Assessment of the Relationship Between Gastric-Acid Suppressants and the Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis

Karamali Kasiri Associate
Catherine M.T. Sherwin
Wright State University - Main Campus, sherwinc@childrensdayton.org
Sahar Rostamian
Saeid Heidari-Soureshjani

Follow this and additional works at: https://corescholar.libraries.wright.edu/pediatrics

Repository Citation

This Article is brought to you for free and open access by the Pediatrics at CORE Scholar. It has been accepted for inclusion in Pediatrics Faculty Publications by an authorized administrator of CORE Scholar. For more information, please contact library-corescholar@wright.edu.
Assessment of the Relationship Between Gastric-Acid Suppressants and the Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis

Karamali Kasiri, Associate1, Catherine M.T. Sherwin, Professor2, Sahar Rostamian, MD3, Saeid Heidari-Soureshjani, MSc4,*

1Department of Pediatrics, Shahrekord University of Medical Sciences, Shahrekord, Iran
2Pediatric Clinical Pharmacology and Toxicology, Department of Pediatrics, Wright State University Boonshoft School of Medicine, Dayton Children's Hospital, Dayton, Ohio
3Shahrekord University of Medical Science, Student Research Committee, Shahrekord, Iran
4Modeling in Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

**Article Info**

Article history:
Received 11 October 2022
Accepted 15 January 2023

Key words:
esophageal adenocarcinoma
gastric acid
histamine-2 receptor antagonists
oncology
proton pump inhibitors

**Abstract**

Background: Esophageal cancer is a cancerous tumor that develops in the esophagus. It is the 10th most common cancer and has a low survival rate. Esophageal adenocarcinoma (EAC) is increasing in incidence globally. Those with EAC are affected by Barrett's esophagus metaplasia, which is attributed to genetic predisposition and is more common in men. Studies suggest that gastric acid suppressants, like proton pump inhibitors and histamine-2 receptor antagonists, have anticancer properties and reduce EAC. However, other research has suggested that they are not cancer-protective, and the use of antisecretory drugs is a risk factor for developing EAC.

Objective: This systematic review and meta-analysis investigated the properties and risk factors associated with using gastric acid suppressants in patients with EAC.

Methods: This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Information selected from selected articles, including the lead author's name, year of publication, study setting, sample size, and gender, was extracted and recorded into an Excel (Microsoft, Redmond, Washington) form. Statistical data included odds ratio, hazard ratio, and/or risk ratio, with a 95% CI associated with patients with EAC and receiving gastric acid suppressants. Data were compared with individuals not receiving treatment. Publication bias was assessed using Begg's and Egger's tests. Statistical analyzes used Stata 14.0 (Stata LLC, College Station, Texas).

Results: The initial electronic literature search retrieved 3761 titles/abstracts. Extensive review selected 20 articles for analysis. Odds ratios associated with EAC in the individuals using gastric acid suppressants were 0.77 (95% CI, 0.49–1.22; P = 0.274) and 0.67 (95% CI, 0.39–1.29; P = 0.240) for proton pump inhibitors and 1.02 (95% CI, 0.44–2.36; P = 0.967) for histamine-2 receptor antagonists.

Conclusions: The results found that gastric acid suppressants do not have a protective role in EAC and are not risk factors. Future studies of confounding variables and risk factors are needed to understand what affects EAC development.

© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

Esophageal cancer is a malignant (cancerous) tumor that starts in the esophagus. It is the 10th most common cancer; even with surgery, chemotherapy, and radiation treatment, it has a low survival rate and can be fatal.1 Reportedly, it is more common in men than in women. Of concern is that the incidence of esophageal adenocarcinoma (EAC) has been rising globally. Histological categories are primarily squamous cell carcinoma and adenocarcinoma.2,3 Many of those with EAC are affected by Barrett's esophagus metaplasia, which results from prolonged tissue injury in the esophagus. Barrett's metaplasia is attributed to a genetic predisposition, gender, gastroesophageal reflux disease, smoking, alcohol

