RESEARCH ARTICLE

No association Between Calcium Channel Blockers and Survival in Patients with Cancer: A systematic Review and Meta-analysis

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Abstract

Background: The association between calcium channel blockers (CCBs) and survival in cancer patients remains unclear and the results of related studies are conflicting. The objective of the study was to investigate the association between calcium channel blockers (CCBs) use and survival in cancer patients. Materials and Methods: We searched PubMed, EMBASE, Web of Science and Cochrane Library for studies published before January 2016 with the terms related to CCBs and survival in cancer patients. The information was reviewed and extracted by two evaluators independently. Data of publications was extracted and calculated into hazard ratios (HRs) for overall survival (OS). Statistical analysis was performed by using Review Manager 5.3. Results: There were 11 studies included in our meta-analysis. Analysis of all studies showed that CCBs use was not associated with survival in cancer patients (HR=1.07; 95% CI: 0.91-1.25; *P*=0.42). No association between CCBs use and overall survival in cancer patients was existed whether in Asian (HR=1.18, 95% CI: 0.72-1.93; *P*=0.52) or Caucasian population (HR=1.03, 95% CI: 0.89-1.20; *P*=0.66). Conclusions: There is no evidence that CCBs use is associated with a better or worse outcome of survival in cancer patients.

Keywords: Calcium channel blockers - cancer - survival - meta-analysis

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Introduction

Although death rates of cancer have been declining globally, cancer is still an important public health concern in the whole world (Moore et al., 2008; Salim et al., 2009; Wirasorn et al., 2014; Woodward et al., 2014; Chong, et al., 2016; Hashim et al., 2016). It is an urgent issue to improve the overall survival for cancer patients. Although cancer and its treatment are attracting more and more attention, comorbidities become increasingly important in cancer patients especially in adults over the age of 65 (Williams et al., 2015). Comorbidities among cancer patients are common with the most common comorbidities including cardiovascular diseases, obesity and metabolic diseases (Sarfati et al., 2016). Thus, the cancer patients with comorbidities will inevitably use drugs to treat comorbidities which may influence cancer survival outcomes (Xuan et al., 2012; Vardar et al., 2015).

Calcium channel blockers (CCBs) are a diverse group of medication that are very important and widely used in the clinical management of cardiovascular diseases including hypertension, angina pectoris, cardiac arrhythmias and vasospasm (Grimaldi-Bensouda et al., 2016). Therefore, a lot of cancer patients with cardiovascular diseases will use CCBs. Recently, the association between CCBs use and cancer has been an area of increased interest to investigators. Recent preclinical in-vivo and in-vitro studies showed that CCBs may interfere with tumor cell proliferation, migration differentiation, and apoptosis (Kaddour et al., 2012; Choi et al., 2014). For example, Guo et al. found that nifedipine can promote the proliferation and migration of breast cancer cells (Guo et al., 2014). If this is true, survival outcomes in cancer patients would be influenced by CCBs. It may have major public health implications as CCBs are extensively used in the treatment of hypertension and other cardiovascular diseases. Furthermore, clinical studies were investigated to explore the association of CCBs use with cancer risk (Coleman et al., 2008; Saltzman et al., 2013; Bergman et al., 2014; Fan et al., 2015), and survival outcomes(Lebuffe et al., 2005; Ning et al., 2014). However, the results of the clinical observations are still inconsistent. Due to the importance of the association between CCBs use and survival in cancer patients to both clinical practice and public health, we performed a meta-analysis to clarify the association between CCBs use and survival outcomes in cancer patients.

Materials and Methods

Data sources and search strategy

Literature searches of PubMed, EMBASE Databases,

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Cochrane Library databases, Web of Science were performed on January 11th, 2016. We used the following search terms: 'calcium channel blocking agent', 'calcium antagonist', 'calcium channel blocker', 'calcium channel blockade', 'calcium channel antagonist', 'calcium inhibit', 'calcium block', 'calcium channel blocking drug', CCB, 'dihydropyridine', 'non-dihydropyridine', 'antihypertensive drug', names of specific calcium antagonists combined with 'neoplasm', 'cancer', 'tumor', 'tumour', other subtypes/synonyms for cancer and 'prognosis', 'prognostic', 'predict', 'predictive', 'prediction', 'morbidity', 'mortality', 'death', 'recurrence', 'recurrent', 'metastasis' 'metastatic', 'survival', 'survive', 'survival analysis'. The search terms and strategies were described in detail in Supplementary Table 1. Additionally, we didn`t take the language, publication status, or article types into account. Two authors manually screened the citation lists of retrieved articles independently. We checked all selected studies according to a Newcastle-Ottawa Quality assessment Scale developed previously (Stang et al., 2010).

