Opportunities for preventing esophageal adenocarcinoma.

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Abstract

Esophageal adenocarcinoma is rapidly increasing in incidence in many Western societies, requires demanding treatment and is associated with a poor prognosis, therefore preventive measures are highly warranted. To assess the opportunities for prevention, we reviewed the available literature and identified seven main potentially preventive targets. Preventive effects were found based on medium level observational evidence following treatment of gastroesophageal reflux disease (both using medication and surgery) and tobacco smoking cessation, which should be clinically recommended among exposed patients. Non-steroidal anti-inflammatory drugs appears to prevent esophageal adenocarcinoma, and the limited existing data also indicates a protective effect of medication with statins or hormone replacement therapy in women, but current evidence is insufficient to guide clinical decision-making regarding these drugs. The evidence is presently insufficient to assess the potentially preventive role of weight loss. Whether avoidance of eradication of *Helicobacter pylori* prevents esophageal adenocarcinoma is not studied, but there is no evidence that such eradication increases symptoms of gastro-esophageal reflux or prevalence of erosive esophagitis. The introduction of preventive actions should be tailored towards high-risk individuals, i.e. older men with obesity and gastroesophageal reflux disease and individuals with Barrett's esophagus rather than the population at large.

Introduction

Esophageal cancer is the eighth most common cancer and the sixth most deadly cancer worldwide (1). There are two major histological types of esophageal cancer, adenocarcinoma and squamous cell carcinoma; squamous cell carcinoma is most common worldwide, while esophageal adenocarcinoma (EAC) is more common in the Western world, especially among white men (1-3). While the incidence of squamous cell carcinoma is decreasing, EAC is characterized by a rapidly increasing incidence among white populations in high-income countries.(3) The increase seems to have begun in the early 1970's, and in the United States the annual incidence increased from 0.40 cases per 100 000 individuals in 1975, to 2.58 per 100 000 in 2009 (4, 5). Changes in prevalence of the main etiological factors, i.e. gastroesophageal reflux, obesity and infection with *Helicobacter pylori* (*H. pylori*), have most likely contributed to the increase (2). Potentially curatively intended treatment of EAC requires demanding and extensive surgery, often followed by severe postoperative complications, including mortality, and severe deterioration in health-related quality of life (2). Despite recent advances in detection and treatment of EAC, the overall prognosis remains poor, with a 5-year overall survival of approximately 15%. The 5-year survival following curatively intended treatment varies greatly (range 24-55%) in Western societies, a variation that at least partly depends on differences in selection of patients for surgery (6-8). The rapidly increasing incidence, demanding treatment and poor prognosis highlight the need for preventive measures, especially among high-risk individuals. Such high-risk groups might be those with a combination of risk factors of EAC or those with the premalignant condition Barrett's esophagus, a specialized columnar metaplasia replacing the native squamous epithelium of the distal esophagus in response to chronic

gastroesophageal reflux (9). We conducted a review assessing potential targets for preventing EAC.

Search criteria

The literature search to identify relevant studies assessing factors that might prevent EAC was conducted using PubMed, Web of Science, and the Cochrane library. The search strings were combinations of different exposures and EAC, with the primary aim of identifying relevant systematic reviews meta-analyses, and secondarily original studies. Due to the rare incidence of EAC, studies including high-grade dysplasia were also included, although there is a risk of inter-observer variation regarding high-grade dysplasia (10, 11). We only included studies of human subjects, and excluded case reports and publications in other languages than English. Backward and forward citation tracking was conducted to further identify relevant literature. The best level of evidence regarding each of these factors was rated according to the Oxford Centre for Evidence-based Medicine's level of evidence, where the level of evidence is graded as: 1 (randomized controlled trials), 2 (cohort studies), 3 (case-control studies), 4 (case-series), and 5 (expert opinions); grades 1-3 are further denoted as a) systematic review, or b) individual study (12). Furthermore, the recommendations were assessed according to the Oxford Centre for Evidence-based Medicine's grades of recommendations, graded as: A (consistent level 1 studies), B (consistent level 2 or 3 studies or extrapolations from level 1 studies), C (level 4 studies or extrapolations from level 2 or 3 studies), D (level 5 evidence of troublingly inconsistent or inconclusive studies of any level (12).

