Prediagnosis aspirin use and outcomes in a prospective cohort of esophageal cancer patients

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Abstract

Background: Esophageal cancer remains associated with poor outcomes, yet little is known regarding factors that influence survival. Aspirin use prior to cancer diagnosis may influence outcomes. We aimed to assess the effects of prediagnosis aspirin use in patients with esophageal cancer.

Methods: We conducted a prospective cohort study of newly-diagnosed esophageal cancer patients at two tertiary care centers. We assessed history of prediagnosis aspirin use, and prospectively followed patients and assessed mortality, cause of death, and development of metastases.

Results: We enrolled 130 patients, the majority of whom were male (81.5%) and had adenocarcinoma (80.8%). Overall, 57 patients (43.9%) were regular aspirin users. In unadjusted analyses, we found no difference in all-cause mortality between aspirin users and nonusers. In multivariate analyses, prediagnosis aspirin use was not associated with all-cause mortality [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.48–1.57] or esophageal cancer-specific mortality (HR 1.07, 95% CI 0.52–2.21). Prediagnosis aspirin use was associated with a significantly increased risk of interval metastasis (HR 3.59, 95% CI 1.08–11.96).

Conclusions: In our cohort of esophageal cancer patients, prediagnosis aspirin use was not associated with all-cause or cancer-specific mortality. However, risk of interval metastatic disease was increased among those who took aspirin regularly prediagnosis. Future studies are warranted to assess whether aspirin influences the molecular characteristics of esophageal tumors, with potential prognostic and therapeutic implications.

Keywords: aspirin, epidemiology, esophageal cancer, metastasis, survival

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Introduction

Esophageal cancer continues to have a dismal prognosis, with a 5-year survival rate of 17% [Siegel *et al.* 2012]. Despite advances in medical and surgical therapy over the past several decades, there has been relatively little reduction in esophageal cancer mortality. Extensive research has been performed in colorectal cancer to identify exposures that influence outcomes, and this information has in turn has led to the identification of clinically-relevant tumor subtypes with potential therapeutic implications [Chan *et al.* 2009; Liao *et al.* 2012b]. However, there is only a limited understanding of exposures that influence esophageal cancer development, behavior, and outcomes.

There is substantial data to suggest that aspirin has chemopreventive effects in esophageal cancer, as prediagnosis use is associated with reduced incidence and esophageal cancer-specific mortality [Thun *et al.* 1993; Rothwell *et al.* 2011; Liao *et al.* 2012a]. However, its effects on outcomes in patients with esophageal cancer are less clear. Aspirin has been best studied in colorectal cancer, where the timing of aspirin exposure relative to diagnosis appears to be extremely important. Postdiagnosis aspirin use is associated with

reduced overall and cancer-specific mortality [Chan *et al.* 2009; Bastiaannet *et al.* 2012; McCowan *et al.* 2013], and there are now ongoing clinical trials to assess its use in the adjuvant setting. A recent study of esophageal cancer patients found that combined pre- and postdiagnosis aspirin as well as postdiagnosis only use was associated with improved overall survival [Van Staalduinen *et al.* 2016]. Studies of prediagnosis aspirin use alone; however, have had heterogeneous results, with some studies showing either no impact on survival or possibly increased mortality in colon cancer [Chan *et al.* 2009, Zell *et al.* 2009; Coghill *et al.* 2011; Bastiaannet *et al.* 2012]. These paradoxical effects are difficult to explain, but conceivably could be due to prevention of less aggressive tumors, thus 'selecting' for a worse phenotype among those patients who do ultimately develop cancer.

In light of the uncertainties regarding the effects of aspirin in esophageal cancer, we aimed to investigate the impact of prediagnosis aspirin use on all-cause mortality, cancer-specific mortality, and metastasis-free survival in a prospective cohort of esophageal cancer patients.

