age, stage, and adjustment treatment. Powe et al. (2010) observed a significant association between breast cancer special survival and beta-adrenoceptor blockers. And only age and other confounding factors were adjusted in this literature. One study found no significant 36% and 65% reduction in risk of OS in beta blocker users with TNBC and breast cancer, respectively. However, the OS ( $P=0.03$ ) of patients with TNBC on beta blockers were significantly improved in the Kaplan-Meier estimates (Melhem et al., 2011). The different statistical methods maybe affect the results. Three studies found no significant association between OS and beta-adrenoceptor blockers, and they also only adjusted age, stage, and other confounding factors (Shah et al., 2011; Sendur et al., 2012; Holmes et al., 2013). The risk of distant metastases was assessed in two studies. And both of them demonstrated a significant reduction in the risk of distant metastases in beta-blocker treated patients compared to non-treated patients (Powe et al., 2010; Botteri et al., 2013). One study demonstrated a significant reduction in the risk of breast cancer recurrence (Powe et al., 2010), and three studies observed no significant reduction (Ganz et al., 2011; Melhem et al., 2011; Botteri et al., 2013). Ganz et al. (2011) observed no significant 14% reduction. Powe et al. (2010), Melhem et al. (2011) and Botteri et al. (2013) adjusted the multiple confounding factors. Powe et al. (2010) adjusted two confounding factors. Hormone receptor status, age, stage, hypertension, menopausal status, adjuvant treatment, diabetes and BMI were important prognostic indicators. Recently, it's demonstrated that diabetes was an adverse factor for breast cancer (Liao et al., 2011; Melhem et al., 2011; De et al., 2013; Xiao et al., 2014), and so did BMI (Ortiz-Mendoza et al., 2014). A diagnosis of diabetes was associated with a worse OS ( $P=0.002$ ) but not a worse RFS ( $P=0.42$ ) (Melhem et al., 2011). Information about performance status (Huber et al., 2002; Van et al., 2011; Werner and Bruchim, 2012), physical activities (Akechi et al., 2011; Ying et al., 2013) and hereditary factors were not adjusted in the majority of studies, which were reported as important factors for cancer prognosis. Adjustment factors of the eligible studies were inconsistent, which maybe have an effect on the risk of breast cancer-specific mortality. There were only five articles referring to selective and non-selective beta blockers (Powe et al., 2010; Barron et al., 2011; Shah et al., 2011; Sendur et al., 2012; Cardwell et al., 2013). The consequences, however, were inconsistent. Only one of these studies reported that the different strategies of beta-adrenoceptor blockers showed a significantly different effect on breast cancer prognosis (Barron et al., 2011).

Potential biases or confounding. First, although we try our best to search all possible relevant data, it was unavoidable to miss data. Second, a part of the eligible studies was observational studies whose observations may have potential bias. Third, patients' information

was obtained from hospital medical records in the cohort studies, which may appear incomplete information for patients due to differences in hospital classification of drugs and other ways to obtain drugs. Four, there are unavoidable differences in the definitions of methods, measurements, and outcomes in the eligible studies. Despite these potential biases or confounding, this systematic review had several noteworthy advantages. First, this is the first systematic review to investigate the association between BBS use and breast cancer progression and survival. Second, due to a considerable number of subjects and cases from different studies, the statistical power of the analysis was significantly increased. Third, all the eligible studies were searched from aforementioned databases, and when there were discrepancies about candidate articles, the articles were discussed and independently screened for inclusion criteria.

Because of the small number of selected articles and the heterogeneity of articles, a meta-analysis was not undertaken. In this systematic review, it's demonstrated that the risk of breast cancer-specific mortality, the risk of DM and the risk of breast cancer recurrence were decreased for BBS users when compared to non-users, despite the fact that some of the data was without statistical significance. Compared with non-users, the OS of breast cancer patients with beta blockers and different type of beta blockers was inconsistent. And the possible influencing factors could be the following. Firstly, the size of some studies' samples are not enough large; secondly, the discrepancy of the data analysis methods may influence the result; thirdly, other inconsistent confounders of the patients perhaps have some effect on the OS; fourthly, compared with non-users, BBS users were more likely to combine with other diseases which may have a influence on breast cancer prognosis and cancer therapy.

## Conclusions

From this system review, it's suggested that beta-adrenoceptor blocking therapy improve breast cancer prognosis. However, it's not fit to reach a definitive conclusion on the effect of beta-adrenoceptor blocking therapy on the breast cancer prognosis. More and more large preclinical studies were needed in order to further investigate the association between beta- adrenoceptor blockers and breast cancer. Meanwhile, more clinical studies on the association between breast cancer progression or survival and the dosage, frequency and duration of use of beta blockers were also needed to be further carried out.

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