Seven potentially preventive measures

The literature search identified seven factors of particular relevance for prevention: 1) treatment of gastroesophageal reflux, 2) weight loss among obese individuals, 3) tobacco smoking cessation, 4) avoidance of eradication of *H. pylori*-infection, 5) hormone replacement therapy, 6) use of nonsteroidal anti-inflammatory drugs, and 7) use of statins. The results of the literature search and evidence grade regarding each of the seven factors are summarized in Table 1. We indicate population-based studies for studies employing this sampling frame, whereas the rest were non-population based.

Treatment of gastroesophageal reflux

Gastroesophageal reflux disease (GERD) is a common condition with a reported prevalence ranging from 10 to 20% in most Western societies. GERD is also the main risk factor for EAC, an association established in the late 1990's (13, 14). A recent meta-analysis (including five population-based case-control studies) found that the odds ratio (OR) of EAC was nearly 5 times higher among individuals experiencing weekly reflux symptoms (heartburn or acid regurgitation) than those with less frequent or no such symptoms (OR 4.92, 95% confidence interval [CI] 3.90-6.22), and over 7-fold increased for individuals experiencing daily reflux symptoms (OR 7.40, 95% CI 4.94-11.1) (15). GERD can be treated medically, typically using proton-pump inhibitors (PPI), or surgically, with fundoplication. PPIs are generally considered to be the first line of treatment, while surgery is mainly an option if inadequate response is achieved from adequate doses of PPI or when treatment is believed to be ongoing for a long time, particularly in younger individuals (16). Studies have shown that long-term use of PPI increases the serum levels of gastrin, which in turn is believed to

promote cell-survival in the gastrointestinal tract and might facilitate carcinogenesis from Barrett's esophagus, and it is debated whether this in a long-term clinical setting could increase the risk of EAC (17-19). Most earlier studies have failed to show reduction in risk of EAC following PPI use, but rather indicated an increased risk. However, these results are debated since they might be due to confounding by the severity of GERD, i.e., those with severe GERD, who have the highest risk of EAC, are more likely to be prescribed PPIs than those with mild reflux. A recent meta-analysis (including four hospital-based cohort studies, one population-based cohort study and two case-control studies) concluded that there was a decreased risk of EAC or high-grade dysplasia among patients with Barrett's esophagus who used PPIs compared to non-users (OR 0.29, 95% CI 0.12-0.79) (20). On the other hand, a recent Danish population-based case-control study assessing the risk of EAC following PPI treatment found an increased risk of high-grade dysplasia or EAC following treatment with PPIs, with a relative risk of 2.2 (95% CI 0.7-6.7) and 3.4 (95% CI 1.1-10.5) among long-term low- and high-adherence users, respectively (21). However, also, after combining this Danish study with the results from the previous meta-analysis (20), a protective effect of PPIs on EAC remained (22).

Fundoplication is generally performed laparoscopically, where the fundus of the stomach is wrapped completely or partially around the lower part of the esophagus. Since individuals eligible for fundoplication tend to have particularly severe GERD or GERD that did not respond satisfactorily to PPIs, a valid comparison with untreated patients is usually not feasible. Yet, a recent meta-analysis (including 10 cohort studies, of which 2 were population-based, and 2 RCTs) comparing patients undergoing fundoplication with medically treated patients indicated a non-significantly decreased pooled incidence rate ratio (IRR) of EAC in favor of surgery (IRR 0.76, 95% CI 0.42-1.39), and the risk estimate further decreased

but remained nonsignificant in analyses restricted to patients with Barrett's esophagus (IRR 0.46, 95% CI 0.20-1.08) (23). In an analysis restricted to studies published after the year 2000, when the surgically treated patients typically underwent laparoscopic fundoplication, the IRR was statistically significantly decreased in patients with Barrett's esophagus (IRR 0.26, 95% CI 0.09-0.79) (23).

Taken together, there is medium level evidence that medical treatment of GERD have a preventive effect on the development of EAC, although it is debated whether long-term use of PPI might actually have a carcinogenic effect on Barrett's esophagus (evidence level 3a, grade of recommendation D). There is also medium level evidence suggesting that prevention of EAC following surgical treatment of GERD goes in line with, or might be slightly more effective, than medical treatment (evidence level 2a, grade of recommendation B).