Methods

Study population
Starting in 2009 we prospectively enrolled individuals with newly diagnosed esophageal cancer at Columbia University and Weill Cornell Medical Centers, two tertiary care centers in New York, NY, USA. Adults 18 years of age or older with histologically confirmed primary esophageal cancer were eligible for enrollment in the study. We excluded from analysis individuals in whom the highest degree of esophageal neoplasia was high-grade dysplasia (previously classified as esophageal carcinoma *in situ*), who were enrolled at, or greater than, 180 days after diagnosis, or who had a coexisting malignancy (excepting nonmelanoma skin cancers) within 3 years leading up to the diagnosis and initial workup of esophageal cancer. We obtained written informed consent from all study participants, including permission to obtain all follow-up clinical records. At the time of enrollment, we administered a questionnaire pertaining to demographics, medical history, medication use, and lifestyle factors (see below), and collected blood and urine samples for storage. The institutional review boards at both Columbia University

Medical Center and Weill-Cornell Medical College approved the study protocol.

Baseline assessment
We recorded patient demographics and self-reported height and weight, both at enrollment and 1 year prior. Using a combination of patient self-reporting and manual review of the medical records, we recorded co-morbidities, specifically noting any history of cardiovascular disease (including coronary artery disease, congestive heart failure, arrhythmia, peripheral vascular disease, and cerebrovascular disease). We used the Charlson comorbidity index to quantify overall comorbidity burden [Charlson *et al.* 1987], excluding esophageal cancer from the calculation as this was the disease of interest. We also recorded family cancer history, medication use (including specific notation of aspirin, non-aspirin antiplatelet medications (i.e. clopidogrel, dipyridamole), statins, proton-pump inhibitors, smoking history (current/former/never and pack-years), and history of alcohol use.

Aspirin exposure
As part of the administered baseline questionnaire, we asked patients whether they regularly used aspirin ('Do you take aspirin regularly?' Yes or no'). Among those who were current aspirin users, we recorded the dose (81 mg, 325 mg, or other) as well as the number of years that the subject had been taking aspirin prior to enrollment ('For how many years have you been taking aspirin regularly?'). For the purposes of analyses, we categorized duration of aspirin use as follows: none, <5 years, 5–10 years, >10 years.

Tumor characteristics
For each subject, we recorded the date of diagnosis, tumor histology (adenocarcinoma, squamous cell, other) and differentiation (well, moderate, poor). If the differentiation straddled two grades, then we assigned the tumor the worse of the two grades (e.g. well-to-moderate was classified as moderate). We used endoscopy reports and surgical resection descriptions to assign subsite location (classified as esophagogastric junction, lower esophagus, mid-esophagus, or upper esophagus) based on the most proximal extent of tumor. Any tumor whose epicenter was located either: (1) greater than 5 cm distal to the esophagogastric junction; or (2) within the proximal 5 cm of the

stomach but did not extend to the esophagogastric junction or esophagus, was reclassified as a primary gastric cancer and excluded from analysis.

We assessed tumor stage using a modification of the TNM classification from the 7th edition of the American Joint Committee on Cancer [Edge *et al.* 2010]. We recorded clinical T stage based on the results of endoscopic ultrasound, as well as pathologic T stage for those patients who underwent curative resection (esophagectomy or endoscopic mucosal resection). For analysis purposes, we used the clinical T stage unless the subject had the tumor resected without previously receiving any chemo- or radiation therapy, in which case we assigned the pathologic T stage. We used a simplified lymph node assessment, assigning lymph node status as positive if there was clinical or pathologic evidence of lymph node involvement prior to receiving any chemo- or radiation therapy. We recorded the presence of distant metastases (yes or no) as well as the site(s) of metastases. We classified subjects with involved celiac, paraesophageal, or cervical lymph nodes as lymph node positive but not distant metastasis positive [Edge *et al.* 2010]. For tumors in which human epidermal growth factor receptor-2 (HER-2) overexpression was assessed, we recorded HER-2 status as negative, equivocal, or positive.

Follow up

For each subject, we collected follow-up data with regard to treatment received, imaging studies, and follow-up endoscopies. Our primary outcome of interest was all-cause mortality as it relates to aspirin use. We identified deaths through chart review, next of kin, and the Social Security Death Index, and we recorded the date of death. Cause of death was determined by consensus among two of the investigators who were blinded to aspirin exposure. We defined death from esophageal cancer as a death that occurred as a result of tumor burden (e.g. failure to thrive due to inoperable obstructive disease or due to extensive metastases), tumor-related complications (e.g. hemorrhage due to tumor), or as a result of any treatments directly related to esophageal cancer (e.g. post-esophagectomy respiratory failure).

