World Journal of Surgery and Surgical Research

Research Article
Published: 16 Aug, 2021

# Association between the Use of Proton Pump Inhibitors with the Risk and the Prognosis of Breast Cancer: A Systematical Review

*Jingtao Hu[1#], Wenjie Hu[2#], Chenyu Sun[3], Ce Cheng[4], Qin Zhou[5] and Lei Yue[6*]*

[1]Aviation Hygiene Branch, Anhui Branch, China Eastern Airlines Co., Ltd, Xinqiao avenue, Anhui, China

[2]Department of Neurology, The First Affiliated Hospital of Anhui Medical University, China

[3]AMITA Health Saint Joseph Hospital Chicago, USA

[4]The University of Arizona College of Medicine at South Campus, USA

[5]Mayo Clinic, Rochester, USA

[6]Nanjing Center for Disease Control and Prevention, China

[#]These authors contributed equally to this work

## Abstract

**Purpose:** To evaluate the association between the uses of Proton Pump Inhibitors (PPIs) and the risk of Breast Cancer (BC) before patients having a BC diagnose and explore the prognosis of using PPIs after patients diagnosed with BC.

**Methods:** Candidate publications were identified in the online databases up to February 20th, 2020. Literature selection and data extraction were carried out according to preset criterion by two independent reviewers. Using the pooled Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) to calculate the relationship between PPIs use and BC risk with a random-effect model in Stata 14.0. The dose-response relationship between the two was further explored. While the prognosis of BC patients using PPIs was described qualitatively.

**Results:** Six studies met in our inclusion criteria including 172,063 participants in which 70,070 were BC patients. The overall result of one cohort study and two case-control studies suggested an inverse correlation between PPIs use and BC risk. The pooled OR was 0.70 (95% CI: 0.50-0.97) with high heterogeneity (I2= 95.1%, P=0.000). Dose-response analysis did not find a dose-response relationship. Two retrospective cohort studies showed survival benefit from using PPIs in BC patients was not significant. While one Randomized Controlled Trial (RCT) revealed that intermittent high-dose of PPIs use could improve the survival benefit of Metastatic Breast Cancer (MBC) patients.

**Conclusion:** Our findings suggested that women ever used PPIs had a decreased risk of BC but the dose-response relationship could not be found. While the prognosis of BC patients using PPIs still remained controversial.

**Keywords: Proton Pump Inhibitors; PPIs; Breast Cancer; Meta-analysis**

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***Correspondence:***
*Lei Yue, Nanjing Center for Disease Control and Prevention, No. 3, Zizhulin, Xufu Lane, Nanjing 210003, Jiangsu, China, Tel/Fax: 18375327675; E-mail: 1270272791@qq.com*

**Received Date**: *21 Jul 2021*
**Accepted Date:** *12 Aug 2021*
**Published Date:** *16 Aug 2021*

***Citation:***
*Hu J, Hu W, Sun C, Cheng C, Zhou Q, Yue L. Association between the Use of Proton Pump Inhibitors with the Risk and the Prognosis of Breast Cancer: A Systematical Review. World J Surg Surgical Res. 2021; 4: 1327.*



## Introduction

According to global monitoring, 18.1 million new cancer cases were diagnosed and 9.6 million people died from cancers in 2018 [1]. Cancer is the leading cause of death worldwide at present [2]. Breast Cancer (BC) is not only the most common primary malignancy [3] but also the second leading cause of death after lung cancer among women in America [4]. Though early detection and treatment were improved [5], 12.4% of women will still suffer from invasive BC during their lifetime [6].

High rate of glycolysis, one characteristic of cancer cells, made cancer cells produce excess protons [7]. Vacuolar $H^+$ ATPases (V-ATPases), a family of ATP-dependent proton pumps, are essentially complex multi-subunit proteins existing in cytoplasm, which facilitated the transport of protons and further acidified the tumor internal environment [8,9]. There was a bulk of evidence declared that V-ATPases have been shown to promote the drug resistance and metastasis of cancers

including BC [10-12]. Moreover, V-ATPases specific inhibitors played an anticancer role by inhibiting the function of V-ATPases, which were reported in cells-based and animal-based models [13-17].