Weight loss

There is a strong association between high body mass index (BMI) and many cancer types, but a comprehensive meta-analysis (based on 221 datasets) concluded that EAC had the strongest association with BMI (24). A recent meta-analysis (22 studies; 14 case-control studies, of which 12 were population-based, and 8 population-based cohort studies) found that compared to individuals with normal BMI, the overall risk ratio (RR) of EAC was 1.71 (95% CI 1.50-1.96) for individuals with a BMI 25-30, and 2.34 for those with a BMI ≥30 (95% CI 1.95-2.81) (25). A pooled analysis of 12 observational studies (10 population-based case-control studies and 2 population-based cohort studies) comparing individuals with a BMI <25 with those with a BMI ≥40, found an OR of EAC of 3.65 (95% CI 2.50-5.34) (26). The

available literature indicates a linear association between increasing BMI and risk of EAC. A meta-analysis (2 population-based cohort studies, 1 hospital-based cohort study and 3 population-based case-control studies) concluded that abdominal or visceral adiposity, independent of BMI, significantly increased the risk of EAC (27). The increased risk of esophageal metaplasia and EAC due to obesity is attributable to mechanical effects of obesity (e.g. gastroesophageal reflux), but also metabolic and endocrine effects (such as macrophage activation and release of proinflammatory cytokines) (28).

Despite the established association between BMI and EAC, the potentially preventive role of weight loss is uncertain. This is at least partly due to inherent problems in assessing weight loss as an exposure in larger cohorts, and challenges in identifying a large enough cohort of individuals with voluntary weight loss that is both substantial and long-lasting. In this context, obesity surgery might be seen as a potential human model for assessing the risk of developing EAC following weight loss, because of its drastic and stable long-term weight reduction starting from a specific date (29, 30). However, a recent systematic review identified only 11 cases of EAC occurring after obesity surgery, and statistical analyses were not conducted (31). In a subsequent population-based cohort study in Sweden, including 34,437 patients undergoing obesity surgery, only 8 participants developed EAC during follow-up, resulting in a hazard ratio of 0.9 (95% CI 0.4-1.9) compared to non-operated obese individuals (32). This might be explained by the rather short follow-up time in the studies published to date, where there might be a longer period of time before a risk reduction can be seen, or attributable to metabolic or endocrine effects due to obesity. Thus, no clearly preventive effect of obesity surgery was revealed, although the statistical power was low.

In summary, while obesity is associated with increased EAC risk, there is only limited evidence indicating that weight loss does *not* decrease the risk of EAC among obese individuals. However, long follow-up of large cohorts of patients, e.g. those undergoing obesity surgery, should provide important knowledge regarding this topic (evidence level 2b, grade of recommendation B).

Tobacco smoking cessation

Tobacco smoking is associated with a moderately increased risk of EAC. A meta-analysis based on 33 studies (30 case-control studies, of which 13 were population-based, and 3 cohort studies, of which 2 were population-based) found a RR of 1.76 (95% CI 1.54-2.01) for EAC, including the gastric cardia, when comparing ever and never smokers (33). A pooled analysis of 10 population-based case-control studies found an OR of 2.08 (95% CI 1.83-2.37) when comparing ever and never smokers (34). The pooled analysis found that smoking cessation decreased the risk of EAC, and that a longer time since smoking cessation reduced the risk increase in a time-dependent manner (34). Compared to current smokers, smoking cessation <10 years entailed an OR of 0.82 (95% CI 0.60-1.13), and smoking cessation of ≥10 years entailed an OR of 0.71 (95% CI 0.56-0.89) (34). However, the risk of EAC among previous smokers did not return to the level of non-smokers; even after ≥10 years of smoking cessation, the pooled analysis, found a 1.7-fold risk of EAC compared to never smokers (34). There are currently no published cohort studies regarding smoking cessation.

Thus, there is consistent evidence showing that tobacco smoking cessation decreases the risk of EAC among tobacco smokers, although the risk might not return to the level of never smokers (evidence level 3b, grade of recommendation B).