https://doi.org/10.1016/j.curtheres.2023.100692
0011-393X/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
consumption, high body mass index, and a poor diet lacking fruit and vegetables. In previous studies, antisecretory drugs, including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), were assumed to induce anticancer properties and reduce EAC development. Some studies have reported that treatment with PPIs can significantly decrease the risk of EAC. In these patients, there is evidence that high-dose PPIs have a chemopreventive effect and can reduce the incidence of Barrett’s esophagus metaplasia. In contrast, other studies have shown that the use of antisecretory drugs does not induce cancer-protective properties in these patients. Conversely, other studies have concluded that the use of antisecretory drugs is a risk factor that increases the occurrence of developing EAC. Various risk factors have been identified and linked to the growing incidence of EAC. However, with the complexity of genetic risk factors and insufficient information available on other potential risk factors, it has not been easy to prevent and/or choose the appropriate treatment for those with EAC. Therefore, it is essential to investigate the disease further and reduce the knowledge gap concerning risk factors related to the disease. In addition, there is an overall need to find adequate health strategies that can be adopted to prevent the disease. Previous meta-analyses have been conducted concerning this topic, however, to the best of our knowledge, none have comprehensively investigated antisecretory drugs as a preventive or potential risk factor associated with the incidence of EAC. As mentioned above, there are inconclusive and varying results from historical studies related to EAC. Therefore, in this systematic review and meta-analysis, we aimed to investigate the properties and the risk factors associated with using PPI and H2RA therapies for patients with EAC.

Methods

Data sources and search strategy

This meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist as a guideline (http://prisma-statement.org/prisma-statement/Checklist.aspx). A systematic literature search was undertaken on June 28, 2022, using PubMed, Web of Science, Embase, and Scopus databases. The following keywords were used for searching in the databases: ((esophageal adenocarcinoma OR esophageal cancer OR esophageal squamous-cell carcinoma) AND (acid suppress OR proton pump inhibitor OR PPIs OR histamine receptor antagonists OR H2RAs OR H2 blocker OR omeprazole OR esomeprazole OR dexlansoprazole OR lan- soprazole OR pantoprazole OR rabeprazole OR azacitidine OR famotidine OR lafutidine)).

Study selection

After entering the key words mentioned into the databases, relevant records were imported into EndNote X8 (Clarivate Analytics, Philadelphia, Pennsylvania). This software was used to organize the articles and identify and remove duplicate records. Two researchers independently identified the studies by reviewing the titles and abstracts of the publications based on the selected inclusion and exclusion criteria. The inclusion criteria included the study’s goals and looked for publications that addressed the association between gastric acid suppressants and the risk of developing EAC. The exclusion criteria included removing non-English language studies and any studies where a complete publication was unavailable. After gathering all eligible full-text articles to be included in the study, they were independently reviewed. If there was any conflict during the review of the studies, a discussion occurred to reach a consensus. Finally, a third team member was asked to help decide if no consensus could be reached. Figure 1 outlines the strategy flowchart used to identify and screen the literature.

Data extraction and quality assessment

Two researchers independently screened the records and extracted specific data to be included in this review. Information was collected from the selected articles, including the lead author’s name, year of publication, study setting, sample size, patient gender, the mean age of the study population, length of follow-up, duration of treatment (receiving antisecretory drugs), and adjusted variables. In addition, all data were extracted and recorded into an Excel (Microsoft, Redmond, Washington) form. Statistical information, including odds ratio (OR), hazard ratio, and/or risk ratio, with a 95% CI associated with patients who had EAC and were receiving gastric acid suppressants, were compared with individuals who did not receive this type of treatment.

Evaluating the quality of the studies

Quality assessment and risk of bias assessment tools pertinent to observational studies were determined using the Newcastle-Ottawa scale. Several items, such as selection, comparability, and exposure/outcome, determined these results. Studies with at least a score of 7 on this scale were high-quality studies. The quality and the risk of biased estimates of treatment used in the randomized controlled trial articles were measured by the Jadad scale. Jadad scores were from 0 to 5, and those clinical trials scoring 3 points or above were considered indications of decent quality studies.

Statistical analysis

This systematic review and meta-analysis used ORs to measure the relationship between those receiving gastric acid suppressants and the risk of developing EAC. The effect size of the association between study exposure and the relevant outcome was conducted using OR with 95% CI. The random-effect models from the meta-analysis were used to estimate the overall summary. Forest plots were used to illustrate the graphical representations of the individual OR and summary estimates. According to an a priori decision, subgroup analyses used factors such as geographic regions, which included Europe, North America, Asia, and Australia. The sample size of studies was (>1000 vs ≤1000); duration of treatment (receiving antisecretory drugs) was (>5 years vs ≤5 years); study designs were case-control, cohort, or randomized controlled trials; and the study period was between 2000-2010 and 2011-2022. The quality of the studies was determined to be medium, good, or excellent.