Proton Pump Inhibitors (PPIs), a class of V-ATPases inhibitors, are one of the most commonly used drugs worldwide due to their unparalleled safety and well tolerated [18-20]. They are generally used to treat gastrointestinal diseases related to gastric acid [21,22] and as a complementary therapy for cancer [23]. While more and more studies indicate that PPIs had a series of side effects including hypomagnesemia, osteoporosis, intestinal infection, pneumonia, and Vitamin B12 deficiency [24-28]. Additionally, PPIs were reported to be closely associated with the development of a various types of cancer such as gastric, liver and pancreatic cancers [29-31]. Also, increasing number of population studies focus on the potential effect of PPIs acting on BC, this paper aims to explore the association between the use of PPIs with the risk and the prognosis of BC.

## Material and Methods

### Search strategy

Publications were searched from PubMed, Web of Science, Cochrane Library, Wiley Online Library, Science Direct, CNKI (Chinese National Knowledge Infrastructure), CBM (Chinese Biomedical Database), VIP (Chinese) and WANFANG (Chinese) database published before February 20th, 2020. The literature retrieval were conducted without language and time limits: ((“proton pump inhibitor” OR “omeprazole” OR “lansoprazole” OR “pantoprazole” OR “rabeprazole” OR “esomeprazole”) AND (“breast neoplasms” OR “breast cancer” OR “mammary cancers” OR “malignant neoplasm of breast” OR “breast malignant neoplasms” OR “malignant tumor of breast” OR “cancer of the breast” OR “human mammary carcinoma” OR “human mammary neoplasms” OR “breast carcinomas”)). Besides, the highly corresponding relevant studies were retrieved from the reference lists to identify additional eligible studies.

### Selection criteria

**Our inclusion criteria were as follows:** (a) PPIs used before or after BC diagnosis and PPIs could be one of “omeprazole”, “lansoprazole”, “pantoprazole”, “rabeprazole”, “esomeprazole” or any combination of them; (b) the evidence of PPIs use were reliable and explicit; (c) studies evaluated the association between PPIs use and the BC risk; (d) studies conferred prognostic outcome indicators of PPIs use in BC patients such as mortality rates, overall survival, disease free survival and so on. Literature meeting any of the following criteria was excluded: (a) non-clinical nature studies or animals experiments; (b) duplicated study; (c) unclear outcome indicators and evaluation; (d) non-original studies such as reviews, meta-analysis, letters, case report, editorials and commentaries.

### Data extraction

Data extraction was carried out by two reviewers independently according to a standardized data extraction form: The first author, publication years, country, study design, total sample size and some characteristics of participants. Disagreements arising in the progress were resolved through discussion.

### Quality assessment

Methodological quality of the observational studies was evaluated based on the Newcastle–Ottawa Scale (NOS). We regarded studies with a score of 7 and above as high quality studies [32] Randomized Controlled Trial (RCT) was evaluated according to the Cochrane collaboration’s tool for assessing risk of bias. Using “low risk of bias”, “unclear risk of bias” and “high risk of bias” to estimate each of item in six domain-based evaluation [45].

### Statistical analyses

We performed a quantitative synthesis analysis of the impact of PPIs use on BC before BC diagnosis. Meta-analysis of the relationship between BC risk and PPIs use was performed in Stata 14.0 software. The Cochran Q test and I2 statistics were used to estimate heterogeneity. Considering the heterogeneity between the included studies, the pooled Odds Ratios (ORs) and their 95% Confidence Intervals (CIs) were used to calculate the total effect value with a random-effects model on the way of DerSimonian and Laird [33]. Sensitivity analysis was performed to evaluate the stability of included studies. Pre-determined subgroup analysis could not be performed due to the limits on the number of included studies. It could not separate chance from real asymmetry when articles included in meta-analysis were less than ten [34,35]. Likewise, we did not conduct the test of publication bias. Besides, using the method of restricted cubic splines with four knots of the distribution, dose-response analysis between the relations of PPIs intake and risk of BC was performed in Stata14.0 (StataCorp LP, College Station, Texas) according to Greenland and Longnecker (GL) [36]. The prognosis of BC patients using PPIs were described qualitatively, as it could not be analyzed quantitatively due to different prognostic factors were used in the included studies.

## Results

### Study selection

A total of 5,117 publications were identified initially. After excluding 474 duplicate articles and 4,555 irrelevant studies by filtering title and abstract, the full texts of 88 articles were reviewed ultimately. Among these potentially relevant studies, only 6 studies were compliant with our inclusion criteria [23,37-41]. Among them, three studies were related to PPIs use and BC risk, and three were associated with the prognosis of BC patients using PPIs. The remaining 82 candidates were excluded for the following reasons: 41 articles were not consistent with the research topic, 18 articles were unrelated to either BC or the PPIs use, 11 articles were studies on mechanism or animal experiments, 10 articles were reviews or meta-analysis, one was case report, one could not find full text. We retrieved the highly corresponding literature from the reference lists but no one was accepted. The specific screening process was shown in Figure 1.

