Review Article

Aspirin acts in esophageal cancer: a brief review

Weiming Hao[1], Yaxing Shen[2], Mingxiang Feng[2], Hao Wang[2], Miao Lin[2], Yong Fang[2], Lijie Tan[2]

[1]Shanghai Medical College, [2]Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China

Contributions: (I) Conception and design: Y Shen, L Tan; (II) Administrative support: M Feng; (III) Provision of study materials or patients: H Wang, M Lin; (IV) Collection and assembly of data: Y Shen, W Hao; (V) Data analysis and interpretation: W Hao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yaxing Shen, MD. Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China. Email: shen.yaxing@zs-hospital.sh.cn.

Abstract: Improved survival in esophageal cancer patients with regular aspirin use have been reported. However, with conflicting experimental results existed, an explicit definition on the role of aspirin as an adjuvant chemotherapy of esophageal cancer remains unestablished. We have summarized the current epidemiologic trials evidence over antitumor effect of aspirin in esophageal cancer in the past decades, and most of the clinical data supports that long-term regular aspirin use could reduce the mortality and improve the survival in patients with esophageal cancer. Although most of the clinical trials of aspirin on esophageal cancer are designed focusing on the prediagnosed chemo-preventive role, other than the post-diagnosed therapeutic role, it has been suggested by some studies that aspirin use as an adjuvant treatment after the standard surgery in esophageal cancer may benefit more. In the meanwhile, post diagnosed aspirin use may lead to lower risk of hemorrhage and other side effects of NSAIDs. Potential involved molecular pathways in the antitumor activities of aspirin are under studied worldwide for years and the possible mechanisms so far are reviewed in this article as cyclooxygenase (COX)-dependent pathways and COX-independent pathways, involving anti-inflammatory activity, apoptosis, platelet deactivation, PIK3CA mutation specificity and heparanase-related microenvironment changes of tumor cells. NOSH-aspirin has been developed as a succedaneum of aspirin with a wider application ranges by reducing the risk of hemorrhage in aspirin users. Further clinical and basic studies are suggested focusing on whether regular aspirin use as an adjuvant treatment prolongs survival and prevents recurrence in patients with esophageal cancer.

Keywords: Aspirin; esophageal cancer; adjuvant chemotherapy; cyclooxygenase; PIK3CA mutation; heparanase; NOSH-aspirin

Submitted Jan 06, 2018. Accepted for publication Feb 27, 2018.
doi: 10.21037/jtd.2018.03.110
View this article at: http://dx.doi.org/10.21037/jtd.2018.03.110

Introduction

With the increasingly high incidence and mortality rates of esophageal cancer (1-4), standard multidisciplinary therapy consisting of esophagectomy and perioperative therapy is highly recommended, while has not been well established. Preoperative fluorouracil-based chemotherapy and chemoradiotherapy are two mainly accepted standard therapies for patients diagnosed as local advanced esophageal cancer (5-7). However, the prognosis of the patients with esophageal cancer remains unsatisfactory, and conflicting results of well-designed and powered studies failed to show significant survival benefits in patients with standard neoadjuvant or adjuvant therapies (8-10). For the reasons above, studies focusing on new perioperative therapies have been receiving increasing attentions, when the antitumor possibility of aspirin emerged.

Powered evidences have been raised in past decades showing that regular low dose aspirin use may reduce the morbidity and mortality of cancers (11-17), mainly including gastrointestinal cancer, breast cancer, prostate cancer. There are growing evidence in recent years suggesting that aspirin

could reduce the mortality in patients with esophageal cancer, especially after diagnosed or treated by standard therapy like esophagectomy (11,18,19). In spite of many efforts made, the molecular mechanisms of antitumor effect of aspirin remain unclear. Hereby we make a review of the recent clinical and biological evidences on the antitumor effect of aspirin in esophageal cancer, especially in patients who have received esophagectomy, and have a further discussion on the possible antitumor mechanisms of aspirin.