Statistical analysis

We analyzed categorical variables using Chi-square tests, and for continuous variables we used rank sum tests for non-normally distributed variables,

and Student's *t* tests for normally distributed variables. For time-to-event analyses for all-cause mortality, we used the date of diagnosis as time zero. We then calculated time to death for those subjects who died and censored all others at the last time point at which they were known to be alive, based on direct contact with the subject or the most recent data in the medical records. For esophageal cancer-specific mortality analyses, we censored subjects at the last time point at which they were known to be alive or, for those who died from other causes, at the date of death. For metastasis analyses, we only included individuals who were metastasis-free at baseline and for whom at least 6 months of surveillance imaging was available. We calculated the time from date of diagnosis to the date of the first imaging study to demonstrate metastatic disease. All others were censored either at the date of death or at the date of the most recent imaging.

We used the log-rank test to compare survival curves in aspirin users and nonusers. We performed multivariable time-to-event analyses using Cox proportional hazards modeling. We first performed univariate Cox modeling to assess the unadjusted association between each variable and mortality. We subsequently tested each one of these terms for interaction with aspirin use; we found no evidence of significant interaction between aspirin and any of the other variables. In the full model we included aspirin use as well as all of the variables associated with survival at $p < 0.20$ in the univariate analyses. The variables included in the full model were the following: age at diagnosis, year of diagnosis, race, marital status, use of non-aspirin antiplatelet medications, use of proton-pump inhibitors, smoking history, tumor histology, tumor subsite, T stage, N stage, M stage, receipt of surgery. We subsequently removed from the model one variable at a time, choosing the variable with the highest p value that was >0.15.

The sample size for the present analysis was not based on predetermined power calculations. The sample size from our analyses ($n = 130$) had 82% power to detect a hazard ratio (HR) of 2.0 for the effects of prediagnosis aspirin exposure on all-cause mortality, and 80% power to detect a HR of 3.3 for development of metastasis.

We defined statistical significance as $p < 0.05$. All analyses were performed using STATA 12.1 (StataCorp, College Station, TX, USA).

Table 1. Baseline patient characteristics of an esophageal cancer cohort at Columbia University and Weill Cornell Medical Centers (2009–2014).

Characteristic	(*n* = 130)
Age at diagnosis, mean (SD)	65.2 (11.4)
Sex, male (%)	106 (81.5)
Race, white (%)	116 (89.2)
Ethnicity, non-Hispanic (%)	116 (89.2)
BMI 1 year prior, mean (SD) †	28.4 (5.7)
Aspirin use (%)	57 (43.9)
81 mg‡	44 (77.2)
325 mg‡	11 (19.3)
Years taking aspirin, median (IQR)§	5 (3–10)
Non-aspirin antiplatelet use (%)	14 (10.8)
Statin use (%)	53 (40.8)
Proton-pump inhibitor use (%)	70 (53.9)
Tobacco exposure (%)	
Never	33 (25.4)
Former	71 (54.6)
Current	26 (20.0)
History of cardiovascular disease (%)	35 (26.9)
Charlson comorbidity index score (%)	
0	66 (50.8)
1	34 (26.2)
>1	30 (23.1)

†Data missing in 3 individuals.
‡Data missing in 2 individuals.
§Data missing in 9 individuals.
BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 2. Tumor characteristics of an esophageal cancer cohort at Columbia University and Weill Cornell Medical Centers (2009–2014).

Characteristic	(*n* = 130)
Histology (%)	
Adenocarcinoma	105 (80.8)
HER-2 positive†	18 (28.1)
Squamous cell carcinoma	25 (19.2)
Grade (%)	
Well	5 (3.9)
Moderate	43 (33.1)
Poor	59 (45.4)
Unknown	23 (17.7)
Location (%)	
Gastroesophageal junction	33 (25.4)
Lower third	73 (56.2)
Middle third	20 (15.4)
Upper third	4 (3.1)
T stage (%)	
T1–T2	49 (37.7)
T3–T4	59 (45.4)
Tx	22 (16.9)
Lymph node status (%)‡	
Negative	47 (36.2)
Positive	82 (63.1)
M stage (%)	
0	120 (92.3)
1	10 (7.7)

†64 out of 105 adenocarcinomas assessed for HER-2 status.
‡Data missing in 1 individual.
HER-2, human epidermal growth factor receptor 2.