Heterogeneity in the studies was determined using the Cochran χ² test (reported by χ² with a P < 0.1 level of significance) and also included the I² statistic. A series of sensitivity analyses were conducted to evaluate the findings’ robustness and to characterize potential statistical heterogeneity sources. Initially, the effect of individual studies on the summary estimates was determined using sensitivity analyses. Subsequently, pooled estimates were re-calculated after deleting 1 study after each run. The meta-regression analysis determined the differences between studies and the observed effect size. Any potential publication bias was detected using Begg’s and Egger’s tests. All statistical analyses
were conducted using Stata 14.0 (Stata LLC, College Station, Texas), where \( P < 0.05 \) was considered statistically significant.

**Results**

**Search results and study characteristics of selected studies**

Figure 1 illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram and outlines the search strategy. The initial electronic literature search retrieved 3761 titles and abstracts. Duplicate publications were omitted (\( n = 1851 \)), and 1451 were removed based on the study inclusion and exclusion criteria. In the screening process, there were 459 records. A thorough review of the remaining records identified irrelevant articles that did not fit the study’s focus and therefore were excluded. This left 33 records to be retrieved for more advanced screening. Additional records were excluded (\( n = 13 \)). Three records were removed because of an inability to retrieve the full text of articles.\(^{17-19}\) Nine records did not include data consistent with this research’s goal.\(^{20-27}\) One study did not contain results that were useful.\(^{28}\) Finally, 20 articles were selected for the final evaluation to investigate the association between gastric acid suppressants and the risk of developing EAC.\(^{29-45}\)

**Characteristics of selected studies regarding the association between gastric acid suppressants and the risk of developing EAC**

From the 20 studies in this analysis, there were 1,155,699 patients. Of these, 11 studies used a cohort design, which included 1,125,437 patients\(^{10,11,29-31,34,35,38,39,42,45}\) and 8 studies had a case–control design, with 27,727 participants.\(^{9,32,33,36,40,41,43,44}\) One study was conducted as an randomized controlled trial and included 2,535 patients.\(^{37}\) The articles selected for this systematic review and meta-analysis were published between 2004 and 2022. The studies were geographically diverse, comprising 9 conducted in North America, (\( n = 38,469 \) participants),\(^{10,32,34,39,40,42-45}\) and 8 studies had a case–control design, which included 1,125,437 patients.\(^{10,11,29-31,34,35,38,39,42,45}\) Eight studies included 804,032 participants from Europe (eg, United Kingdom, Netherlands, Denmark, and Sweden).\(^{5,30,31,33,36-38,41}\) Finally, 1 was undertaken in Australia, comprising 350 patients.\(^{35}\) The mean (SD) follow-up of the participants was 81.38 (32.71) months (Tables 1 and 2).

**Relationship between gastric acid suppressants and EAC**

Based on the adjusted OR (Table 3) obtained from each study in the meta-analysis, when compared with the group not receiving
antisecretory drugs, the OR of EAC in the recipients of antisecretory drugs group was 0.77 (95% CI, 0.49–1.22; P = 0.274). Similarly, the OR of EAC in the individuals from the PPIs drug group was 0.67 (95% CI, 0.39–1.29; P = 0.240) and in those in the H2RAs drug group was 1.02 (95% CI, 0.44–2.36; P = 0.967) (Figure 2).

Meta-regression model and sensitivity analysis

There was significant heterogeneity identified within the results from the meta-analysis ($\chi^2 = 972.92; df = 27; P \leq 0.001; I^2 = 97.2\%$). To further investigate the source of heterogeneity, a meta-regression model was performed, which considered variables such as year, follow-up time, study design, sample size, study period, the quality of the study, duration of treatment and geographic region. The meta-regression analysis results show no significant source of heterogeneity ($P > 0.10$). During each run, a sensitivity analysis was done by excluding each study from the analysis 1 by 1. However, the estimated OR did not change significantly, indicating the robustness of the meta-analysis results (Table 3 and Figure 3).