Aspirin and esophageal cancer

Antitumor effect of aspirin

As a salicylic acid drug, aspirin has been widely used for anti-inflammation, analgesia and prevention of cardiovascular disease. Its new role in antitumor field has only become apparent recently. In 1988, the study of Kune *et al.* (20) showed a significantly lower risk in developing colon cancer in patients with regular aspirin use than non-users which indicates the possibility of the association between aspirin and malignant tumors. Rothwell and his colleagues evaluated the cancer death based on several clinical trials (11,15,21-23) and found an aspirin-related improvement of overall survival in the participants [odds ratio (OR) 0.85, 95% confidence interval (CI), 0.76–0.96; P<0.05]. Among cancer patients who had taken low dose aspirin for over 5 years, a significant decrease of cancer risk was stated, and the antitumor effect of aspirin was positively correlated to the duration of drug use (21).

Antitumor effect of aspirin in patients with esophageal cancer

With these inspiring results in colorectal cancer, the association between aspirin and esophageal cancer receives more and more attention this century. In 2003, a systematic meta-analysis of nine studies (two cohorts, seven case controls) containing 1,813 cases indicated a protective role of aspirin for esophageal cancer, both esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (OR =0.5, 95% CI, 0.38–0.66) (24). Later in 2006, a hospital-based case control study with consistent frequency and duration of drug use of aspirin designed by Jayaprakash *et al.* found a significantly lower risk of esophageal cancer in regular aspirin users compared to non-users (OR =0.54; 95% CI, 0.36–0.86) (25). Studies on antitumor effect of aspirin are focusing on the prevention both of occurrence and recurrence of the disease, and it has been showed post diagnosed aspirin use is more likely to be associated with higher survival rates in patients with esophageal cancer (26). In this regard, it is suggested aspirin could be developed as an adjuvant treatment in patients with cancer (18).

Aspirin as adjuvant treatment in patients with esophageal cancer

Studies on antitumor strategies in other solid tumors such as colorectal cancer, has recommend aspirin as adjuvant chemotherapy after potentially curative surgeries (19). In patients with esophageal cancer, Liu and his colleges had evaluated the antitumor effect of aspirin as an adjuvant treatment in 1,716 patients in China who had underwent esophagectomy for ESCC or adenocarcinoma (18). The result of their study supported, although not confirmed, that aspirin could be used in patients with esophageal cancer as an adjuvant chemotherapy following the standard surgery.

van Staalduinen *et al.* also reported that aspirin works better as an adjuvant chemotherapy than neoadjuvant therapy based on analysis of overall mortality. In patients who had undergone esophagectomy, the risk ratio of the group followed by aspirin treatment versus non-aspirin use group was 0.40 (95% CI, 0.20–0.79) while in the patients who received no esophagectomy the risk ratio was 0.45 (95% CI, 0.31–0.66). Moreover, the survival in patients who had only received post-diagnosis aspirin treatment was better than those had received both pre-diagnosis and post-diagnosis aspirin treatment, which could be explained by the hypothesis that the tumor in pre-diagnosis users has survived in presence of aspirin in plasma, it would also survive the similar dose after post-diagnosis aspirin treatment (26). As for the difference based on different histological types of esophageal cancer, Staalduinen *et al.* studied two major histological types of esophageal cancer in 560 patients observational study and made a stratified survival analysis in the aspirin use group, which showed that participants with ESCC [risk ratio (RR) 0.34, 95% CI, 0.18–0.63; P<0.001] are under lower risks of cancer death compared to the participants with adenocarcinoma (RR 0.43, 95% CI, 0.28–0.65; P<0.001). It is not clear which mechanism contributes to this difference.

However, conflicting results have been reported in the oncological efficacy of aspirin. Another two large cohort studies in England (27) contained 4,654 esophageal cancer patients and 3,833 gastric cancer patients showed that the cancer mortality proportions of participants surviving 1 year

were similar in aspirin users versus non-users after diagnosis with esophageal cancer (48% *vs.* 50% in England and 49% *vs.* 46% in Scotland, respectively) and this nonsignificant result may be explained by the short duration of aspirin use [pooled adjusted hazard ratio (HR), 1.03; 95% CI, 0.85–1.25].

