World Journal of Gastrointestinal Pharmacology and Therapeutics

Online Submissions: http://www.wjgnet.com/esps/
wjgpt@wjgnet.com
doi:10.4292/wjgpt.v5.i1.27

World J Gastrointest Pharmacol Ther 2014 February 6; 5(1): 27-39
ISSN 2150-5349 (online)

REVIEW

Role of chemoprophylaxis with either NSAIDs or statins in patients with Barrett's esophagus

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Received: August 24, 2013 Revised: November 9, 2013
Accepted: November 15, 2013
Published online: February 6, 2014

Abstract

The incidence of esophageal adenocarcinoma, a poor prognosis neoplasia, has risen dramatically in recent decades. Barrett's esophagus represents the best-known risk factor for esophageal adenocarcinoma development. Non-steroidal anti-inflammatory drugs through cyclooxygenase-2 inhibition and prostaglandin metabolism regulation could control cell proliferation, increase cell apoptosis and regulate the expression of growth and angiogenic factors. Statins can achieve equivalent effects through prenylation and subsequently control of cellular signaling cascades. At present, epidemiological studies are small and underpowered. Their data could not justify either medication as a chemo-preventive agent. Population based studies have shown a 43% reduction of the odds of developing an esophageal adenocarcinoma, leaving out or stating a 25% reduction in patients consuming non-aspirin nonsteroidal anti-inflammatory drugs and a 50% reduction in those patients consuming aspirin. They have also stated a 19% reduction of esophageal cancer incidence when statins have been used. Observational studies have shown that non-steroidal anti-inflammatory drugs could reduce the adenocarcinoma incidence in patients with Barrett's esophagus by 41%, while statins could reduce the risk by 43%. The cancer preventive effect has been enhanced in those patients taking a combination of non-steroidal anti-inflammatory drugs and statins (a 74% decrease). Observational data are equivocal concerning the efficacy of non-steroidal anti-inflammatory drug subclasses. Non-steroidal anti-inflammatory drugs clearly have substantial potential for toxicity, while statins are rather safe drugs. In conclusion, both non-steroidal anti-inflammatory drugs and statins are promising chemopreventive agents and deserve further exploration with interventional studies. In the meanwhile, their use is justified only in patients with cardiovascular disease.

Key words: Esophageal adenocarcinoma; Barrett's esophagus; Non-steroidal anti-inflammatory drugs; Aspirin; Statins; Cancer chemoprevention

Core tip: Esophageal adenocarcinoma remains a major burden upon health. Experimental studies have suggested that non-steroidal anti-inflammatory drugs and statins may have useful actions against esophageal cancer cells. This review of observational studies shows that non-steroidal anti-inflammatory drugs reduced adenocarcinoma incidence in patients with Barrett's esophagus by 41%, while statins reduced the risk by 43%. The cancer preventive effect is enhanced in those patients taking a combination of non-steroidal anti-inflammatory drugs and statins (a 74% decrease). Non-steroidal anti-inflammatory drugs clearly have substantial potential for toxicity, while statins are rather safe drugs. Their combination offers promise for chemoprevention and further interventional studies are warranted.

Tsibouris P, Vlachou E, Isaacs PET. Role of chemoprophylaxis

with either NSAIDs or statins in patients with Barrett's esophagus. *World J Gastrointest Pharmacol Ther* 2014; 5(1): 27-39 Available from: URL: http://www.wjgnet.com/2150-5349/full/v5/i1/27.htm DOI: http://dx.doi.org/10.4292/wjgpt.v5.i1.27

INTRODUCTION

A rapid increase in incidence and mortality from esophageal adenocarcinoma (EAC) has been observed over the past four decades in the Western world[1,2]. Although the absolute incidence of EAC varies dramatically by gender and race, few demographic groups have been spared from the increases[3]. Moreover, survival of persons with EAC remains abysmal, with most succumbing to the disease within a year[4], while the 5-year survival rate is less than 15%[5].

Barrett's esophagus (BE), replacement of the squamous esophageal mucosa by metaplastic columnar epithelium due to prolonged reflux[6] of the gastric content into the esophagus, represents the best-known risk factor for EAC development[7]. The annual incidence of EAC development in patients with BE is 0.2%-0.5%[8,9].

Clinical and demographic factors that have shown some promise in being predictive of malignant transformation in BE are male gender[10,11], increasing age[11], length of Barrett's segment[12-14], duration of BE[13] and size of hiatal hernia[14]. There is little evidence to suggest that total alcohol consumption or specific alcoholic beverages modifies the risk of EAC in the general population[15,16], while smoking[16-19] and obesity[16,20] raise the risk for neoplastic progression.