Subgroup analysis

A subgroup analysis was performed to determine the association between gastric acid suppressants and EAC by assessing the study design, sample size, study period, study quality, and geographic location. The OR of EAC in those that receiving gastric acid suppressants was 0.74 (95% CI, 0.45–1.22; P = 0.245) from the case-control studies, 0.76 (95% CI, 0.43–1.35; P = 0.353) in the cohort studies, and 1.04 (95% CI, 0.67–1.61; P = 0.861) from the random-
K. Kasiri, C.M.T. Sherwin, S. Rostamian et al.  
Current Therapeutic Research 98 (2023) 100692

Figure 2. Forest plot of the relationship between gastric acid suppressants and esophageal adenocarcinoma. ES = Effect size; HR2A = histamine-2 receptor antagonist; PPI = proton-pump inhibitor.

Table 3  
Sensitivity analysis for the assessment of the relationship between gastric acid suppressants and esophageal adenocarcinoma

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Drug type</th>
<th>Estimated odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillman</td>
<td>2004</td>
<td>PPI</td>
<td>0.83 (0.52–1.31)</td>
</tr>
<tr>
<td>Cooper</td>
<td>2006</td>
<td>PPI</td>
<td>0.80 (0.50–1.27)</td>
</tr>
<tr>
<td>Nguyen</td>
<td>2009</td>
<td>PPI</td>
<td>0.80 (0.50–1.27)</td>
</tr>
<tr>
<td>Nguyen</td>
<td>2010</td>
<td>PPI</td>
<td>0.75 (0.47–1.21)</td>
</tr>
<tr>
<td>Kastelein</td>
<td>2013</td>
<td>PPI</td>
<td>0.81 (0.51–1.29)</td>
</tr>
<tr>
<td>Gaddam</td>
<td>2014</td>
<td>PPI</td>
<td>0.79 (0.50–1.27)</td>
</tr>
<tr>
<td>Hvid-Jensen</td>
<td>2014</td>
<td>PPI</td>
<td>0.75 (0.47–1.20)</td>
</tr>
<tr>
<td>Masclee</td>
<td>2015</td>
<td>PPI</td>
<td>0.77 (0.48–1.23)</td>
</tr>
<tr>
<td>Krishnamoorthi</td>
<td>2016</td>
<td>PPI</td>
<td>0.78 (0.49–1.24)</td>
</tr>
<tr>
<td>Thota</td>
<td>2017</td>
<td>PPI</td>
<td>0.79 (0.49–1.26)</td>
</tr>
<tr>
<td>Jankowski</td>
<td>2018</td>
<td>PPI</td>
<td>0.76 (0.48–1.23)</td>
</tr>
<tr>
<td>Tan</td>
<td>2018</td>
<td>PPI</td>
<td>0.80 (0.49–1.25)</td>
</tr>
<tr>
<td>Loomans-Kropp</td>
<td>2021</td>
<td>PPI</td>
<td>0.81 (0.52–1.27)</td>
</tr>
<tr>
<td>Aral</td>
<td>2022</td>
<td>PPI</td>
<td>0.79 (0.49–1.24)</td>
</tr>
<tr>
<td>de Jonge</td>
<td>2006</td>
<td>PPI</td>
<td>0.85 (0.54–1.33)</td>
</tr>
<tr>
<td>Garcia Rodriguez</td>
<td>2006</td>
<td>PPI</td>
<td>0.77 (0.48–1.23)</td>
</tr>
<tr>
<td>Crane</td>
<td>2007</td>
<td>PPI</td>
<td>0.75 (0.47–1.19)</td>
</tr>
<tr>
<td>Jung</td>
<td>2011</td>
<td>PPI</td>
<td>0.80 (0.50–1.27)</td>
</tr>
<tr>
<td>Brusselaers</td>
<td>2018</td>
<td>PPI</td>
<td>0.71 (0.42–1.21)</td>
</tr>
<tr>
<td>Choi</td>
<td>2022</td>
<td>PPI</td>
<td>0.69 (0.44–1.18)</td>
</tr>
<tr>
<td>Kastelein</td>
<td>2013</td>
<td>H2RA</td>
<td>0.77 (0.49–1.23)</td>
</tr>
<tr>
<td>Gaddam</td>
<td>2014</td>
<td>H2RA</td>
<td>0.78 (0.49–1.25)</td>
</tr>
<tr>
<td>Thota</td>
<td>2017</td>
<td>H2RA</td>
<td>0.78 (0.49–1.25)</td>
</tr>
<tr>
<td>Tan</td>
<td>2018</td>
<td>H2RA</td>
<td>0.76 (0.47–1.22)</td>
</tr>
<tr>
<td>Garcia Rodriguez</td>
<td>2006</td>
<td>H2RA</td>
<td>0.76 (0.47–1.22)</td>
</tr>
<tr>
<td>Crane</td>
<td>2007</td>
<td>H2RA</td>
<td>0.75 (0.47–1.20)</td>
</tr>
<tr>
<td>Brusselaers</td>
<td>2018</td>
<td>H2RA</td>
<td>0.79 (0.49–1.25)</td>
</tr>
<tr>
<td>Choi</td>
<td>2022</td>
<td>H2RA</td>
<td>0.71 (0.42–1.20)</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td>0.77 (0.49–1.22)</td>
</tr>
</tbody>
</table>