To get more convincing evidence, a multicenter, double-blind, phase III randomized controlled trial with four parallel cohorts of breast, colorectal, gastro-esophageal and prostate cancer has been in progress in the United Kingdom (28). In this trial, some participants with standard potentially curative treatment for esophageal cancer, which refers to surgery with standard neo-adjuvant or adjuvant therapy, or only primary chemoradiotherapy, will receive regular different dose of aspirin as an adjuvant therapy. Higher quality of data and more reliable results are expected on this 5-year long trial named ADD-Aspirin investigating whether long-term regular aspirin use as adjuvant treatment would prolong survival and reduce mortality and recurrence in non-metastatic cancer patients.

Barrett's esophagus and aspirin

Barrett's esophagus is convinced to be a precursor of esophageal adenocarcinoma (29). The risk of developing into esophageal adenocarcinoma in Barrett's esophagus patients was 11.3 times higher than general population (95% CI, 8.8–14.4) (30). Although it is reported effective of aspirin in reducing the incidence of Barrett's esophagus-derived esophageal adenocarcinoma (31), epidemiological evidences of aspirin on the risk of Barrett's esophagus remain inadequate to reach a definitive conclusion (32). Another nested case-control study failed to demonstrate the association between aspirin or non-aspirin NSAIDs and esophageal cancer (33). These findings indicate that the targeting procedures of antitumor activity of aspirin may be the neoplastic progression from Barrett's esophagus to adenocarcinoma or the metastasis of tumor cells other than the development into Barrett's esophagus from normal epithelial tissue.

In vitro and *in vivo*, Piazuelo *et al.* examined whether aspirin exert antitumor activity in esophageal adenocarcinoma. They found that *in vitro* cells, proliferation and migration of human esophageal adenocarcinoma cells were significantly inhibited and the apoptosis of the cells was promoted ($P<0.05$) by aspirin. In vivo, the progression of the esophageal cancer was lower in aspirin use mice than the non-aspirin use group. Maximum tumor inhibition in this study was 92% (low-dose group) and 85% (high-dose group), respectively (31).

Antitumor mechanisms of aspirin

COX-dependent mechanisms

Inhibition of cyclooxygenase (COX)-2

Epidemiological studies showed that approximately 25% of different types of tumor attribute to multi-determined chronic inflammation (34). One broad biological effect of aspirin is anti-inflammation based on the inhibition of cyclooxygenase (mainly including COX-1 and COX-2), for which reason it is earliest theorized that inhibition of COX-2 may be involved in the antitumor activity of aspirin (35). Chronic inflammation can activate specific transcription factors, which may participate in esophageal carcinogenesis through affect the activities of NF-κB and MAPK (36). NF-κB could inhibit the growth of cells through regulates kinases like IκB kinase, p38 MAPK, extracellular signal-regulated kinase, and cell-cycle-dependent-protein kinases (CDK) (36-38). Therefore, it is speculated that aspirin participates in the inhibition of inflammation-related carcinogenesis. Supporting clinical results has been reported showing that compared with the general population, regular aspirin users as well as other nonsteroidal anti-inflammatory (NSAIDs) drug users are under lower risks of developing esophageal adenocarcinoma (39).

In 1999, Zimmermann *et al.* (40) examined the expression of COX-2 in ESCC and esophageal adenocarcinoma and found positive COX-2 expression in most of the ESCC and adenocarcinoma cells. COX-2-derived prostaglandin E-2 (PGE-2) promotes the proliferation and apoptosis of cancer cells through different molecular pathways, including MAPK, PI3K and cAMP/PK pathways (41). As a COX-2 inhibitor, aspirin may not only affect the inflammatory pathologies but decrease the proliferation of different types of cancer cells through these interrelated signaling pathways as well. Furthermore, COX-2 has also been shown to be related to the development from Barrett's esophagus to esophageal adenocarcinoma (42,43), which explains why the probable targeting procedures in antitumor activity of aspirin is the neoplastic progression from Barrett's esophagus to adenocarcinoma other than the development into Barrett's esophagus from normal epithelial tissue (33).