According to the most popular theory, carcinogenesis in BE patients is completed in three stages. During the first, a distinct stem cell population develops in the bone marrow of genetically predisposed patients with gastroesophageal reflux disease. Those cells migrate during the second stage to the gastroesophageal junction and lower esophagus, producing a macroscopically visible BE. The inflammatory milieu in the lower esophagus produces the driving force for stem cell migration. Repeat call for repair in the hostile environment of lower esophagus in BE patients leads to increase cell proliferation and frequent mutations. As noxious mutations sum up by a multistep process, metaplastic epithelium evolves into low-grade dysplasia, high-grade dysplasia, early EAC and ultimately invasive cancer[21].

Although cancer surveillance is performed in most institutions, once diagnosis of BE is rendered, the true cost-benefit ratio of this endeavour is still essentially unknown[22]. Surveillance does not interfere with the neoplastic process and could not affect the pre-neoplastic stem cell population generated in the bone marrow. Thus, there is a quest for global and more interventional strategies. Chemoprevention is attractive, especially for the high-risk group of BE individuals, since it can affect the neoplastic process from its early beginning. Moreover, because it could be effective even under insufficient gastric acid suppression[23], it may be superior to BE ablative techniques that presuppose adequate acid suppression to prevent BE recurrence[24] and may prove too expensive[25]. Finally, since BE surveillance cost-effectiveness has been undermined by recent data suggesting a low risk of malignant transformation[26,27], chemoprevention seems to represent an attractive alternative[28]. At present, there are no proven chemo-preventive agents, although non-steroidal anti-inflammatory drugs (NSAIDs) and statins appear to offer the most attractive combination of risks and benefits.

This review is to assess current experimental and epidemiological data that NSAIDs and statins could reduce the risk of developing EAC in BE. Moreover, we aim to clarify how existing findings could be included in the EAC etiological models, as well as any side effects, that would follow clinical application of NSAIDs and statins for cancer prevention.

NSAIDS AND EAC CHEMOPREVENTION

Numerous *in vitro* and animal studies support the possible chemo-preventive effect of cyclooxygenase-2 (COX-2) inhibition in BE. COX-2 inhibitors, either drugs or naturally occurring in plant foods, could produce significant suppression of cell proliferation and induce cell cycle arrest in cultured EAC cells[29]. Selective COX-2 inhibitors have a similar effect in cell cultures from endoscopic biopsies taken from BE patients[30]. Adding COX-2 inhibitors in rat diet after esophagojejunostomy had reduced progression to EAC[31,32] in some studies, while indomethacin, but not selective COX-2 inhibitors, produced a similar effect in others[33].

Several case control studies comparing EAC patients to healthy controls have shown that NSAID use can effectively prevent EAC. A meta-analysis of all human studies published prior to 2003, showed an overall 43% reduction of the odds of developing an EAC in NSAID takers, comprising a 25% reduction in patients consuming non-aspirin NSAIDs and 50% reduction in aspirin users[34], but the analysis included only one small case-control study comparing BE and EAC patients[35] and no prospective study. Thus, it cannot differentiate whether any beneficial effect of NSAID use is produced before or after BE appearance. In 2009, a questionnaire based study that included approximately 300000 members of the American Association of Retired Persons found no significant association between EAC and the use of aspirin or non-aspirin NSAIDs[36].

Since 2003, several observational studies comparing BE and EAC patients have been published (Table 1). These were either case-control retrospective[23,37,38] or cohort studies[39-43]. Prospective chemoprevention trials are underway to evaluate the efficacy of aspirin and NSAIDs. In the United Kingdom, the AspECT trial is currently evaluating the combination of high-dose proton pump inhibitors and aspirin in minimizing the risk of progression to cancer in 9000 BE sufferers[44]. A similar

Table 1 Available epidemiological evidence of benefit of non-steroidal anti-inflammatory drugs and aspirin in prevention of esophageal adenocarcinoma in patients with Barrett's esophagus

Ref.	Type of study	Size-follow-up	Effect on EAC rate	Beneficial effect
Abnet *et al*[36]	Population based	311115 AARP members	Aspirin OR = 1.1 (0.78-1.57) Non-aspirin NSAIDs OR = 0.90 (0.55-1.43)	None
Tsibouris *et al*[23]	Case-control	BE: 382 EAC: 114	Daily use of non-aspirin NSAIDs OR = 0.30 (0.10-0.91) Daily use of low-dose aspirin OR = 1.21 (0.52-2.83)	Non-aspirin NSAIDs
Beales *et al*[37]	Case-control	BE: 170 EAC: 85	Statins + aspirin OR = 0.31 (0.04-0.69)	Statins + aspirin
Nguyen *et al*[38]	Case-control	BE: 696 EAC: 116	All NSAIDs OR = 0.64 (0.42-0.97)	All NSAIDs
Vaughan *et al*[39]	Cohort	BE: 350 1731 PY	All NSAIDs OR = 0.20 (0.10-0.41)	All NSAIDs
Kastelein *et al*[40]	Cohort	BE: 570 4.5years	Non-aspirin NSAIDs OR = 0.50 (0.26-0.97) Aspirin OR = 0.67 (0.31-1.46)	Non-aspirin NSAIDs
Nguyen *et al*[41]	Cohort	BE: 344 2620 PY	All NSAIDs OR = 0.51 (0.25-1.04)	None
Gatenby *et al*[42]	Cohort	BE: 650 3683 PY	Non-aspirin NSAIDs OR = 0.90 (0.34-2.37) Aspirin OR = 0.72 (0.41-1.31)	None
Kantor *et al*[43]	Cohort	BE: 411 2805 PY	All NSAIDs OR = 0.46 (0.34-1.10)	None