Results

We enrolled 159 subjects between January 2009 and August 2014, 29 of whom were excluded due to: enrollment ⩾180 days after diagnosis (*n* = 16); coexisting malignancy within 3 years leading up to diagnosis (*n* = 6); no definitive diagnosis of cancer (*n* = 5); reclassification as gastric cancer (*n* = 1); and withdrawal from study (*n* = 1). Of the remaining 130 subjects, the majority were white (89.2%) and male (81.5%), with a mean age of 65.2 years [standard deviation (SD) 11.4] (Table 1). The median time from diagnosis to study enrollment was 48 days [interquartile range (IQR) 22–109]. The median follow up was 21.3 months (IQR 10–38) for the entire cohort, and 30.5 months (IQR 20–53) for those still alive at the time of the analyses.

There were 57 (43.9%) patients who used aspirin regularly. Overall, 14 (10.8%) subjects were taking non-aspirin antiplatelet agents, and 10/14 (71.4%) also took aspirin. In multivariable logistic regression analysis, aspirin use was associated with a history of cardiovascular disease (odds ratio [OR] 3.62, 95% CI 1.40–9.36) and statin use (OR 4.72, 95% CI 2.07–10.73).

Baseline tumor characteristics are summarized in Table 2. A majority of cases were adenocarcinoma (80.8%), and most tumors were localized to the distal esophagus or gastroesophageal junction (81.5%). HER-2 assessment was performed on 64/105 (61.0%) of the adenocarcinomas, and 18/64 (28.1%) were HER-2-positive. A total of 90 (69.2%) individuals underwent surgical resection with curative intent.

All-cause and esophageal cancer-specific mortality

A total of 55 patients (42.3%) died during the follow-up period, corresponding to a 3-year overall

Table 3. Prediagnosis aspirin use and risk of all-cause mortality, esophageal cancer-specific mortality, and development of metastasis in esophageal cancer patients (2009–2014).

All-cause mortality[†]	HR	95% CI	*p*-value for trend
Aspirin use			
No	1	Reference	
Yes	0.86	0.48–1.57	
Dose			
None	1	Reference	0.96
81 mg	0.73	0.38–1.42	
325 mg	1.25	0.51–3.07	
EC-specific mortality[‡]			
Aspirin use			
No	1	Reference	
Yes	1.07	0.52–2.21	
Dose			
None	1	Reference	0.42
81 mg	0.83	0.36–1.89	
325 mg	2.12	0.73–6.14	
Development of metastasis[§]			
Aspirin use			
No	1	Reference	
Yes	3.59	1.08–11.96	
Dose			
None	1	Reference	0.097
81 mg	2.63	0.78–8.90	
325 mg	4.35	0.37–51.2	

[†]Adjusted for age at diagnosis, non-aspirin antiplatelet medication use, tumor subsite, nodal status, and receipt of surgery.
[‡]Adjusted for Charlson comorbidity score, tumor histology, T stage, nodal status, and receipt of surgery.
[§]Adjusted for cardiovascular disease, smoking, marital status, nodal status, and receipt of surgery.
CI, confidence interval; EC, esophageal cancer; HR, hazard ratio.

survival of 53.7% (95% CI 43.7–62.8%). We found no difference in unadjusted all-cause mortality between prediagnosis aspirin users and nonusers (log-rank *p* = 0.86). In multivariable Cox proportional hazards modeling, we found no association between prediagnosis regular aspirin use and all-cause mortality (HR 0.86, 95% CI 0.48–1.57) (Table 3). There was also no significant association between aspirin dose (*p* for trend = 0.96) or duration (*p* for trend = 0.91) and all-cause mortality. In the final multivariable model, non-aspirin antiplatelet medication use was significantly associated with increased all-cause mortality (HR 2.68, 95% CI 1.17–6.16).