The experiments *in vitro* and *in vivo* are made to evaluate the effect of aspirin in esophageal adenocarcinoma cells, which found decreasing levels of PGE-2 both intracellularly and in cell culture supernatants and supports the correlation of COX-2 dependent mechanisms and the antitumor effects of aspirin (31).

On the contrary, some other studies got results which

cannot be well explained by the inhibition of COX-2 mechanism. Studies of van Staalduinen *et al.* (26) noticed that non-aspirin NSAIDs have no significant effects on survival or mortality of cancer patients, only does the aspirin have, which suggested an aspirin-specific antitumor effect. Moreover, the aspirin drug concentration required for antitumor use in tumor cells is much higher than the concentration required to inhibit COX-1 or COX-2 expressions (44). It has been validated *in vitro* that aspirin could regulate proliferation and apoptosis of cancer cells through pathways irrespective to COX-1 or COX-2 (45). These findings above indicate that inhibition of cyclooxygenase may not be the only mechanism, or even the main mechanism involved in the antitumor activity of aspirin.

Inhibition of COX-1 and platelet activation

Aspirin is considered be able to diminish the metastatic potential through inhibites COX-1 expression in platelet. It can affect the platelet activations and further decrease the secretion of growth factors involved in the epithelial-mesenchymal transition of the tumor cells in circulation (46). Based on the mechanisms above, the COX-1 inhibitors could down-regulate the activation of platelets to affect the tumor progression (47). Platelets can help the tumor cells get rid of the immune elimination and make it easier for the tumor cells to arrest at the endothelium, accelerating the formation of a secondary lesions (47-49). Further, platelet aggregation can protect tumor cells from immunological attack in the circulation (49). The vascular endothelial growth factor (VEGF) from platelets accounts for 80% of the whole VEGF in circulation (50). The decrease in serum VEGF could not only reduce the angiogenesis to disturb the nutrients delivery to tumor cells, but also impede the formation of an appropriate microenvironment of the metastatic cells (51).

Based on five case-control studies (15), it was found that in aspirin users the cancer was less likely to have distant migration than in non-users. In the contrast, no difference in frequency in these studies has been seen between regional spread of esophageal cancer and local disease only, which further indicates that aspirin is more likely to affect the metastasis of tumor rather than the growth of primary cancer.

COX-independent mechanisms

Since more and more studies of aspirin and non-aspirin NSAIDs suggest that the antitumor effect seems to be aspirin-specific (26,52), new plausible mechanisms based on COX-independent biological effects of aspirin are raised recently.

PIK3CA mutation

Liao and his colleagues have reported two cohort studies of 964 patients with colorectal cancer and divided them into two groups based on PIK3CA types. According to their studies, longer survival was thought to be related with regular aspirin use in the colorectal cancer patients with mutated type of PIK3CA (HR for cancer death =0.18, 95% CI, 0.06–0.61; P<0.001), but not in the patients with wild type of PIK3CA (HR =0.96, 95% CI, 0.69–1.32; P=0.76) (53). This finding shows a clue related to varieties of PIK3CA in the antitumor activity of aspirin.

Mutation of PIK3CA can be found in several cancers, including esophageal cancer (54,55). It is speculated that PIK3CA mutations resulted in attenuation of apoptosis in tumor cells and promoted tumor invasion (54). 12.5% mutation in PIK3CA gene was reported in a cohort of 96 Chinese patients with esophageal SCC (55).

PIK3CA encodes a catalytic subunit of the phosphatidylinositol 3-kinases (PI3Ks) (54) and can phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2). As one of the downstream effector protein kinase of PIP2 phosphorylation, AKT plays a crucial role in the cell proliferation, apoptosis and motility (56). It is reported AKT activates in PIK3CA mutation and up regulates the cell proliferation (54). Over activated effects of AKT pathway in PIK3CA mutated individuals has been set up in mouse models first, showing strong activation in AKT pathway (57). In vivo, AKT activated RAS-induced senescence is found to be related with promoted progression of tumor (58).