H2RA = histamine-2 receptor antagonist; PPI = proton-pump inhibitor.

Figure 3. Sensitivity analysis for the assessment of the relationship between gastric acid suppressants and esophageal adenocarcinoma. 

ized controlled trials. The results of the subgroup analysis evaluating study design, sample size, quality of studies, study period, geographic location, and duration of treatment (receiving antise-cretory drugs) are detailed in Table 4.

Evaluation of publication bias related to gastric acid suppressants and EAC

Following the previous statistical assessment of the articles' data, there was evidence of publication bias. This was suspected upon evaluating the reported relationship between gastric acid suppressants and EAC. Statistical tests were conducted to evalu-
Table 4

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study No.</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>11</td>
<td>0.74 (0.45–1.22)</td>
<td>0.245</td>
</tr>
<tr>
<td>Cohort</td>
<td>16</td>
<td>0.76 (0.43–1.35)</td>
<td>0.353</td>
</tr>
<tr>
<td>Randomized controlled trial</td>
<td>1</td>
<td>1.04 (0.67–1.61)</td>
<td>0.861</td>
</tr>
<tr>
<td>Geographic location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>13</td>
<td>0.58 (0.45–0.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Europe</td>
<td>11</td>
<td>0.71 (0.31–1.60)</td>
<td>0.407</td>
</tr>
<tr>
<td>Asia</td>
<td>3</td>
<td>0.77 (0.49–1.22)</td>
<td>0.057</td>
</tr>
<tr>
<td>Australia</td>
<td>1</td>
<td>0.05 (0.006–0.038)</td>
<td>0.004</td>
</tr>
<tr>
<td>Study period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2010</td>
<td>9</td>
<td>0.57 (0.26–1.23)</td>
<td>0.152</td>
</tr>
<tr>
<td>2011–2022</td>
<td>19</td>
<td>0.88 (0.52–1.50)</td>
<td>0.652</td>
</tr>
<tr>
<td>Quality of the studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>6</td>
<td>0.72 (0.44–1.180)</td>
<td>0.198</td>
</tr>
<tr>
<td>Good</td>
<td>8</td>
<td>0.69 (0.22–2.07)</td>
<td>0.514</td>
</tr>
<tr>
<td>Excellent</td>
<td>14</td>
<td>0.78 (0.37–1.64)</td>
<td>0.516</td>
</tr>
<tr>
<td>Sample size</td>
<td>&gt;1000</td>
<td>1.01 (0.59–1.72)</td>
<td>0.961</td>
</tr>
<tr>
<td></td>
<td>≤1000</td>
<td>0.45 (0.21–0.96)</td>
<td>0.040</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>&gt;5 years</td>
<td>0.81 (0.49–1.29)</td>
<td>0.411</td>
</tr>
<tr>
<td></td>
<td>≤5 years</td>
<td>0.63 (0.25–1.43)</td>
<td>0.155</td>
</tr>
</tbody>
</table>

To date, no comprehensive published meta-analysis studies have investigated the effect of H2RA use on EAC. In this study, the OR of EAC in patients in the H2RAs group was 1.02 (95% CI, 0.44–2.36; P=0.967). Unfortunately, there was insufficient evidence to draw a reasonable conclusion from this study. However, other reports have reported an association between H2RA therapy and the risk of EAC, although these studies did not indicate any statistically significant effects.5