PY: Patient years; EAC: Esophageal adenocarcinoma; BE: Barrett's esophagus; NSAIDs: Non-steroidal anti-inflammatory drugs.

prospective study is running in the United States[45]. In the only prospective interventional study published today, Heath *et al*[46] randomized 100 patients who had either low or high-grade dysplasia and BE to receive either a COX-2 selective NSAID (celecoxib) or placebo. After 48 wk of treatment, there was no significant difference between the 2 groups in the proportion of esophageal biopsy specimens showing dysplasia or cancer[46]. This study has limitations (*e.g.*, the use of dysplasia as the primary outcome, the use of a low dose of celecoxib) that prevent definite conclusions on the utility of NSAID chemoprevention.

Although all case control studies have shown that NSAID use is beneficial, there is considerable diversity concerning NSAID subclasses that could reduce EAC risk. Our case control study has shown that daily use of non-aspirin NSAIDs was beneficial; while a daily low dose, as well as infrequent use of either aspirin or non-aspirin NSAIDs, was not[23]. Beales *et al*[37] found that statin and aspirin combination reduced incidence of EAC and Nguyen *et al*[38] that all NSAIDs are beneficial, without a separate report of NSAID subclasses.

Cohort study results are more diverse. Vaughan *et al*[39] found that, comparing current NSAID users to those who never used, NSAIDs had a significantly decreased risk of EAC. Kantor *et al*[43] reported that non-aspirin NSAID use reduced the risk of neoplastic progression but not aspirin use. The other 3 cohort studies were negative[41-43], although Kantor found that NSAID use was beneficial only for patients with high-grade dysplasia. A pooled analysis of 6 population-based studies within the Barrett's and Esophageal Adenocarcinoma Consortium have shown that daily NSAID use can reduce the risk of developing EAC by more than 40% (OR = 0.56, 95%CI: 0.43-0.73, $P < 0.001$)[47]. A meta-analysis of all published observational studies calculated the pooled effect size for COX-inhibitors to 0.59 (95%CI: 0.45-0.77) with minimal heterogeneity[48].

Many of the observational studies have inherent limitations because not all confounding variables (such as socioeconomic status, tobacco and alcohol use, *H. pylori* status, dietary intake) have been taken into account, especially in case-control studies. Use of aspirin and/or NSAIDs may have been associated with certain patient-led behaviors that have an influence on risk. Such behaviors may include vitamin supplementation[49] and dietary habits. Furthermore, patients on aspirin may indeed have been more health conscious and might have been more likely to have their cancers detected than others. Finally, it is likely that those with upper gastrointestinal symptoms such as heartburn and regurgitation, risk factors for EAC, are less likely to have been prescribed NSAIDs or aspirin. The use of acid-reducing agents with the sole aim of reducing BE has not been proven in a long-term controlled trial[45]. Although most studies suggest a synergy between sufficient acid suppression and NSAIDs chemopreventive effect[38,40], we have shown that NSAIDs could be effective despite financially driven reduction of proton pump inhibitor treatment[23].

Typically, diagnosis of BE is made in men older than 50 years of age, a group with elevated frequency of cardiovascular disease. Low-dose aspirin is beneficial for primary cardiovascular events in men older than 50 years of age who are at risk of developing coronary artery disease[50-52]. Today, data concerning BE patients with ischemic heart disease are scarce. We have reported that low-dose aspirin could reduce the risk of EAC in BE patients with ischemic heart disease, but it had no beneficial effect in patients without cardiovascular co-morbidities[53], possibly due to cofactors common to the etiology of ischemic heart disease and EAC, such as alcohol, tobacco, diet and exercise.

Limited data suggest that biomarkers might have a role in identifying those patients with BE who are most likely to benefit from chemopreventive therapies. In BE patients with DNA content abnormalities, such as 17p loss of heterozygosity (LOH), and/or 9p LOH in their esophageal biopsy specimens, NSAID use was associated with a significant reduction in the risk of EAC after 6-10 years of follow-up. In contrast, no beneficial effect was seen in patients without those abnormalities[54].