Avoiding eradication of *Helicobacter pylori*

H. pylori is a gram-negative bacterium, and has been determined to be a main risk factor for peptic ulceration and gastric adenocarcinoma (35-37). A systematic review including 37 studies from 22 countries found that the infection is generally acquired during childhood and the prevalence is over 50% in many populations (38). Infection with *H. pylori* can lead to atrophy of the gastric mucosa, resulting in lower volume and acidity of gastric juices, which in turn could decrease the risk of EAC (39). In keeping with this hypothesis, a meta-analysis of 20 studies (11 case-control studies and 9 cohort studies) found a 40% lower prevalence of *H. pylori* among patients with GERD compared to patients without GERD (OR 0.60, 95% CI 0.47-0.78) (40), and two recent meta-analyses (including 9 cohort studies and 9 case-control studies of which 3 were population-based, and including 15 case-control studies, of which 8 were population-based) found that ongoing infection with *H. pylori* was associated with a nearly halved risk of EAC (OR 0.52, 95% CI 0.37-0.73, and 0.59, 95% CI 0.51-0.68) (41, 42). These findings indicate that broad eradication strategies might not be justified in high-risk individuals of EAC. However, no studies have assessed the association between *H. pylori*-eradication and EAC. Nevertheless, a recent meta-analysis (including 7 randomized clinical trials and 5 cohort studies) found no significant association between eradication of *H. pylori*-infection and prevalence of symptomatic GERD or endoscopically documented GERD (43). Another meta-analysis (including 16 cohort studies), although with some overlap with the previously cited meta-analysis, found no association between *H. pylori*-eradication and symptomatic GERD or erosive esophagitis when analyzing the studies based on sub-groups for geographic region, age, baseline disease or length of follow-up (44).

Taken together, the limited literature has no direct evidence to determine if eradication of *H. pylori* increases the risk of EAC, i.e. if avoidance of eradication might be justified in some individuals. However, such eradication does not seem to increase the risk of GERD or erosive esophagitis, and since these are risk factors of developing EAC, this might indicate that there is no increased risk for EAC per se (evidence level 2a, grade of recommendation D).

Hormone replacement therapy

A possible explanation for the strong male predominance of EAC, with an average three to six fold higher incidence among men (45), is differences in levels of endogenous exposure to female sex hormones. If this hypothesis is true, preventive effects of exogenous HRT might be evident. HRT is administered mainly for climacteric symptoms in postmenopausal women, and has been shown to be effective for treating vasomotor symptoms, vaginal atrophy, and sexual problems, as well as in preventing osteoporosis and bone fractures (46-49). A meta-analysis including five studies (2 population-based cohort studies, 2 case-control studies and 1 pooled analysis of four case-control studies) found a decreased odds ratio of EAC among ever users of HRT, compared to never users (OR 0.75, 95% CI 0.58-0.98), however, no sub analyses based on dosage, type or duration was possible due to few and small studies (50). A recent case-control study found an increased risk of GERD symptoms (HR 1.57, 95% CI 1.45-1.70) when comparing ever users of HRT with never users, but no increased risk of Barrett's esophagus (HR 1.15, 95% CI 0.81-1.63) or EAC (HR 0.89, 95% CI 0.28-2.82) was found (51).

Thus, the available literature addressing HRT in relation to risk of EAC to date is limited, but might suggest a preventive effect (evidence level 3a, grade of recommendation B).

Non-steroidal anti-inflammatory drugs

NSAIDs inhibit cyclooxygenase (COX) on a systemic level, either unselected or COX-2 specifically, and are usually administered for their analgesic, anti-inflammatory, and antipyretic effects (52, 53). COX-2 is an inflammatory enzyme necessary for the production of prostaglandins and other inflammatory mediators, and there is an increased expression of COX-2 in patients with Barrett's esophagus and EAC, hence indicating the possibility of chemoprevention if targeting this mechanism (54-56). A pooled analysis of six studies (5 population-based case-control studies and 1 population-based cohort study) found a reduced risk of EAC among ever-users of any NSAID, including aspirin, compared to never-users (OR 0.68, 95% CI 0.56–0.82) (57). Compared to never-users, a slightly stronger reduction was indicated among daily users of any NSAIDS, including aspirin (OR 0.56, 95% CI 0.43-0.73), than occasional users (OR 0.66, 95% CI 0.44-1.00) (57). A meta-analysis (including eight randomized clinical trials) found that daily treatment with aspirin was followed by a reduction in 20-year risk of death due to esophageal adenocarcinoma (HR 0.36, 95% CI 0.21-0.63) (58). Another meta-analysis (including 9 case-control studies, of which 4 were population-based, and 1 population-based cohort study) assessing NSAID use and risk of EAC found an OR of 0.64 (95% CI 0.52-0.79) among users of aspirin and 0.65 (0.50-0.85) among users of non-aspirin NSAIDs, compared to never-users (59).