Selection criteria

Eligible studies should meet the following inclusion criteria of our meta-analysis: (1) any type of observational study (case-control, nested case-control, or cohort study) investigating the association between CCBs use and survival in cancer patients; (2) a study reporting the HR and its 95% CI for the association between CCBs use and overall survival in cancer patients; (3) a study reporting other indexes that can be used to calculate the HR and its 95% CI according to previously published methods (Parmar et al., 1998; Tierney et al., 2007). In addition, the mechanistic research studies, animal experimentation studies and the reviews were excluded.

Data extraction and quality assessment

Using predefined data summary lists, two investigators performed the data extraction and quality assessment independently. The detailed information for each eligible study was included: first author, year of publication, period of study, age of study population, country of study, ethnicity, sample size, cancer types, types of medication and HR estimates. We included the result adjusting for potential confounding variables, if the studies reported several multivariate-adjusted effect estimates. In addition, the most recent study was chosen to be further analyzed when several publications were overlapped. We resolved the discrepancies through discussion.

The quality assessment of each included study was evaluated by means of the nine-star Newcastle-Ottawa Scale (NOS). The studies with a NOS score equal or greater than seven was considered to be high quality. After data extraction and assessment, an investigator examined and adjudicated the information independently.

Statistical analysis

The association between CCBs use and survival in cancer patients was estimated by HR and related 95% CI reported or obtained by calculating in each study. We used the fixed effects model to estimate the pooled HRs with related 95%CIs if there was no heterogeneity existed; otherwise, we used the random effects model. Study heterogeneity between studies was assessed and presented by the Chi^2 and I^2 statistic. The potential publication bias was assessed by funnel plot and Egger`s test. The shape

Table 1. Main Characteristic of the Studies Included in Meta-analysis

Study	Ethnicity	Country	Study period	No. (cases/all)	Age(years)	Type of medication	Cancer types	HR estimates
Belpomme, 2000	Caucasians	France	NA	52/99	Median: 55	Verapamil	Breast cancer	KM
Chae, 2014	Caucasians	United States	1999-2013	83/960	Median:60	Amlodipine, Diltiazem	Acute myeloid leukemia	HR,95%CI
He, 2015	Caucasians	United States	1998-2012	172/1174	Median:64	All types of CCBs	Esophageal carcinoma	HR,95%CI
Koski, 2012	Caucasians	Spain	2008-2011	36/72	Average:57	Verapamil	Cancer	KM
Lindberg, 2002	Caucasians	Sweden	1989-1990	214/1243	Median:62.7	All types of CCBs	Cancer	HR,95%CI
Millward, 1993	Caucasians	UK.	NA	34/68	Median:57	Verapamil	Non-small cell lung cancer	KM
Mross, 1993	Caucasians	Germany	NA	26/51	Mean:53	Verapamil	Breast cancer	KM
Nakai, 2013	Asians	Japan	2001-2011	67/250	Median:66	All types of CCBs	Pancreatic cancer	HR, 95%CI
Poch, 2013	Caucasians	United States	1993-2010	104/875	Median:60	All types of CCBs	Prostate cancer	KM
Holmes, 2013	Caucasians	Canada	2004-2008	2720/15582	Mean:65	All types of CCBs	Breast, colorectal, lung, prostate cancer	HR,95%CI
Wong, 2015	Asians	China	2001-2005	64043/217910	NA	All types of CCBs	Cancer	HR,95%CI

of the funnel plot was symmetrical and the *P* value of the Egger`s test was more than 0.05 indicated no publication bias existed. What`s more, a HR<1 indicated a better outcome by using CCBs while HR>1 indicated a worse outcome by using CCBs. *P* value less than 0.05 was considered statistically different. The meta-analysis was carried out by the Review Manager 5.3 analysis software (Cochrane Collaboration).

Results

Literature search and study selection

The initial literature search resulted in 7786 studies. After screening the titles and abstracts of all studies, 7753 records were excluded due to duplications or no information on CCBs use and survival in cancer patients. The rest of potentially relevant articles were retrieved for more detailed information. For further evaluation by full texts, we included 11 studies in our meta-analysis. The literature search and selection was shown in Figure 1 and the summary of the main characteristic of the included studies was shown in Table 1. The quality assessment of each study included in the meta-analysis was shown in Supplementary Table 2. Cancer types of these studies mainly included breast cancer, acute myeloid leukemia, esophageal carcinoma, lung cancer, pancreatic cancer, prostate cancer. In addition, there were 9 studies on Caucasian population and only 2 studies focusing on Asian population.

