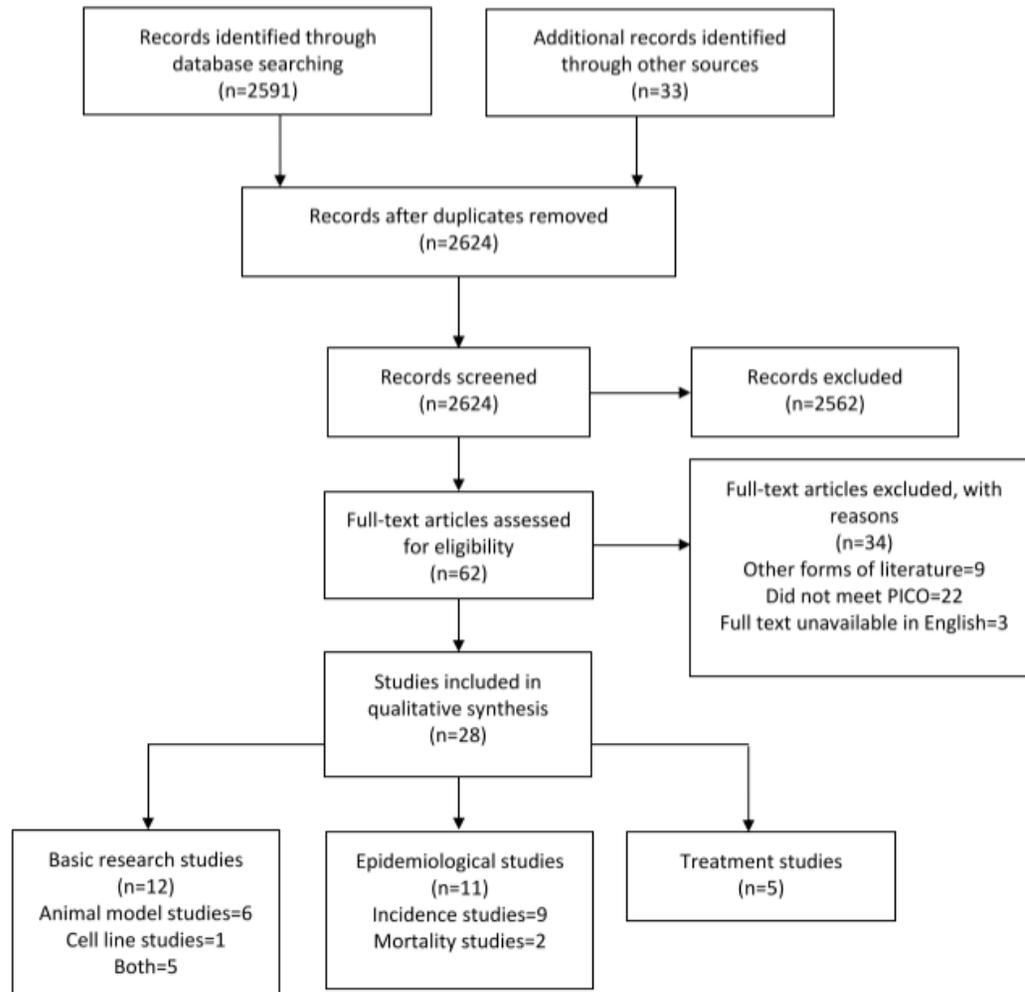


Supplementary Figure 1 PRISMA flowchart



Supplementary Table 1 PICO questions

	Basic studies	Epidemiological studies 1	Epidemiological studies 2	Treatment studies
Patient	Cell studies: studies on human CRC cell lines Animal studies: studies on CRC animal models	Patients diagnosed with CRC	PPI users and non-PPI users	Patients diagnosed with CRC
Intervention	Treated with PPI	Patients with PPI history (current, ever, or never users)	Patients diagnosed with CRC	Concurrent use of PPI with chemotherapy
Comparison	Not treated with PPI	Patients with no PPI use history	Patients not diagnosed with CRC	No use of PPI
Outcome	Cell viability, tumor burden, histological and biochemical analysis	CRC incidence and mortality risk	Hazard risk	Overall survival, disease-free survival, recurrence-free survival

CRC: Colorectal cancer; PPI: Proton pump inhibitors.

Supplementary Table 2 Newcastle-Ottawa Scale assessment of included studies.

	Selection	Comparability	Exposure	Total Score
Robertson <i>et al.</i> 2007	4	2	3	9
Van Soest <i>et al.</i> 2008	4	2	3	9
Yang <i>et al.</i> 2007	4	2	3	9
Lee <i>et al.</i> 2020	4	2	3	9
Chubak <i>et al.</i> 2009	4	2	3	9
Kuiper <i>et al.</i> 2020	4	2	3	9
Hwang <i>et al.</i> 2017	4	2	3	9
Babic <i>et al.</i> 2020	3	2	2	7
Lei <i>et al.</i> 2020	4	2	3	9
Zhang <i>et al.</i> 2017	4	2	3	9
Sun <i>et al.</i> 2016	4	2	3	9
Wong <i>et al.</i> 2019	4	2	3	9

The quality of included studies (in epidemiological and treatment categories) was assessed using the NOS. The overall quality of evidence on the association of PPI use and CRC risk was high. All but one study scored the maximum nine points on NOS, while the remainder scored seven points. The risk of bias of Kichenadasse *et al.* and Kim *et al.* post-hoc analyzes was judged as low to intermediate based on Cochrane ROB 2.0 assessment of included trials. The concerns primarily related to allocation concealment and/or blinding.