Contrary to the results of this study, Chen et al.4 in their meta-analysis, reported that PPI therapy was related to a decrease in the risk of Barrett’s esophagus progression, which was the most substantial risk for to EAC (OR = 0.47; 95% CI, 0.32–0.71). EAC might develop through the advancement of metaplasia to dysplasia to invasive carcinoma. An additional study evaluated the relationship between gastric acid suppressants and the risk of EAC in patients with Barrett’s esophagus. They stated that PPI consumption was associated with a 71% reduction in the risk of EAC in individuals with Barrett’s esophagus (OR = 0.29; 95% CI, 0.12–0.79).6 Different studies have proposed several factors that may affect the relationship between gastric acid suppressants, Barrett’s esophagus, and EAC, contributing to the general lack of consensus.

Overall, there is a lack of control over potential confounding factors within these studies. This is among the significant concerns related to investigations into this disease. Several etiological underlying factors have been proposed to have a role in the occurrence of this disease. For example, age, sex, a diet low in fruits and vegetables, alcohol, smoking, genetic factors, and medication use.48–50

Aside from those factors, variability in results may be related to the study methods, how patients are included, and subsequent available data and calculated statistics. For example, data deficiencies may be caused by a small sample size, poor allocation to therapy groups, and a short follow-up period.

Several potential limitations exist in the current systematic review and meta-analysis that should be considered when interpreting the results. For example, within the literature screening, only 1 randomized controlled trial was included in the analysis, and the rest of the data came from observational studies. This analysis planned to investigate various confounding factors that have been reported to be associated with gastric acid suppressants and EAC. Factors that were to be included in the analysis included smoking, alcohol consumption, and body mass index. It has also been suggested that Barrett’s esophagus length (short, long, or very long segments) can be a risk factor for developing dysplasia and adenocarcinoma. Data for some risk factors, such as Barrett’s esophagus length, was limited in the articles reviewed. In addition, data were missing in other studies, and there was no consistency in the

Figure 4. Funnel diagram to evaluate publication bias in the relation between gastric acid suppressants and esophageal adenocarcinoma.

Discussion

This systematic review and meta-analysis investigated the relationship between gastric acid suppressants and the risk of developing EAC. Results showed that when comparing to groups that did not receive gastric acid suppressants, the OR for EAC in the group taking gastric acid suppressants was 0.77 (95% CI, 0.49–1.22; P = 0.274). In addition, the OR of EAC in the PPI group was also 0.67 (95% CI, 0.39–1.29; P = 0.240). These results are consistent with those outlined by Hu et al.,7 who reported that PPI use is not associated with an increased risk of EAC in patients with Barrett’s esophagus metaplasia (OR = 0.43; 95% CI, 0.17–1.08).
reported confounding factors. This means that some results may be biased in their reported effects between the potential risk and disease relationship (ie, risk factors or exposure are distorted because they are mixed with other variables). Finally, drug–drug and drug–disease interactions could cause adverse effects with the antacid compounds, PPIs, and EAC. However, there have only been limited investigations that have considered including these as confounding factors.

Conclusions

The results determined no statistically significant association between gastric acid suppressants and the risk of developing EAC. Based on the data analysis for PPIs, they do not play a protective role for patients with EAC. Additionally, they were not a risk factor for this disease. However, more randomized controlled trials are needed to investigate potential confounding factors and better assess the relationship between Barrett’s esophagus length as a risk factor for developing dysplasia and adenocarcinoma. Finally, there were only limited data that investigated the effect of H2RA use and the risk of EAC. Due to this, we could not draw robust conclusions related to H2RAs and EAC. The incidence of EAC has been growing globally, and the development of this malignant tumor in the esophagus is the 10th most common cause of cancer. It has a low survival rate and can be fatal. With the paucity of research in this area, we urgently need future studies with consistent and robust data that report confounding factors that offer clinically valuable conclusions leading to improved treatment and reduced risk of developing EAC.

Conflicts of Interest

The authors have indicated that there is no conflict of interest regarding the content of this article.

Acknowledgments

K. Kasiri and S. Heidari-Soureshjani participated in conceptualization, investigation, and methodology. S. Rostamian and C. Sherwin participated in data curation. S. Heidari-Soureshjani did the formal analysis. All authors collaborated in writing (original draft and writing), review, and editing of the manuscript.

References