MECHANISMS OF NSAID CHEMOPREVENTIVE EFFECT

Esophageal carcinogenesis is mainly related to the inflammatory process in macroscopically visible Barrett epithelium, due to persistent gastroesophageal reflux[47] in addition to angiogenesis up-regulation[55]. The inflamed mucosa produces several inflammatory intermediates. Interleukin-1 and tumor necrosis factor induce nuclear factor (NF)-κB over-expression[56]. After activation, NF-κB translocates to nucleus, where it activates gene transcription[57]. In BE patients, NF-κB binds the promoter region of *COX-2* gene, increasing COX-2 expression[58]. Most observational studies suggest that NSAIDs, in doses adequate to suppress COX-2, can effectively prevent BE progression to EAC[23,37-40].

Reactive oxygen species may damage DNA, RNA, lipids and proteins, leading to increased mutation and altered functions of enzymes and proteins (*e.g.*, activation of oncogene products and/or inhibition of tumor suppressor proteins). They also related to cellular immunity, signal transduction and modification of extracellular matrix. In normal esophagus, low levels of reactive oxygen species are produced in non-phagocytic cells and are thought to be by-products of aerobic metabolism[59]. Pulsed acid treatment and bile significantly increases H_2O_2 production in BE cells *via* NADPH oxidase NOX-5-S overexpression. It also increases calcium ion influx and cyclic adenosine monophosphate (AMP) reactive element binding protein[60,61]. Increased cellular calcium ion influx causes up-regulation of NADPH oxidase NOX5-S[62]. Overproduction of reactive oxygen species derived from up-regulation of NADPH oxidase NOX5-S, as well as H_2O_2 overproduction, can up-regulate NF-κB[63] and as a result leads to COX-2 over-expression[64].

Because acid and bile contents of refluxate represent the main driving forces for COX-2 over-expression in BE patients[65] and because proton pump inhibitors enhance COX-2 anti-proliferated effect *in vitro* and prevent vascular endothelial growth factor overexpression[66], acid suppression should be an essential cofactor of EAC chemoprevention. This suggestion is also supported by epidemiological data[38,40,45].

COXs (or prostaglandin H synthases) are a family of myeloperoxidases located at the luminal side of the endoplasmic reticulum and nuclear membrane, which catalyze the rate-limiting step of prostaglandin biosynthesis from arachidonic acid[67]. COX-2 induction or over-expression is associated with an increased production of prostaglandin E2 (PGE2), which is known to modulate cell proliferation, cell death and tumor invasion in many types of cancer. In addition to COX overexpression, pulsed acid exposure can up-regulate microsomal PGE synthase 1 and through it, PGE2 production and cell proliferation. Acid-induced microsomal PGE synthase 1 over-expression depends on NADPH oxidase 5S activation and NF-κB1 over-expression[68] and it is regulated through the increase of cytosolic calcium[69]. Epidemiological data suggest that the acid related route of PGE2 production is of minor importance since COX-2 inhibitors can be effective even under inadequate acid suppression[23].

PGE2 acts through different membrane receptors called EP receptors (EP1, EP2, EP3 and EP4). These receptors are all located on the cell surface but trigger different signaling pathways. Thus, it is known that EP1 signaling acts through phospholipase C/inositol triphosphate signaling, leading to intracellular mobilization of calcium. EP2 and EP4 receptors are coupled with G proteins and activate adenylate cyclase, leading to an increase of intracellular cyclic AMP[70]. Cyclic AMP is then able to activate various kinases, such as protein kinase A, phosphoinositide-3 kinase and glycogen synthetase kinase-3, leading to an activation of β-catenin, a pathway regulating cell proliferation[71]. Contrary to EP2 and EP4, EP3 is coupled with Gi protein, leading to an inhibition of adenylate cyclase and decreases of cAMP inside the cells[70]. Dietary elements entering arachidonic acid metabolism can interfere with PGE2[49] and therefore they should not be overlooked. Unfortunately, almost all epidemiological studies ignore this parameter[23,37-43].

Cell circle regulatory mechanisms form checkpoints where the cell cycle can be stopped after cellular damage in order to allow repair and to maintain cellular integrity or, alternatively, to eliminate mutated and potentially dangerous cells. Different serine-threonine kinase proteins called cyclin-dependent kinases (Cdk) are important cell circle regulators. They interfere with the cell cycle by phosphorylating many substrates[72]. The inhibitors of cyclin kinase 4 (INK4) family (p16, p15, p18 and p19) and the Cip/Kip family (p21, p27 and p57)[72,73] are key regulators of cell transition from G1 to S phase. INK4 family inhibits Cdk4 and Cdk6, whereas Cip/Kip family inhibits all Cdks. After DNA damage, p53, a tumor suppressor gene, activates transcription of p21, which inhibits cyclin E phosphorylation, leading to hypophosphorylation of retinoblastoma protein[71]. After phosphorylation, retinoblastoma protein releases transcription factor E2F activating genes involved in the S phase-like proliferating cell nuclear antigen[74]. p53 also regulates cell transition from G_2 to M phase through cyclin B-Cdk 2 complex activation. Cyclin B-Cdk 2 complex accumulates during the previous step of the cell cycle. It is inactivated by phosphorylation at tyrosine 15 and threonine 14 by Wee 1 and Myt 1 and can be reactivated when these phosphate groups are removed by the phosphatase CDC25A, a cyclin related phosphatase, when cells enter mitosis[75].