A total of 35 patients (63.6% of all deaths) died from esophageal cancer. In unadjusted analyses, there was again no difference in esophageal cancer-specific mortality between aspirin users and nonusers (log-rank *p* = 0.85). In multivariable analyses, we found no association between prediagnosis aspirin use and esophageal cancer-specific mortality (HR 1.07, 95% CI 0.52–2.21) (Table 3). We did not observe an association with increased aspirin dose (*p* for trend = 0.42) or duration (*p* for trend = 0.84). Non-aspirin antiplatelet medication use was not included in the final multivariable model.

Metastasis-free survival
At baseline, 120 individuals were metastasis-free, of whom 89 had at least 6 months of surveillance imaging. Of these patients, 21/89 (23.6%) developed interval metastatic disease. In multivariable analyses we observed a significantly increased risk of development of metastasis among patients who reported prediagnosis aspirin use (HR 3.59, 95% CI 1.08–11.96) (Table 3). We found a nonsignificant trend towards increased risk of metastasis

with increasing doses of prediagnosis aspirin (*p* for trend = 0.097). We found no increased risk of metastasis with increased duration of aspirin use (*p* for trend = 0.15). Non-aspirin antiplatelet medication use was not included in the final multivariable model.

We considered the possibility that aspirin users may have been less likely to receive surgery. We therefore repeated the analyses restricted to those who underwent surgery for curative intent (*n* = 79), and found no qualitative change in the association between prediagnosis aspirin use and development of metastases (HR 3.26, 95% CI 0.93–11.44). We found a similar association in analyses restricted to adenocarcinomas (*n* = 74; HR 3.32, 95% CI 0.94–11.7).

Discussion

In this analysis of a prospective cohort of esophageal cancer patients at two large tertiary care centers, prediagnosis aspirin use was not associated with all-cause or cancer-specific mortality. However, prediagnosis aspirin use was associated with a greater than 3-fold increased risk of developing metastases.

There are limited published data specifically assessing the impact of prediagnosis aspirin use on esophageal cancer outcomes. Tsibouris and colleagues performed a retrospective case-control study to assess the association between nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, and esophageal adenocarcinoma, with Barrett's esophagus patients serving as controls [Tsibouris *et al.* 2004]. In secondary analyses, the authors reported no significant unadjusted association between prediagnosis NSAID or aspirin use and overall survival, consistent with our findings. Overall, two prior studies reported no significant association between NSAID use and esophageal cancer survival [Trivers *et al.* 2005; Thrift *et al.* 2012]. These studies combined aspirin and non-aspirin NSAID use in the analyses, and defined regular use as at least weekly. The effects of aspirin alone as well as dose and duration effects were not reported.

Parallels can be drawn with studies of aspirin exposure and colorectal cancer outcomes. Bastiannet and colleagues conducted a population-based study in the Netherlands, in which colorectal cancer cases were identified using a national cancer registry, and aspirin use was determined based on a linked prescription record database [Bastiaannet *et al.* 2012]. The authors found significantly higher mortality among patients who took aspirin prior to diagnosis for both colon cancer (HR 1.5, 95% CI 1.2–1.8) and rectal cancer (HR 1.4, 95% CI 1.0–2.0). These effects may not be limited to cancers of the gastrointestinal tract. In a large population-based cohort study of breast cancer patients from Scotland, prediagnosis aspirin use was associated with significantly increased all-cause (HR 1.62) and breast cancer-specific (HR 2.10) mortality [Fraser *et al.* 2014]. Other studies; however, have had mixed results with regard to the effects of prediagnosis aspirin and cancer outcomes [Chan *et al.* 2009; Zell *et al.* 2009; Coghill *et al.* 2011; Brasky *et al.* 2012; Li *et al.* 2012]. While we did not observe an association between prediagnosis aspirin use and all-cause or cancer-specific mortality, our cohort was not sufficiently powered to detect small to moderate effects.