### Study characteristics and quality assessments

A total of six studies on the role of PPIs use before and after BC diagnosis were included, of which five were observational studies and one was RCT. Three observational studies [37-39] described the relationship between the use of PPIs and the risk of BC, however their conclusions were controversial. One case-control study [37], conducted stratified analyses by assessing the impact of high use of PPIs, cumulative dose and cumulative duration of PPIs use on the hypothetical associations, found no evidence to support a chemopreventive effect of PPIs use on breast cancer, with the adjusted OR of 1.03 (95% CI: 0.92-1.16). However, 365-730 Defined Daily Doses (DDDs) of cumulative dose were found to be associated with an increased BC risk. The other two studies [38,39], including one cohort study and one case-control study, suggested PPIs use had a negative association with BC. The cohort study [38] demonstrated that the use of PPIs reduced the risk of BC in cohort of peptic ulcer women, with an adjusted Hazard Ratio (HR) of 0.32 (95% CI:

**Table 1:** Characteristics of included studies on PPI use and breast cancer.

| First author, Year | Country | Study design | Total size (T/C) | PPIs use (T/C) | Event (T/C) | Mean/ median age (years) | Age rang (years) | Adjustment for covariates | Description | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Tvingsholm, 2018 | Danish | Cohort | 809/12500 | 809/0 | 279/2230 | 67 | ≥ 30 | Adjusted for gender, age at diagnosis, year at diagnosis, highest achieved education and disposable income, various ills and drugs | Risk of mortality in breast cancer patients using PPIs | High |
| Hálfdánarson, 2018 | Iceland | Case-control | 1739/17390 | 531/5201 | 1739/0 | 62 | ≥ 18 | Adjusted for age, sex, calendar time, and NSAID use | Using PPIs and risk of breast cancer | High |
| Chao-Hung, 2018 | Taiwan of China | Case-control | 64234/64234 | 5179/6692 | 64234/0 | 51 | ≥ 18 | Adjusted age, income ,geographic location, urbanization level, comorbidities ,index year | Using PPIs and risk of breast cancer | High |
| Dah-Ching, 2019 | Taiwan of China | Cohort | 4838/4838 | 4838/0 | 25/82 | 44 | 20~64 | Adjusted for age, pregnancy, and all comorbidities and medications | Using PPIs and risk of breast cancer | Moderate |
| Bi-Yun, 2015 | China | RCT | Total: 94 | Total: 62 | Total: 94 | 52 | 31~67 | / | Survival benefits of metastatic breast cancer patients using PPIs | Unclear risk of bias |
| Josiah, 2018 | America | Retrospective cohort | Total: 1387 | Total: 419 | Total: 1387 | 58 | / | Adjusted for chemotherapy and hormone therapy | Survival benefits of breast cancer patients using PPIs | / |

**Abbreviations:** PPIs: Proton Pump Inhibitors; T: Trial, C: Control; NOS: Newcastle-Ottawa Scale; RCT: Randomized Controlled Trial

0.20-0.49). Evidence from age stratification analysis in this cohort study [38] indicated that this benefit increased with age, especially among older PPIs users aged 50 to 65 years old, with an adjusted Hazard Ratio (HR) of 0.17 (95% CI: 0.07- 0.41). The case-control study [39], with an adjusted OR of 0.75 (95% CI: 0.72-0.78), found a dose-response effect, showing the highest dose group (116 DDDs) decreased the BC risk most (HR: 0.65, 95% CI: 0.61-0.70), and age stratified risk associations found a potential protective effect of PPIs use on women aged <50 and ≥ 50 years old and the strength of the connection did not differ considerably.

The remaining two retrospective cohort studies focused on the survival outcomes of BC patients taking PPIs. One [23] illustrated an association between BC patients using PPIs and increased mortality, with the adjusted HR of 1.30 (95% CI: 1.18-1.43). That was to say the use of PPIs in BC patients did not bring survival benefits, but increased the risk of mortality, which was regard as a manifestation of poor prognosis. The other [40,41] reported clearly that the use of omeprazole in BC confer no survival benefits in Disease-Free Survival (DFS) or Overall Survival (OS). However, a RCT [40] using the endpoints of Time to Progression (TTP) and OS showed a survival benefits of PPIs use in MBC patients. In which 94 Metastatic Breast Cancer (MBC) patients were randomly divided into three groups for docetaxel add cisplatin chemotherapy while PPIs were used as adjuvant therapy. The results indicated that only the intermittent high-dose PPIs can enhance the anti-tumor effects of chemotherapy.