Table 2. Sensitivity Analysis for the Meta-analysis: HRs with 95%CIs and *P* value were Results After Excluding Each Study

Study	HR	95%CI	*P* value
Belpomme, 2000	1.11	0.94-1.30	0.2
Chae, 2014	1.04	0.88-1.23	0.66
He, 2015	1.07	0.90-1.28	0.41
Koski, 2012	1.06	0.90-1.25	0.49
Lindberg, 2002	1.02	0.87-1.21	0.79
Millward, 1993	1.11	0.94-1.30	0.23
Mross, 1993	1.1	0.94-1.30	0.24
Nakai, 2013	1.08	0.92-1.27	0.35
Poch, 2013	1.06	0.89-1.26	0.53
Holmes, 2013	1.07	0.88-1.31	0.51
Wong, 2015	1.02	0.89-1.18	0.75

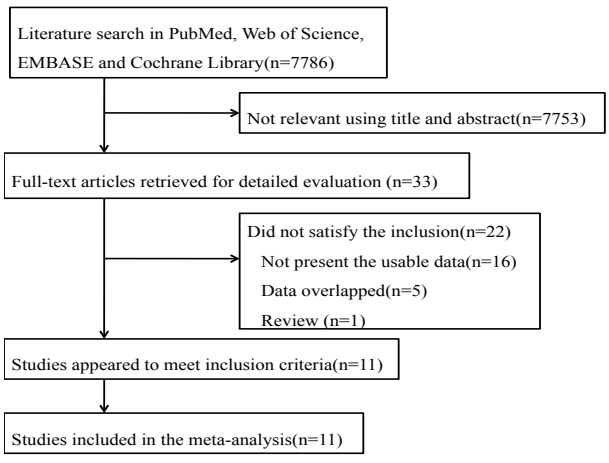

Figure 1. Flow Diagram of the Study Selection Process

Calcium channel blockers use and survival in cancer patients

As shown in Figure 2, the overall HR of the association between CCBs use and overall survival in cancer patients was 1.07 (95% CI 0.91-1.25; *P*=0.42) which indicated that evidence was lacking in an association with CCBs use and overall survival in cancer patients. Then we performed subgroup analysis by ethnicity. The results was shown in Figure 3, which suggested that no association between CCBs use and overall survival in cancer patients was existed whether in Asian (HR=1.18, 95% CI: 0.72-1.93; *P*=0.52) or Caucasian population (HR=1.03, 95% CI: 0.89-1.20; *P*=0.66).

Sensitivity analysis

Sensitivity analysis was analyzed by deleting one single study from the overall pooled analysis each time (Table 2). No significant alteration of the pooled HRs was found, which indicated that any single study had little impact on the overall HRs and the result of this meta-analysis was relative stable.

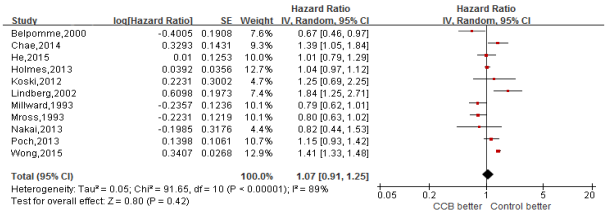

Figure 2. Forest Plot for the Association between CCBs Use and Overall Survival in Cancer Patients

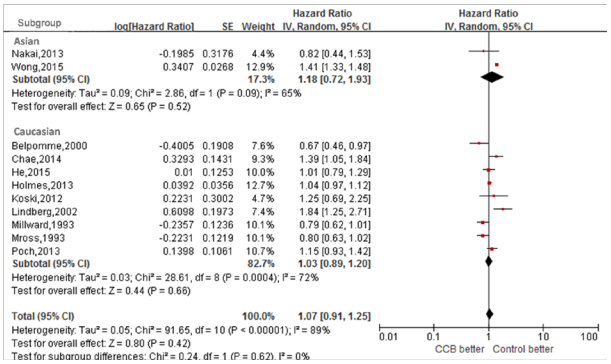

Figure 3. Funnel Plot for the Subgroup Analysis of Ethnicity

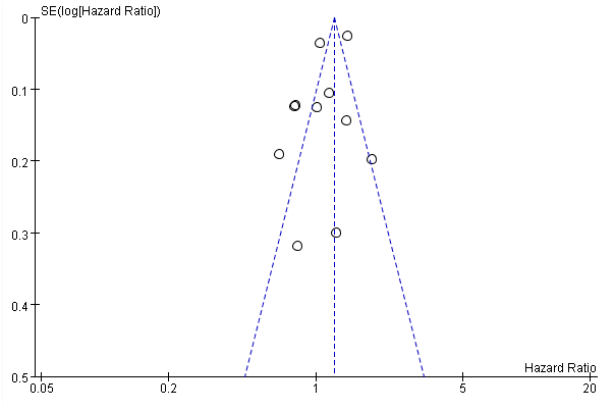

Figure 4. Funnel Plot of the Association between CCBs Use and Overall Survival in Cancer Patients for Publication Bias

