Do non-steroidal anti-inflammatory drugs provide a protective effect on developing Barrett's esophagus and esophageal cancer? A systematic review and meta-analysis

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Citation

Trace Heavener, Cole Wayant, Ahmed Memon, Chase Meyer, Margaret Foster, Matt Vassar. Do non-steroidal anti-inflammatory drugs provide a protective effect on developing Barrett's esophagus and esophageal cancer? A systematic review and meta-analysis. PROSPERO 2018 CRD42018118489 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018118489

Review question

To determine if NSAIDs have a protective effect of developing Barrett's esophagus or esophageal cancer.

Searches

An electronic literature search will be conducted on MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to November 2018. Concepts included in the search are NSAIDs and esophageal cancer. Language and year will not be restricted. Full reports and abstracts (if able to obtain sufficient data) irrespective of language will be included. A manual search using reference lists of pertinent publications and conference presentation will be included.

Keywords include: 1) "anti-inflammatory agent," "aspirin," "acetylsalicylic acid," "non-steroidal anti-inflammatory drug," "COX," or "cyclooxygenase,"; 2) combined with "esophageal cancer," "oesophageal cancer," "esophageal adenocarcinoma," "neoplasm," "esophageal carcinoma," "squamous cell carcinoma of the esophagus" or "Barrett's esophagus".

Types of study to be included

Observational studies (such as case control and cohort)

Condition or domain being studied

Non-steroidal anti-inflammatory drugs provide a protective effect on developing Barrett's esophagus and esophageal cancer.

Participants/population

Adults (18 years of age or greater) with exposure to NSAIDs, aspirin, or both who have measured occurrence of esophageal cancer diagnosis or death from esophageal cancer.

Intervention(s), exposure(s)

Use of NSAIDs (salicylates such as aspirin, selective COX-2 inhibitors such as celecoxib, and non-selective COX-2 inhibitors such as meloxicam, ibuprofen, and indomethacin).

Comparator(s)/control

No use of NSAIDs

Context

Inclusion criteria: observational studies (such as case control and cohort); adults (18 years of age or greater); exposure to NSAIDs, aspirin, or both; measured occurrence of esophageal cancer diagnosis or death from esophageal cancer; and reported a relative risk (RR) or odds ratios (ORs) with confidence intervals, or sufficient data to permit their calculation.

Exclusion criteria: case reports, case series

In situations where multiple publications were from the same trial, data will be used from the publication with the longest follow up.

Main outcome(s)
Development of Barrett's esophagus, esophageal adenocarcinoma, or squamous cell carcinoma of the esophagus

Additional outcome(s)
Frequency and type of adverse effects

Data extraction (selection and coding)
After final selection of studies for the quantitative analysis, a pilot test of data extraction will be completed. Two authors (A.M., C.W.) will then independently extract the following data points: type of study, status of trial, type of intervention, gender, ethnicity, age, Barrett's esophagus, outcome assessment, exposure ascertainment, sample size, lost to follow-up, location of study and disclosed conflict of interests in a standardized data collection form.

All citations identified from the literature search will be merged, de-duplicated and stored in the reference manager database, Rayyan (https://rayyan.qcri.org/). A data collection form will be created using Google forms and all extracted data will be stored in Google drive will all authors having access. Following pilot testing, two authors (A.M., C.W.) will independently review all citations by title and abstract for a list of potential articles. Following title and abstract screening, a comparison of the selections from the two reviewers will be performed, and disagreements will be settled by a third author (T.H.). At this point, the full text of remaining articles will be retrieved and pilot test screening will be conducted by two authors (A.M., C.W.). They will then independently assess all papers to determine the final selection (dependent on eligibility) of relevant studies for inclusion in the review. An unweighted kappa score will be calculated to ensure agreement between the two reviewers for inter-rater concordance. A flow diagram will be created and included in the published results.

Risk of bias (quality) assessment
Two authors (A.M., C.W.) will independently assess each study for its risk of bias using the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) (https://sites.google.com/site/riskofbiastool/welcome/home/current-version-of-robins-i/robins-i-tool-2016) at the study level.

Strategy for data synthesis
If possible, a meta-analysis will be conducted with the following considerations. Meta-analysis will be assessed using random effects model according to Dersimonian and Laird method to account for expected clinical heterogeneity between studies. The corresponding fixed-effects analysis will also be provided. Summary effects will be calculated as risk ratios with 95% confidence interval with a prespecified alpha level of 0.05 for significance. Heterogeneity will be assessed with Cochran Q and I^2 method with 0.1 to represent significance. The number needed to treat with corresponding confidence intervals will be presented. All statistical analysis will be carried out using Stata (version 15.1) software.

Analysis of subgroups or subsets
A priori subgroup analyses include: Gender (female vs. male); Ethnicity (Asian vs. Western populations, based on study location); Age; Risk of bias (High versus low). The following prespecified criteria will be performed as sensitivity analysis: (1) each study omitted in turn with recalculation of summary of effects; (2) removal of those with high risk of bias, (3) removal of unpublished studies, (4) removal of studies that imputed missing data (if applicable).

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Anticipated or actual start date
03 December 2018

Anticipated completion date
03 June 2019

Funding sources/sponsors
None

Conflicts of interest

Language
English

Country
United States of America

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Anti-Inflammatory Agents, Non-Steroidal; Barrett Esophagus; Esophageal Neoplasms; Humans

Date of registration in PROSPERO
20 December 2018

Date of publication of this version
20 December 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
20 December 2018