The quality of the included observational studies was assessed based on the Newcastle–Ottawa Scale (NOS). In five observational studies, result of three studies [23,37,39] with scores greater than six points were considered of higher quality. Quality assessment score of one study [38] was six regarding as moderate quality. Another retrospective cohort study [41] was only an abstract which could not perform quality assessment. According to the Cochrane collaboration's tool for assessing risk of bias, we found that the RCT [40] did not describe the random sequence generation in detail, and did not illustrate the implementation details of the blind method. Thus, quality assessment of the RCT showed an unclear risk of bias. The main characteristics of included studies and quality evaluation were showed in Table 1.

### Results of the meta-analysis

A meta-analysis of three studies [37-39] reporting inconsistent conclusions on the relationship between PPIs use and BC risk was conducted. A dose-response analysis of two included studies [37,39] was also performed. Our finding revealed the use of PPIs reduced the risk of BC. The pooled adjusted OR was 0.70 (95% CI: 0.50-0.97) and the Cochran Q value of heterogeneity was 40.91 ($I^2$=95.1%, P=0.000). While the dose-response analysis did not find a dose-dependent correlation between the two. Two studies [38,39] showed that the protective efficacy of PPIs was pronounced in patients older than 50 years old. Their adjusted ORs were 0.17 (95% CI: 0.07-0.41) and 0.74 (95% CI: 0.70-0.77), respectively. But the pooled adjusted OR was 0.38 (95% CI: 0.09-1.59) with no statistical significance. A forest plot of relationship between PPIs use and the risk of BC was shown in Figure 2. Result of the dose-dependence between the two was shown in Figure 3.

### Sensitivity analyses

We found one study [39] had the greatest influence on stability via sensitivity analysis. After omitting this literature, the result illustrated no association between the use of PPIs and the risk of breast cancer. The pooled OR was 0.59 (95% CI: 0.19, 1.84). Actually, the results would be reversed from PPIs use had a protective effect on BC to PPIs use had no association with BC after omitting any one of the other two studies [37,38].

## Discussion

This systematical review and meta-analysis was aim to investigate the association between use of PPIs and the risk of breast cancer and explore the impact on prognosis of using PPIs after patients diagnosed with BC. Through quantitative synthetic analysis, our finding revealed the use of PPIs reduced the risk of BC. While in the qualitative analysis of the prognosis of BC patients using PPIs, the survival benefits of using PPIs in BC patients are still controversial.

The result of meta-analysis showed that the use of PPIs could reduce the risk of BC, which was consistent with the conclusion that PPIs exhibited antitumorigenic effects in many cancer types. The antitumor effects of PPIs had been widely reported in cell-based and