In summary, treatment with NSAIDs appears to decrease the risk of developing EAC (evidence level 1a, grade of recommendation A), but introduction of NSAID as chemoprevention solely for this purpose requires further research.

Statins

Statins are usually prescribed as prevention of cardiovascular disease, but may also have a cancer preventive effects. Statins have anti-proliferative, pro-apoptotic, anti-invasive, and radio-sensitizing properties in pre-clinical studies (60). A meta-analysis (13 studies: 5 cohort studies, of which 2 were population-based, 7 case-control studies, of which 6 were population-based, and 1 post hoc analysis of 22 RCTs) of individuals without Barrett's esophagus found an adjusted OR of 0.72 for developing esophageal cancer (95% CI 0.60-0.86), in a sub analysis of patients with Barrett's esophagus (5 studies: 3 cohort and 2 case-control studies, of which 1 was population-based) found a 43% reduction in risk of EAC (adjusted OR 0.59, 95% CI 0.45-0.78) among users of statins compared to never-users (61). However, these results are debated, since a meta-analysis of only randomized clinical trials failed to show significant reduction in risk, although this was based on a smaller number of esophageal cancer cases (total 164 cancer cases compared to 9285 cancer cases), and no separate analysis of only EAC was performed (62).

Thus, most available studies indicate a preventive effect on the development of EAC of treatment with statins (evidence level 3a, grade of recommendation B), but the literature is too limited to allow robust conclusions and therefore statins should not be used solely for EAC chemoprevention.

High-risk individuals for EAC

To determine who might benefit from preventive measures, high risk individuals for EAC need to be identified. A recent Australian prediction model study aiming to identify individuals at high risk of developing EAC found that men over 70 years old with a BMI ≥30, who were current smokers, experiencing at least weekly symptoms of GERD, were medicated with PPIs and had never used NSAIDs were at the highest risk (63). The model revealed that the absolute 5-year risk in individuals who fulfilled all of these criteria was 837 per 100,000 person-years, while the corresponding risks among individuals who were at least 60 years old and 50 years old were 506 and 185 per 100,000 person-years, respectively (64). A similar study in Sweden identified the highest risk (533 per 100,000 person-years) among male smokers, aged 70-74 years, with a BMI ≥25.5, experiencing weekly symptoms of GERD for at least five years, and requiring antireflux medication (64). An earlier study on the same Swedish study showed that age, sex, BMI and reflux symptoms were the strongest predictors of developing EAC, although these factors have not been found to solely explain the male predominance (65, 66). Individuals with Barrett's esophagus have already entered the metaplasia-dysplasia-adenocarcinoma-axis. A meta-analysis concluded that the overall risk of Barrett's esophagus to progress to EAC was 6.1/1000 person-years, and twice as high among men as women (67), but recently, two large and well-designed studies showed that the annual risk of EAC in persons with non-dysplastic Barrett's esophagus may be lower than previously reported, i.e. 0.12% and 0.16% (68, 69).

Overall, these studies indicate that older men with obesity and GERD are at the highest risk of developing EAC, and might benefit most from preventive measures. Individuals with

Barrett's esophagus also constitute a high-risk population, in whom preventive measures might be cost-effective.

Conclusions

This review indicates several promising targets for prevention of EAC among high-risk individuals in the clinical setting. The strongest evidence of preventive effects was seen following treatment of GERD, particularly after antireflux surgery in individuals with Barrett's esophagus. There is medium level evidence of a preventive effect of tobacco smoking cessation in relation to the risk of EAC. There is no substantial evidence showing that weight loss, including weight loss after obesity surgery, reduces the risk of EAC, although available studies are few in number and have a limited follow-up. Whether eradication of *H. pylori* increases the risk of EAC is unknown, but there is no evidence that eradication of *H. pylori* increases the risk of GERD, which would be believed to mediate any increased risk of EAC. HRT might decrease the risk of EAC, but the available studies are few in number and more research is required. Use of NSAIDs, both aspirin and non-aspirin, seems to prevent EAC, and results from randomized clinical trials are approaching. Regarding treatment with statins, the available literature shows a strong risk reduction of EAC among patients with Barrett's esophagus. Yet, more research is needed to establish this association. Among these potential options for preventing EAC, clinicians should recommend treatment of GERD and tobacco smoking cessation. There is a need for more research on these as well as other targets before clinical recommendations can be made, and it remains to be established which individuals are most favorable for any such preventive actions.