Preclinical data on mice experiments shows that aspirin inhibits PI3 kinase activity by affecting COX-2 dependent mechanisms, supporting that the antitumor effect of aspirin might varies in different PIK3CA types (59). It is speculated that mutations of PIK3CA may influence the antitumor effects of aspirin as adjuvant treatment through regulating cell apoptosis and tumorigenesis (53). Furthermore, the results in a 96 cases observational study in China reported 12.5% mutation of PIK3CA in patients with ESCC (55), we may suspect that the PIK3CA status is also related to the antitumor effect of aspirin in ESCC and further investigations on esophageal cancer are suggested.

Heparanase

A recent study of Dai and her colleges suggested heparanase

participating in the antitumor activity of aspirin through affecting the metastasis and angiogenesis of tumor cells (60).

Heparanase works as a glucuronidase and degrades the heparan sulfate chain of heparan sulfate proteoglycans on the tumor cell surface and in the extracellular matrix (61). As the only heparan sulfate degrading endoglycosidase involved in extracellular matrix metabolism, the level of heparanase determines tumor cells microenvironment and thus facilitates the invasion and metastases of them (62).

Heparanase-based anti-metastatic and anti-angiogenic activities of aspirin were illustrated in Dai's study supporting by experiments *in vivo* and *in vitro*: aspirin acts upon heparanase and inhibits its enzymatic activities in cancer cells. For the anti-metastatic effect, aspirin could inhibit heparanase-related cell metastasis and invasion activities, which is proved to be COX-independent. For the anti-angiogenic effect, aspirin down-regulates heparanase-related VEGF levels which decreases tumor angiogenetic activity. They further verified the binding sites for aspirin in heparanase as Lys159 and Glu225, which may propose new inhibitors of heparanase by binding to these two sites (60).

Heparanase-based anti-metastatic and anti-angiogenic activities of aspirin may contribute to the explanation of the role of aspirin as adjuvant treatment in patients already having cancer other than as primary preventive method.

Side effects

As in the studies on cardiovascular disease, it is also concerned that the application of aspirin in cancer prevention or treatment may be limited by the side effects of this drug, particularly serious hemorrhage. Based on cohort studies and randomized clinical trials, Cuzick *et al.* concluded that regular aspirin use increases the risks of serious gastrointestinal bleeding (RR =3.1, 95% CI, 2.8–3.3), gastric or duodenal ulcer (RR =1.68, 95% CI, 1.51–1.88) and hemorrhage stroke in high-risk patients (RR =1.22, 95% CI, 1.03–1.44) (52). There are studies showed that the increased risk was mainly non-fatal bleedings, though. The incidence of fatal bleeding seems even lower in patients with aspirin versus those taking placebo drugs (OR =0.32, 95% CI, 0.12–0.83, P<0.05) (22). A few studies have evaluated the bleeding risk of aspirin use for antitumor as follows: Din's study showed no major bleedings were observed in patients taking NSAIDs regularly for antitumor (63); Liu also noted no side effects in participants with cancer, neither in the aspirin use group or the placebo group (18). The risk is thought to be related to the dosage of daily aspirin use and duration of treatment with this drug.

Moreover, concerned of the side effects of aspirin, Lee *et al.* has developed a safer aspirin succedaneum, NOSH-aspirin, a nitric oxide and hydrogen sulfide releasing hybrid (64). The cell growth inhibitory effects of NOSH-aspirin showed in their studies were dose-dependent and led to inhibitions of cell proliferation significantly. In xenografts, tumor volume decreased strikingly: colorectal cancer 89%, P=0.005; breast cancer 91%, P=0.006; pancreatic cancer 75%, P=0.003 (65).