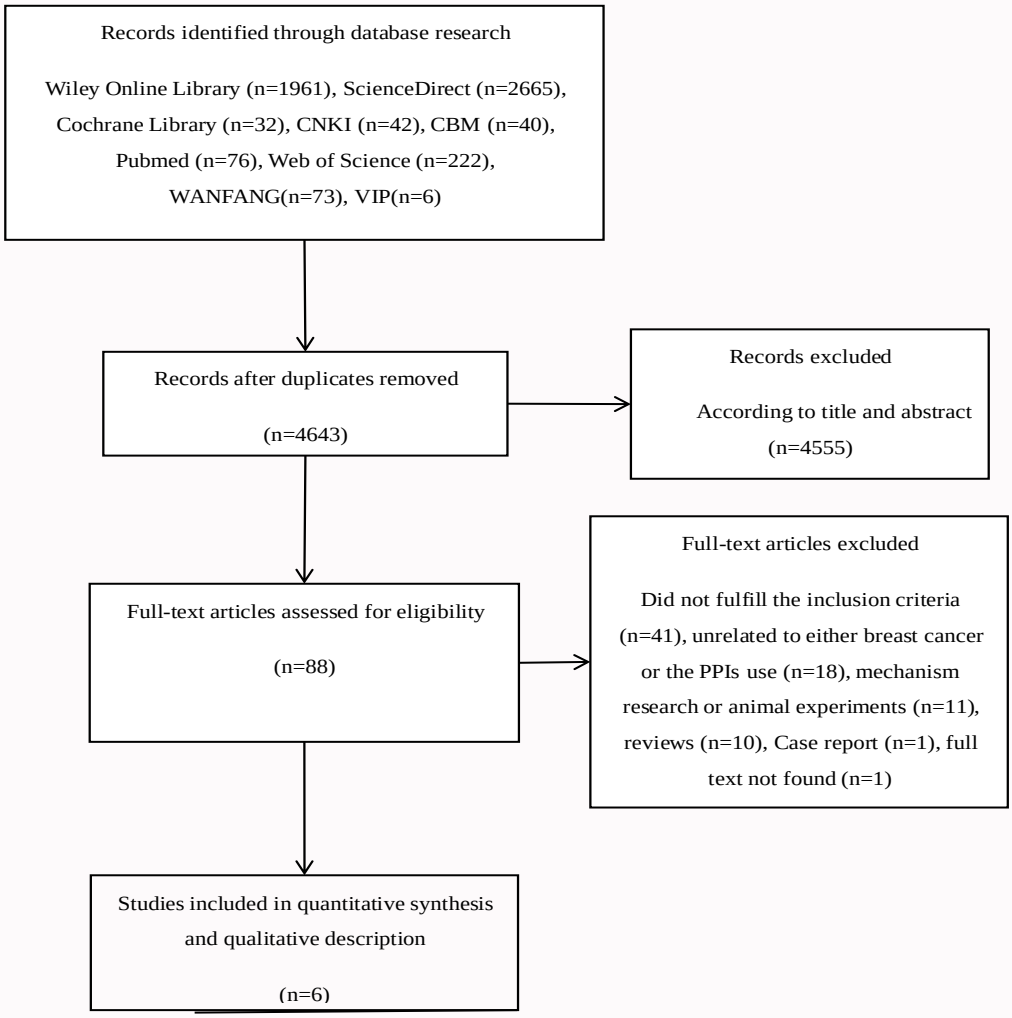


**Figure 1:** Study selection flow diagram.

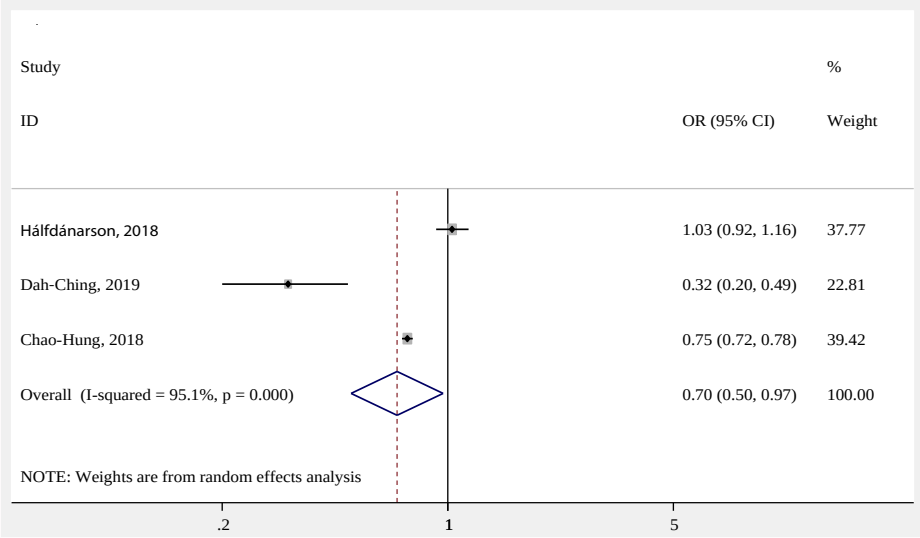


**Figure 2:** A forest plot of the relationship between PPIs use and the risk of breast cancer.

animal-based models [37]. It had been shown to have anti-tumor activity both in vitro and *in vivo* [39]. The accumulation of the PPIs in body may be the reason. As prodrugs, PPIs will be converted to active form and accumulate in acidic environments, inhibiting acid secretion, reducing V-ATPases activity and playing a role of anticancer through protonation [18,19, 42]. Theoretically, the anti-