We were surprised to find a significant increase in risk of metastasis among those exposed to aspirin prior to esophageal cancer diagnosis. Multiple studies have demonstrated that aspirin use is associated with a reduced incidence of and lower mortality due to esophageal cancer [Thun *et al.* 1993; Rothwell *et al.* 2011; Liao *et al.* 2012a]. We speculate that aspirin may prevent esophageal cancers that are associated with better outcomes, thus 'selecting' for more invasive tumors. The cyclooxygenase-2 (COX-2) enzyme is commonly implicated in the aspirin–cancer paradigm. Expression of COX-2 is increased in both esophageal squamous cell cancer and adenocarcinoma, and higher levels of COX-2 expression have been associated with more severe disease and worse outcomes [Morris *et al.* 2001; Buskens *et al.* 2002; Bhandari *et al.* 2006; Liu *et al.* 2006; Takatori *et al.* 2008; Li *et al.* 2009; Jimenez *et al.* 2010]. If aspirin exerts chemopreventive effects exclusively through COX-2, then one would expect selective prevention of these more aggressive tumors. However, in a randomized clinical trial in patients with Barrett's esophagus and dysplasia, COX-2 inhibition with celecoxib had no impact on expression of COX-2 or on other markers associated with neoplastic progression [Heath *et al.* 2007]. Studies in colorectal cancer suggest that the effects of aspirin may be influenced by the PI3K pathway as well as other factors such as BRAF mutation status, 15-hydroxyprostaglandin dehydrogenase (HPGD) expression, and circulating macrophage inhibitory cytokine (MIC)-1 [Liao *et al.* 2012b;

Nishihara *et al.* 2013; Fink *et al.* 2014; Mehta *et al.* 2014].

We found that prediagnosis use of non-aspirin antiplatelet medications was associated with significantly increased all-cause mortality, but not with esophageal cancer-specific mortality or development of metastases. Patients taking non-aspirin antiplatelet medications were significantly less likely to undergo surgery and had higher Charlson comorbidity scores (data not shown). We therefore suspect that patients who used these medications were at increased risk of death due to poorer overall health status rather than a direct effect of the medications, and that poorer health status may not have been fully captured in our analyses.

Strengths of our study include its prospective design with aspirin exposure ascertainment at the beginning of the study, thus minimizing recall bias. All enrolled patients completed the administered baseline questionnaire, and we thus had complete data on prediagnosis aspirin use, including dose and duration history. We successfully obtained vital status information on all patients at the time of data analysis. Histologic and staging data were collected for all patients, and we were able to adjust for important confounders in our analyses. We were able to collect comprehensive information on cancer treatment and progression, including development of recurrence and metastasis.

Study limitations include our lack of information about indications for aspirin use. Additionally, our baseline assessment likely did not capture intermittent aspirin use. We also did not collect data on non-aspirin, NSAID medications. We did not assess postdiagnosis aspirin use, which may have beneficial effects. Compared with prospectively-collected data, retrospective assessment of postdiagnosis aspirin use would likely have been less accurate and subject to potentially significant misclassification bias. We suspect that postdiagnosis aspirin use likely correlated with prediagnosis use, and postdiagnosis use would therefore be expected to bias towards the null for the association between prediagnosis aspirin and metastasis. However, we cannot rule out the possibility that many patients in the cohort were started on aspirin only after diagnosis. The size of the study cohort was not large, thus limiting our ability to detect smaller, potentially meaningful effects of aspirin on outcomes. The effects of aspirin may differ by histological subtype, and the cohort size

limited out ability to perform stratified analyses. Assessment of cause of death has inherent limitations; however, we used an accepted definition of cancer-specific mortality [Howlader *et al.* 2010; Sarfati *et al.* 2010], and we used two-physician consensus for each case. Lastly, our cohort consisted of a heterogeneous group of patients who were referred to two large tertiary care centers, which may restrict the generalizability of our data.

In conclusion, in a prospective cohort of patients with esophageal cancer, prediagnosis aspirin use was not associated with all-cause or cancer-specific mortality. However, we did find a significantly increased risk of developing metastases. The reason underlying these observations are unclear, although we speculate that aspirin may 'selectively' prevent the development of less-invasive esophageal cancers. The effects of prediagnosis aspirin use should be investigated and confirmed in separate populations of esophageal cancer patients. Future studies should also be aimed at assessing the molecular and genetic characteristics of esophageal tumors in patients with and without aspirin use prior to diagnosis, as these biological differences may have important prognostic and therapeutic implications.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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