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Table 1. Associations between the seven preventive targets and risk of esophageal adenocarcinoma (EAC), evidence of preventive effects, and the level of evidence according to the Oxford Centre for Evidence-based Medicine.

Etiological factor	Risk of EAC	Preventive measure	Best available evidence	Prevention of EAC	Level of evidence *
Gastroesophageal reflux disease	Weekly symptoms: OR 4.92, 95% CI 3.90-6.22 (15) Daily symptoms: OR 7.40, 95% CI 4.94-11.1 (15)	Medication with PPI	M-A of patients with BE	PPI versus no PPI: OR 0.29, 95% CI 0.12-0.79 (20)	3a
		Anti-reflux surgery	M-A of patients with BE	Antireflux surgery versus medication: IRR 0.46, 95% CI 0.20-1.08 (23)	2a
Obesity	BMI 25-30: RR 1.71, 95% CI 1.50-1.96 (25) BMI ≥30: RR 2.34, 95% CI 1.95-2.81 (25) BMI ≥40: OR 3.65, 95% CI 2.50-5.34 (26)	Weight loss by obesity surgery	Not sufficient data		
Tobacco smoking	Ever versus never: OR of 2.08, 95% CI 1.83-2.37 (34)	Tobacco smoking cessation	Pooled analysis of 10 studies	Tobacco smoking cessation <10 years: OR 0.82, 95% CI 0.60-1.13 (34) Tobacco smoking cessation ≥10 years: OR 0.71, 95% CI 0.56-0.89 (34)	3b 3b
***Helicobacter pylori*-infection**	Current infection: OR 0.52, 95% CI 0.37-0.73, (41) and OR: 0.59, 95% CI 0.51-0.68 (42)	*Helicobacter pylori* eradication	M-A of eradication and risk of GERD and erosive esophagitis	Eradication and risk of erosive GERD: OR 1.17, 95 % CI 0.94-1.45 (43) Eradication and risk of GERD: OR 0.84, 95% CI 0.60-1.18 (44) Eradication and risk of erosive esophagitis: OR 0.97, 95% CI 0.72-1.31 (44)	2a
Hormone replacement therapy (HRT)		Medication with HRT	M-A of women receiving HRT	Ever versus never: OR 0.75, 95% CI 0.58-0.98 (50)	3a
Nonsteroidal anti-inflammatory drugs (NSAID)		Medication with NSAID	Pooled analysis of 6 studies	Daily versus never: OR 0.56, 95% CI 0.43-0.73 (57) Occasional versus never: OR 0.66, 95% CI 0.44-1.00 (57)	3b 3b
			M-A of 8 RCTs 20 year follow-up	Daily versus placebo: HR 0.36, 95% CI 0.21-0.63 (58)	1a

Statins	Medication with statins	M-A of patients with BE	Users versus non-users: OR 0.59, 95% CI 0.45-0.78 (61)	3a
		M-A of patients irrespective of BE	Users versus non-users: OR 0.72, 95% CI 0.60-0.86 (61)	3a

*Level of Evidence according to the Oxford Centre for Evidence-based Medicine's levels of evidence; the level of evidence is graded: 1 (randomized controlled trials), 2 (cohort studies), 3 (case-control studies), 4 (case-series), and 5 (expert opinions); grades 1-3 are also denoted as a (systematic review) or b (individual study).(12)

Abbreviations: EAC, Esophageal adenocarcinoma; OR, Odds ratio; CI, Confidence interval; PPI, Proton-pump inhibitors; M-A, Meta-analysis; BE, Barrett's esophagus; IRR, Incidence risk ratio; BMI, Body mass index; RR, Rate ratio; GERD, Gastroesophageal reflux disease; HRT, Hormone replacement therapy; NSAID, Nonsteroidal anti-inflammatory drugs; RCT, Randomized controlled trials; HR, Hazard ratio