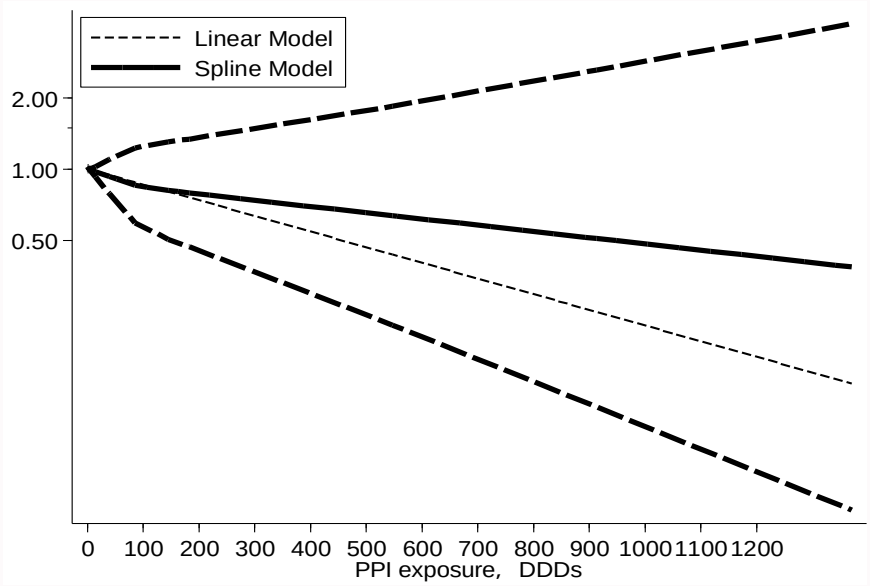


**Figure 3:** Result of the dose-dependence between the PPIs use and breast cancer risk.

tumor effects of PPIs should be related to the using dose. In fact, previous studies showed that the inhibitory effects of PPIs on BC have a dose-response relationship [15], and it was also reflected in the population studies we included [39]. Nevertheless, our dose-response meta-analysis did not reveal the dose-response relationship between PPIs and BC for limited studies.

Researches on the role of PPIs in the treatment of BC were limited. We evaluated the potential impacts of PPIs on BC patients by analyzing their prognosis qualitatively. No survival benefit associated with BC patients using PPIs were found, based on the two included retrospective cohort studies [23,41], whereas antitumor effects of intermittent high-dose PPIs were found in a RCT [40]. The most significant difference between the three studies was the combination of PPIs and chemotherapeutic drugs in RCT, while the other two studies only looked at the effect of PPI on BC patients. It is well known that the prominent characteristic of tumor cells was cellular resistance and limited drug distribution by creating an acidic environment [18]. PPIs were reported to improve the efficacy and distribution of drugs by raising cellular PH and remitting the acidic environment of tumor cells [18]. Furthermore, some studies showed that the treatment with PPIs may enhance chemical sensitivity and cytotoxicity of tumor cells to chemotherapeutic drugs [43,44]. Consequently, the RCT [40] showed that PPIs could enhance the anti-tumor effect of MBC patients probably because it could promote the role of chemotherapeutic drugs of tumor cells and thus exerted a stronger anti-tumor effect. Moreover, PPIs were not specific anti-tumor drugs and due to the complexity of co-morbidity and diversity of medication exposures for BC, the overall efficacy of PPIs in BC patients might be affected by the interaction. This might explain why no survival benefit was found when considering only the effect of PPIs on prognosis of BC patients.

Pre-set subgroups analyses were not statistical significance and publication bias were not tested as a result of the limited number of included studies. Interestingly, two studies [38,39] found that statistically significant protective effects of PPIs on BC for patients whose age is 50 years old and above. However, the pooled result of these two studies found a non-significant protective result. Due to limited number of studies, this protective effect needs to be confirmed by further studies.

There were some deficiencies in our research. Firstly, the number of identified studies was limited and the stability of the results was not well. Secondly, samples of the two studies [38,39] existed crossover accounting for they all came from the National Health Insurance Research Dataset (NHIRD). Moreover, accompanying by different type of BC and other drugs interference more or less, large heterogeneity situated between the researches. Although each study had adjusted for corresponding confounders, the stability of the results may still be affected.

In conclusion, women who ever used PPIs are likely at a lower risk of BC, without being on a dose-dependent manner. In addition, the prognosis of BC patients using PPIs still remained controversial. It seemed that the combination of PPIs and chemotherapy drugs had a significant anticancer effect. More well-designed studies are needed to elucidate the effect of PPIs on risk and prognosis of BC.

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