COX-2 up-regulation increases Barrett's epithelium

and esophageal adenocarcinoma cell proliferation by induction of retinoblastoma tumor suppressor protein phosphorylation and up-regulation of cyclins, cyclin-dependent kinases[76] and p53 LOH[77]. NSAIDs could also increase the proportion of Barrett cells in G_0-G_1 phase and reduce those in S and G_2-M phase[78,79].

Two major cascades of intracellular events are commonly involved in mediating apoptosis. (1) The intrinsic pathway, also called the mitochondrial or stress-induced apoptotic pathway, which is activated in response to damaging stresses; and (2) the extrinsic, or physiological, apoptotic pathway. Typical hallmarks of the intrinsic pathway are mitochondrial outer membrane permeabilization, accompanied by a collapse of the mitochondrial membrane potential[80]. These events lead to the release of cytochrome *c* into the cytosol and the death complex formation by apoptotic protease activating factor-1 and procaspase-9. Once recruited, procaspase-9 is cleaved to its activated form (caspase-9) to further activate the executor caspase-3 and to finalize the apoptotic program. The intrinsic pathway can be triggered upon binding of specific ligands to death receptors characterized by the presence of a death effector domain[81]. Ligands include cytokines, such as tumor necrosis factor α, tumor necrosis factor-related apoptosis inducing ligand-induced apoptosis or Fas. After binding, death inducing silencing complex is formed. The adaptor proteins, tumor necrosis factor receptor-associated death domain and Fas associated death domain, form the death inducing silencing complex that is able to recruit and activate pro-caspase-8. The latter activates caspase-3 in order to trigger the final steps of apoptosis.

Cross talks between the two pathways take place. The extrinsic apoptotic pathway can activate the intrinsic pathway *via* truncation of the BH3-only protein Bid by caspase-8. BH3-only protein Bid interacts with mitochondria, by favoring the activation of the pro-apoptotic Bcl-2 family members Bak and Bax, thus leading to mitochondrial outer membrane permeabilization and caspase-9 activation[80]. The intrinsic apoptotic pathway may, in turn, activate caspase-8, downstream to caspase-3[82]. NSAIDs can inhibit programmed cell death in BE cells *via* prevention of Bcl-2 suppression[83], a key checkpoint in COX-2 controlled apoptotic cascade[84].

Anoikis is a form of apoptosis mediated by the loss of cell anchorage. This pathway plays a fundamental role during development and maintenance of tissue homeostasis by killing damaged cells or detached cells in order to maintain tissue architecture. It is dependent on caspase activation and cytochrome *c* release by mitochondria and is regulated by Bcl-2 family members[71]. Cell anchorage is due to cell-cell and cell-matrix interactions. Cell-cell interactions are mainly mediated by integrins, transmembrane receptors located at the cell surface[85]. Many intracellular signals can act downstream to integrins, which, correctly switched on, can ensure cell survival. Some of them are mediated by kinases such as focal-adhesion-kinase or integrin-linked kinase. Focal-adhesion-kinase is phosphorylated upon integrin adhesion, leading to activation of other signaling pathways like phosphoinositide 3 kinase and mitogen-activated protein kinase (MAPK)[71].

NSAIDs can up-regulate MAPK signaling cascade[86] through Cl/HCO3 membrane exchange channel after intracellular acidification[87]. COX-2 inhibitors can regulate mesenchymal-epidermal cross talk[88]. In non-dysplastic Barrett, COX-2 is selectively increased only in stromal cells, while in adenocarcinoma it is also increased in neoplastic epithelium[89,90].

COX-2 can also regulate the expression of angiogenetic factors, especially vascular endothelial growth factor[90], mainly through a MAPK dependent pathway[91]. Because reactive oxygen species are overproduced in the ischemic tissue[92] and various angiogenic factors are abundant in patients with cardiovascular diseases[93], NSAIDs are expected to be more effective in this patient group. Nevertheless, non-aspirin NSAID are not effective in BE patients with ischemic heart disease, while aspirin is especially effective in this patient group[53].

Although low-dose aspirin clearly prevents EAC when prescribed in healthy controls, it suppresses COX insufficiently[34]. Thus, apart from COX-related, there are also other mechanisms implicated in NSAID chemopreventive action. Epidemiological data doubt the significance of COX-independent mechanisms[23,37-43].