The dosage of aspirin for antitumor use, an important point for both the antitumor effects and risk of bleeding, remains another controversy. The dosage of aspirin for antitumor effect varies from study to study. The daily dose of aspirin reported in Liu *et al.* study (18) was 50 mg per day, and it should be reduced to 25 mg per day in patients complaining any gastric discomfort. In ADD-aspirin trials (26), the patients under 75 years old are divided into three groups taking either 100 mg aspirin per day, 300 mg aspirin per day or placebos, while patients over 75 years old, are having either 100 mg aspirin or placebo. Consistency of aspirin taking shows better effect on reducing the risk of cancer (66). Rothwell *et al.* study used low dose aspirin for over 5 years and resulted a significantly reduction of cancer risk (21). The data on the dosage of aspirin use for antitumor effect by now is too limited to assess the dosage risks or duration risks. Further studies on the dosage would be necessary if the therapeutic role of aspirin in antitumor is confirmed.

Conclusions

Different clinical studies with well-quality evidences strongly indicate that aspirin plays a role in inhibiting the development of malignancy. Aspirin shows potentials to decrease the invasion and metastasis of tumor cells as chemo-treatment, especially adjuvant treatment of esophageal cancer. Conceivable mechanisms of the antitumor effect of aspirin involve COX-dependent pathways and COX-independent pathways, including COX-1, COX-2 related pathways, PIK3CA/AKT pathway, and heparanase-mediated mechanism, which may contribute to the antitumor activity of aspirin separately or interactively. NOSH-aspirin has been developed as a succedaneum of aspirin to reduce the risk of hemorrhage and other side effects in aspirin users. Further molecular biochemistry investigation and high quality clinical trials are highly

suggested on the antitumor effect of aspirin in patients with esophageal cancer.

Acknowledgements

Funding: This study was supported by National Nature Science Foundation for Young Scholars of China (Grant No. 81400681) and Foundation for Outstanding Young Scholars of Zhongshan Hospital (Grant No. 2017ZSYQ19).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Torre LA, Bray F, Siegel R, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Jemal A, Bray F, Center M, et.al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
3. Castro C, Bosetti C, Malvezzi M, et al. Patterns and trends in esophageal cancer mortality and incidence in Europe (1980-2011) and predictions to 2015. Ann Oncol 2014;25:283-90.
4. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. Lancet 2013;381:400-12.
5. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68-74.
6. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
7. Jones DR. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781 Tepper J, Krasna MJ, Niedzwiecki D, et al (Univ of North Carolina School of Medicine, Chapel Hill; Duke Univ, Durham, NC; Saint Joseph Cancer Inst, Towson, MD; et al) J Clin Oncol 26:1086-1092, 2008. Yearb Surg 2009;2009:365-6.
8. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979-84.
9. Saeed NA, Mellon E, Meredith K, et al. Adjuvant chemotherapy and outcomes in esophageal carcinoma. J Gastrointest Oncol 2017;8:816-24.
10. Malthaner RA, Wong R, Rumble R, et al. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. Bmc Med 2004;2:35.
11. Langley RE. Clinical evidence for the use of aspirin in the treatment of cancer. Ecancermedicalscience 2013;7:297.
12. Elwood PC, Morgan G, Pickering J, et al. Aspirin in the treatment of cancer: reductions in metastatic spread and in mortality: a systematic review and meta-analyses of published studies. PLoS One 2016;11:e0152402
13. Mills EJ, Wu P, Alberton M, et al. Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. Am J Med 2012;125:560-7.
14. Phillips I, Langley R, Gilbert D, et al. Aspirin as a treatment for cancer. Clin Oncol (R Coll Radiol) 2013;25:333-5.
15. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012;13:518-27.
16. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348:883-90.
17. Uddin S, Ahmed M, Hussain A, et al. Cyclooxygenase-2 inhibition inhibits PI3K/AKT kinase activity in epithelial ovarian cancer. Int J Cancer 2010;126:382-94.
18. Liu JF, Jamieson G, Wu T, et al. A preliminary study on the postoperative survival of patients given aspirin after resection for squamous cell carcinoma of the esophagus or adenocarcinoma of the cardia. Ann Surg Oncol 2009;16:1397-402.
19. Langley RE, Burdett S, Tierney J, et al. Aspirin and cancer: has aspirin been overlooked as an adjuvant therapy? Br J Cancer 2011;105:1107-13.
20. Kune GA, Kune S, Watson L. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer Res 1988;48:4399-404.
21. Rothwell PM, Fowkes G, Belch J, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31-41.
22. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet

2012;379:1591-601.
23. Rothwell PM, Price J, Fowkes F, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602-12.
24. Corley DA, Kerlikowske K, Verma R, et al. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology 2003;124:47-56.
25. Jayaprakash V, Menezes R, Javle M, et al. Regular aspirin use and esophageal cancer risk. Int J Cancer 2006;119:202-7.
26. van Staalduinen J, Frouws M, Reimers M, et al. The effect of aspirin and nonsteroidal anti-inflammatory drug use after diagnosis on survival of oesophageal cancer patients. Brit J Cancer 2016;114:1053-9.
27. Spence AD, Busby J, Johnston B, et al. Low-dose aspirin use does not increase survival in 2 independent population-based cohorts of patients with esophageal or gastric cancer. Gastroenterology 2018;154:849-60.e1.
28. Coyle C, Cafferty F, Rowley S, et al. ADD-ASPIRIN: A phase III, double-blind, placebo controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. Contemp Clin Trials 2016;51:56-64.
29. Cameron AJ, Souto E, Smyrk T. Small adenocarcinomas of the esophagogastric junction: association with intestinal metaplasia and dysplasia. Am J Gastroenterol 2002;97:1375-80.
30. Hvid-Jensen F, Pedersen L, Drewes A, et al. Incidence of adenocarcinoma among patients with Barrett's Esophagus. N Engl J Med 2011;365:1375-83.
31. Piazuelo E, Esquivias P, Martino A, et al. Acetylsalicylic acid exhibits antitumor effects in esophageal adenocarcinoma cells in vitro and in vivo. Digest Dis Sci 2016;61:2896-907.
32. Thrift AP, Anderson L, Murray L, et al. Nonsteroidal anti-inflammatory drug use is not associated with reduced risk of barrett's esophagus. Am J Gastroenterol 2016;111:1528-35.
33. Masclee GM, Coloma P, Spaander M, et al. NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus: a population-based case-control study. BMJ Open 2015;5:e006640.
34. Schetter AJ, Heegaard N, Harris C. Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. Carcinogenesis 2010;31:37-49.
35. Hanif R, Pittas A, Feng Y, et al. Effects of nonsteroidal anti-inflammatory drugs on proliferation and on induction of apoptosis in colon cancer cells by a prostaglandin-independent pathway. Biochem Pharmacol 1996;52:237-45.
36. Yousif NG, Al-Amran FG, Hadi N, et al. Expression of IL-32 modulates NF-κB and p38 MAP kinase pathways in human esophageal cancer. Cytokine 2013;61:223-7.
37. Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. Science 1994;265:956-9.
38. Karin M. NF-κB as a critical link between inflammation and cancer. Cold Spring Harb Perspect Biol 2009;1:a000141
39. Liao LM, Vaughan T, Corley D, et al. Nonsteroidal anti-inflammatory drug use reduces risk of adenocarcinomas of the esophagus and esophagogastric junction in a pooled analysis. Gastroenterology 2012;142:442-452.e5.
40. Zimmermann KC, Sarbia M, Weber A, et al. Cyclooxygenase-2 expression in human esophageal carcinoma. Cancer Res 1999;59:198-204.
41. Lin HR, Wu Y, Yen W, et al. Diminished COX-2/PGE2-Mediated Antiviral Response Due to Impaired NOX/MAPK Signaling in G6PD-Knockdown Lung Epithelial Cells. PLoS One 2016;11:e0153462.
42. Shirvani VN, Ouatu-Lascar R, Kaur B, et al, Triadafilopoulos G. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: Ex vivo induction by bile salts and acid exposure. Gastroenterology 2000;118:487-96.
43. Wilson KT, Fu S, Ramanujam K, et al. Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's esophagus and associated adenocarcinomas. Cancer Res 1998;58:2929-34.
44. Din FV, Valanciute A, Houde VP, et al. Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. Gastroenterology 2012;142:1504-15.e3.
45. Vogt T, McClelland M, Jung B, et al. Progression and NSAID-induced apoptosis in malignant melanomas are independent of cyclooxygenase II. Melanoma Res 2001;11:587.
46. Lou XL, Deng J, Deng H, et al. Aspirin inhibit platelet-induced epithelial-to-mesenchymal transition of circulating tumor cells. Biomed Rep 2014;2:331-4.
47. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123-34.
48. Gasic GJ, Gasic TB, Stewart CC. Antimetastatic effects