Publication bias

We performed the publication bias of the literatures by funnel plot and Egger's test. The shape of the funnel plot seemed approximately symmetrical (Figure 4) and the Egger's test did not show any evidence of publication bias (P =0.191).

Discussion

Comorbidities are common in cancer patients and their treatment may influence cancer survival outcomes (Williams et al., 2015; Sarfati et al., 2016). It has great significance to investigate the association between the use of drugs for comorbidities and cancer survival which may pave way to guide the rational use of drugs for comorbidities and provide optimal care to cancer patients with comorbidities.

Calcium channel blockers (CCBs) are one of the most frequently used drugs in the treatment of hypertension and have been applied in clinical for years. In recent years, it has been suggested that CCBs may associated with survival outcomes in cancer patients. However, the results are controversial. While several studies showed an association between CCBs use with better or worse survival outcomes in cancer patients, others reported no association (Belpomme et al., 2000; Chae et al., 2014; He et al., 2015; Koski et al., 2012; Lindberg et al., 2002; Millward et al., 1993; Mross et al., 1993; Nakai et al., 2013; Poch et al., 2013; Holmes et al., 2013; Wong et al., 2015). Considering the clinical importance of the association between CCBs use and cancer survival, we conducted a meta-analysis to investigate the relationship between CCBs use and cancer in light of conflicting results of several observational studies. To our knowledge, this is the first meta-analysis to investigate the association between CCBs use and survival in cancer patients. 11 studies investigating the effect of CCBs use on the survival of cancer patients met the selection criteria and were included in our meta-analysis. The results of our meta-analysis showed that there was no significant association between CCBs use and overall survival in cancer patients. What`s more, no association between CCBs use and overall survival in cancer patients was existed whether in Asian or Caucasian population.

In addition, in the 11 studies which were included in the meta-analysis, three studies focused on the association between CCBs use and survival in patients with breast cancer. Belpomme et al. (2000) found that CCBs use can significantly improve the overall survival in breast cancer patients. Mross et al. (1993) also found that breast cancer patients treated with CCBs had longer overall survival in tendency. However, Holmes et al. (2013) had found the opposite conclusion. The contradictory conclusions may be caused by the differences of sample sizes, types of CCBs, countries of studies and other prognosis factors. Two studies investigated the association between CCBs use and survival in patients with prostate cancer. Poch et al. (2013) and Holmes et al. (2013) had arrived at the consistent conclusion that no association was existed in the CCBs use and survival in patients with prostate cancer. The result of the research performed by Millward et al. (1993) indicated that CCBs use can significantly improve overall survival in non-small cell lung cancer. Holmes et al. (2013) also investigated the association between CCBs use and survival in patients with lung cancer. However, they found no association existed. The inconsistent results of the two studies may be caused by the differences of subtypes of lung cancer, sample sizes, types of CCBs and countries of studies. It is worth mentioning that CCBs use can significantly reduce survival in patients with respiratory cancer (Wong et al., 2015).Four studies focused the association between CCBs use and digestive cancer survival. No associations were existed between the CCBs use and survival in patients with esophageal carcinoma (He et al., 2015), colorectal cancer (Holmes et al., 2013) and digestive cancer (Wong et al., 2015). It seemed that CCBs use can improve the overall survival in patients with pancreatic cancer (Nakai et al., 2013). Chae et al. (2014) reported that CCBs use may lead to a worse outcome in overall survival in patients with acute myeloid leukemia. Therefore, it seems that cancer types may influence the association between CCBs use and survival in cancer patients.

Some limitations of our meta-analysis should be considered. First, we only searched the selected databases and some studies of other databases might be missing. Second, some relevant studies couldn`t be included in our meta-analysis due to the publication limitations or incomplete raw data. Third, the adjustment for confounding factors of the included studies was varied. Some studies which did not adjust for enough potential confounding factors might have obscured a true relationship. In addition, the heterogeneity was existed among our included studies which might have led to an inaccurate conclusion.

In conclusion, the meta-analysis indicates that CCBs use appears to have no significant influence on survival in cancer patients. However, for further verification of our results, more large-scale and well-designed studies are warranted in the future.

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