Independently to COX, NSAIDs can bind and inhibit protein kinase B/Akt, an important mediator of cell proliferation and in apoptosis. Protein kinase B is able to phosphorylate Cdk inhibitors, such as p21 and p27, leading to proliferating cell nuclear antigen activation[94]. Moreover, it inhibits apoptosis by phosphorylating the pro-apoptotic protein Bad and by inhibiting caspase-9 cleavage[80]. Independently to COX, NSAIDs can also activate the extrinsic apoptotic pathway by modulating the sensitivity of several tumor cells to Fas and tumor necrosis factor-related apoptosis inducing ligand[95]. They can also up-regulate Bax expression and mitochondrial cytochrome c translocation[96]. Finally, NSAIDs are able to decrease intracellular content of glutathione, the most important intracellular non-protein antioxidant defense against free radicals and, in such a way, affect both cell proliferation and apoptosis[97].

Although *in vitro* studies suggest that NO-aspirin is more effective than aspirin to prevent Barrett cell hyperproliferation[98], this did not prove to be the case in a clinical study[23].

COST-EFFECTIVENESS AND SIDE EFFECTS OF NSAIDS CHEMOPREVENTION

Assuming that aspirin use can reduce EAC development risk by 50% in BE patients, the cost of the chemo-preventive intervention was calculated to 40000 Euros for every quality year of life saved[28].

NSAIDs clearly have substantial potential for toxic-

ity, including serious gastrointestinal and cardiovascular side effects that should be balanced with their potential cancer-preventive effects. Generally the risk for low-dose aspirin is low. A meta-analysis of randomized controlled trials comparing low-dose aspirin (75-325 mg) and placebo for cardiovascular prophylaxis found that the absolute annual increase in risk attributable to aspirin was only 0.13% (95%CI: 0.08-0.20) for major bleeding, 0.12% (95%CI: 0.07-0.19) for major gastrointestinal bleeding, and 0.03% (95%CI: 0.01-0.08) for intracranial bleeding[99]. Moreover, concomitant proton pump inhibitor therapy could reduce the risk of gastrointestinal bleeding by a factor of 2 to 9[100,101].

We have shown that complications, including upper gastrointestinal bleeding, esophageal ulcers and benign esophageal strictures, were no more common in NSAID users with BE than NSAID non-users. Moreover, the majority of those complications were acid related and could be prevented by adequate acid suppression, preferentially with high dose proton pump inhibitors. On high dose proton pump inhibitors, only 14% of BE patients consuming NSAIDs presented with any complication[23]. In accordance to our findings, Hillman *et al*[102] have shown that esophageal ulcers and stenosis can be effectively prevented with adequate acid suppression[102].

Because thromboxane biosynthesis depends on sustained inhibition of COX-1, several NSAIDs present serious cardiovascular side effects. In the two meta-analyses published today, major vascular events were increased by about a third for COX-2 selective and non-selective NSAIDs, with the exception of naproxen. Analyses showed that the excess risk was mainly attributable to an increase of about three quarters in the risk of major coronary events. Vascular death increased by about two-thirds, heart failure risk roughly doubled, while risk for stroke was not affected[103,104].

Nitro-NSAIDs represent an NSAID subclass with lower risk for gastrointestinal bleeding[105]. We have shown that combination of NSAID use to nitrates in BE patients neither affected EAC risk nor improved NSAID safety profile[23].

STATINS AND EAC CHEMOPREVENTION

Cellular effects of statins on EAC cell lines have been evaluated in three *in vitro* studies. All reported anti-proliferative and pro-apoptotic effects[106-108]. Qresearch, a prospective study based on 24 general practice research databases from England and Wales, have shown that statins were protective against esophageal cancer development in both men and women. The risk of esophageal carcinoma decreased in both men and women prescribed simvastatin, as well as in men prescribed atorvastatin. There were inadequate data for other statins. There was some evidence of a dose-response associated with simvastatin in men only[109]. A more recent analysis of the same database revealed no protective effect from statin use[110]. An analysis of General Practice United Kingdom Research Database in 2002 that included only 9 esophageal carcinoma cases revealed no protective effected related to statin use[111]. Bhutta *et al*[112] case control study found that statin use was negatively associated with the development of esophageal carcinoma. Both lipophilic and hydrophilic statins were protective. The magnitude of this negative association was similar for time periods extending beyond one year. When statin use and cancer development was accessed through a health care program database from northern Calofornia, esophageal carcinoma was more common among statin users[113]. Population studies published today, although they have been adjusted for many covariates including age, body mass index, smoking, do not differentiate between EAC and squamous carcinomas and do not allow evaluation of statin use in EAC prevention.

Three population studies[110-112] were included in the meta-analysis of risk of esophageal carcinoma among general population cohorts with statin use. The pooled effect size was 0.86 (95%CI: 0.78-0.94, $P = 0.001$) with minimal heterogeneity[114]. A recent meta-analysis of all published studies calculated the pooled effect size for statins to 0.81 (95%CI: 0.75-0.88) with substantial heterogeneity[48].