associated with platelet reduction. Proc Natl Acad Sci U S A 1968;61:46-52.
49. Stegner D, Dütting S, Nieswandt B. Mechanistic explanation for platelet contribution to cancer metastasis. Thromb Res 2014;133:S149-S157.
50. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353-64.
51. Kaplan RN, Riba R, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 2005;438:820-7.
52. Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009;10:501-7.
53. Liao X, Lochhead P, Nishihara R, et al. Aspirin Use, Tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med 2012;367:1596-606.
54. Samuels Y, Diaz L, Schmidt-Kittler O, et al. Mutant PIK3CA promotes cell growth and invasion of human cancer cells. Cancer Cell 2005;7:561-73.
55. Hou J, Jiang D, Zhang J, et al. Frequency, characterization, and prognostic analysis of PIK3CA gene mutations in Chinese esophageal squamous cell carcinoma. Hum Pathol 2014;45:352-8.
56. Katso R, Okkenhaug K, Ahmadi K, et al. Cellular function of phosphoinositide 3-kinases: implications for development, immunity, homeostasis, and cancer. Annu Rev Cell Dev Biol 2001;17:615-75.
57. Wu X, Zhang J, Zhen R, et al. Trastuzumab antitumor efficacy in patient-derived esophageal squamous cell carcinoma xenograft (PDECX) mouse models. J Transl Med 2012;10:180.
58. Kennedy AL, Morton J, Manoharan I, et al. Activation of the PIK3CA/AKT Pathway Suppresses Senescence Induced by an Activated RAS oncogene to promote tumorigenesis. Mol Cell 2011;42:36-49.
59. Kaur J, Sanyal S. PI3-kinase/Wnt association mediates COX-2/PGE2 pathway to inhibit apoptosis in early stages of colon carcinogenesis: chemoprevention by diclofenac. Tumour Biol 2010;31:623-31.
60. Dai X, Yan J, Fu X, et al. Aspirin Inhibits Cancer Metastasis and Angiogenesis via Targeting Heparanase. Clin Cancer Res 2017;23:6267-78.
61. Vlodavsky I, Elkin M, Pappo O, et al. Mammalian heparanase as mediator of tumor metastasis and angiogenesis. Isr Med Assoc J 2000;2 Suppl:37-45.
62. Talmadge JE, Fidler I. AACR Centennial Series: The biology of cancer metastasis: historical perspective. Cancer Res 2010;70:5649-69.
63. Din FV, Theodoratou E, Farrington S, et al. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 2010;59:1670-9.
64. Lee DH, Nesbitt DE, Chattopadhyay M, et al. Abstract 3898: NOSH-aspirin: A novel nitric oxide- and hydrogen sulfide-releasing hybrid for treatment of colon cancer. Cancer Res 2012;72:Abstract nr 3898.
65. Kashfi K. Utility of nitric oxide and hydrogen sulfide-releasing chimeras as anticancer agents. Redox Biol 2015;5:420.
66. Fuchs C, MeyerhardtJ , Heseltine D, et al. Influence of regular aspirin use on survival for patients with stage III colon cancer: Findings from Intergroup trial CALGB 89803. J Clin Oncol 2005;23:3530.

Cite this article as: Hao W, Shen Y, Feng M, Wang H, Lin M, Fang Y, Tan L. Aspirin acts in esophageal cancer: a brief review. J Thorac Dis 2018;10(4):2490-2497. doi: 10.21037/jtd.2018.03.110