Several observational studies evaluating NSAIDs chemopreventive effect have also analyzed the utility of statin use (Table 2). In their case control study, Beales *et al*[37] found that regular statin use was associated with a significantly lower incidence of EAC. Longer duration of statin use and higher doses were both associated with a significantly greater reduction in EAC. Kastelein *et al*[40] reported that statin use for greater than one mo was associated with a statistically significant inverse risk for neoplastic progression, although this was only observed in men over 60 years of age. The concomitant use of both statins and NSAIDs was associated with a greater risk reduction. Nguyen *et al*[41] reported that having any filled statin prescription was associated with 45% lower risk of EAC. Patients with a cumulative filled statin prescription for > 12 mo have a reduced risk of EAC compared to those with ⩽ 12 mo or those with no statin prescription. Kantor *et al*[43] found that statin use was not associated with a reduced risk of neoplastic progression in BE patients. Nevertheless, when the analysis was limited to persons with high-grade dysplasia at baseline, a subgroup at particularly high risk of EAC development, statin use was definitively protective. The combination of statins and NSAIDs was also protective. The main draw back of most observational studies was that authors did not adjust for important covariates, namely body mass index and smoking[40,41,43].

Kastelein *et al*[40] and Nguyen *et al*[41] cohort studies were included in the meta-analysis of risk of EAC. The pooled effect size was 0.53 (95%CI: 0.36-0.78, $P = 0.001$) with minimal heterogeneity[115]. A recent meta-analysis, including all 5 studies published today, calculated the pooled effect size for statins to 0.57 (95%CI: 0.43-0.75) with minimal heterogeneity. For the combination of statins and COX inhibitors, pooled effect size was 0.26 (95%CI: 0.10-0.68)[48].

Table 2 Available epidemiological evidence of benefit of statin use in prevention of esophageal adenocarcinoma in patients with Barrett's esophagus

Ref.	Type of study	Size-follow-up	Effect on EAC rate	Beneficial effect
Hippisley-Cox *et al*[109]	Population based	General population 2004692 cases	Statins Men[1] OR = 0.78 (0.66-0.91) Women[1] OR = 0.68 (0.52-0.88) Simvastatin Men[1] OR = 0.69 (0.50-0.94) Women[1] OR = 0.82 (0.68-0.99) Atorvastatin Men[1] OR = 0.73 (0.55-0.96) Women[1] OR = 0.73 (0.47-1.13)	Statins[1]
Vinogradova *et al*[110]	Population based	General population 2004692 cases	Statins[1] OR = 0.88 (077-1.01)	None[1]
Kaye *et al*[111]	Population based	Esophageal cancer: 9	Statins[2] OR = 0.8 (0.3-1.8)	None[2]
Bhutta *et al*[112]	Population based	Esophageal cancer: 4242 Controls: 17233	Statins[1] OR = 0.84 (0.73-0.95) Lipophylic statins[1] OR = 0.86 (0.75-0.98) Hydrophilic statins[1] OR = 0.71 (0.51-0.98)	Statins[1]
Beales *et al*[37]	Case-control	BE: 170 EAC: 85	Statins OR = 0.57 (0.28-0.94)	Statins
Kastelein *et al*[40]	Cohort	BE: 570 4.5 years	Statins OR = 0.46 (0.21-0.99) Statins + NSAIDs OR = 0.22 (0.06-0.85)	Statins Statins + NSAIDs
Nguyen *et al*[41]	Cohort	BE: 344 2620 PY	Statins OR = 0.55 (0.36-0.86)	Statins
Kantor *et al*[43]	Cohort	BE: 411 2805 PY	Statins OR = 0.68 (0.30-1.54) Statins + NSAIDs OR = 0.41 (0.13-1.26)	Statins + NSAIDs

[1]Results pertain to esophageal carcinoma; [2]Results pertaining to all cancers. PY: Patient years; EAC: Esophageal adenocarcinoma; BE: Barrett's esophagus; NSAIDs: Non-steroidal anti-inflammatory drugs.

At present, there are no published observational studies evaluating statin chemopreventive effect in BE patients in the general population. Moreover, there are no interventional studies underway.

MECHANISMS OF STATIN CHEMOPREVENTIVE EFFECT

Statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in the biosynthesis of cholesterol. Although this is their most appreciated biological action, statins have several other important roles. They inhibit biosynthesis of L-mevalonate[116], a precursor of cholesterol, and they produce two isoprenoid intermediates: farnesyl pyrophosphate and geranylgeranyl pyrophosphate[117]. Farnesyl pyrophosphate and geranylgeranyl pyrophosphate attach to several cellular proteins including G proteins by a posttranslational modification termed isoprenylation. The isoprenylation of G proteins is crucial for membrane attachment and normal functioning. The low molecular weight G proteins, including Ras, Rho, Rab and Cdk 42, play crucial roles in signal transduction and therefore influence important cellular functions, such as proliferation, apoptosis and differentiation. Ras represents the most important G protein and is predominantly farnesylated, while all other GTPases are predominantly geranylated. Ras mutations in preneoplastic cells determine their susceptibility to statin treatment[118]. Because Ras in EAC cells is very susceptible to statin treatment[106], statins are very effective in all available epidemiological studies[37,40,41,43].

Ras pathway down-regulation could reduce phosphoinositide 3 kinase/Akt and extra-cellular signal regulating kinase activities, enhancing cell proliferation and modulating cell-cell interactions. Moreover, it up-regulates the pro-apoptotic proteins Bad and Bax through phosphoinositide 3 kinase/Akt pathway, preventing cell apoptosis[106,107,118-120]. Through Ras modification, statins attenuate total cellular and cell-surface intracellular adhesion molecule-1 expression and activate NF-κB[121].

Through a G-protein independent mechanism, statins can suppress angiogenesis. Angiogenesis inhibition is a result of the inhibition of the expression or activity of monocyte chemoattractant protein-1, inhibition of metalloproteinase, angiotensin-2, preproendothelin gene, as well as inhibition of actin filament and by focal adhesion molecules formation[122]. Finally, they present with an anti-inflammatory effect by reducing tumor necrosis factor-alpha[107] and intracellular adhesion molecule-1 (a critical adhesion molecule involved in transendothelial tumor cell migration)[123,124].

Because statins do not interfere with various proliferation pathways, such as MAPK pathway and transcription factor AP1/c-jun terminate kinase[106], NSAIDs can enhance statin chemopreventive effect by blocking those metabolic routes[125]. As a result, whenever statins and NSAIDs are combined, lower doses of either chemopreventive agent are necessary, leading to a reduction of side effects[106]. Current epidemiological data unanimously verify NSAID and statin synergy[37,40,41,43].

Because adiponectin and ghrelin can interfere in vitro with EAC cell apoptosis[126], obesity, a parameter overlooked by most observational studies[40,41,43], mandates further attention.

SIDE EFFECTS OF STATIN CHEMOPREVENTION

Statins are generally safe medications. Out of the various adverse effects of statins, only liver and muscle-related toxicity is consistently reported[127]. Between 1987 and 2001, the Food and Drug Administration (FDA) recorded 42 deaths from rhabdomyolysis induced by statins, translated to one death per million prescriptions (30 day supply). Although 5%-10% of patients complain of muscle symptoms, only 1%-3% of them are actually statin related. Muscle symptoms usually occur within the first 6 mo of starting statins but can occur months or years after the initiation of statin therapy and automatically resolve within 2 mo of discontinuing statin therapy[128]. The incidence of statin-associated myopathy is quite low (approximately 0.01%) and rhabdomyolysis even lower (0.002%)[129]. Fatal rhabdomyolysis has been estimated to occur in approximately 1.5 in 10 million prescriptions[130].

Post-marketing surveillance studies of statins revealed that elevation in hepatic aminotransferases are dose related, mild and unrelated to low-density lipoprotein lowering effect. Thus, most hepatologists no longer consider statins to have any significant hepatotoxicity[131]. Although serious hepatotoxicity is rare, 30 cases of liver failure associated with statin use were reported to the FDA between 1987 and 2000, the rate being about one case per million person-years of use. Thus, the occurrence of acute liver failure thought to be caused by statins is well below the background rate of idiopathic acute liver failure in the general population[132].

Evidence from four cohort studies and case reports suggest that statins cause reversible peripheral neuropathy. Nevertheless, the attributable risk is small (12 per 100000 person-years) and no change in cognitive function was found in randomized trials of statins in elderly patients[130].

Because BE patients are usually old with various multi-systemic comorbidities[36], increased toxicity is expected[133] with statin use. No study today has specifically addressed statin toxicity in BE patients.

FUTURE DIRECTIONS

The poor prognosis of patients diagnosed with EAC presents a challenge to the clinician. Consequently there is burgeoning interest in potential chemo-preventive strategies. Considerable evidence of medium quality is available of a protective effect of NSAIDs, yet because of their side-effect profile, widespread use cannot be currently justified. Although statin safety profile is good, epidemiological and animal data are limited to justify their use as chemo-preventive agents. Because mortality due to cardiovascular disease is high in BE patients, "technical review on the management of Barrett's esophagus today" suggests screening for cardiovascular factors in BE patients and aspirin and statin use as warranted[45]. Because we have shown no benefit for non-aspirin NSAID use in BE patients with ischemic heart disease[53] and substantial cardiovascular side effects are expected[103,104], use of non-aspirin NSAIDs should be withheld in patients with BE and cardiovascular co-morbidities, at least until more clinical data might justify their use.

Large randomized control trials in the near future are expected to safely evaluate NSAIDs and statins as chemopreventive agents and possibly introduce their widespread use in patients with BE. Because of their synergistic effect[106], such trials ought to test either and both medications against proton pump inhibitors alone.

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