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2013 SSAT PLENARY PRESENTATION

Does the Incidence of Adenocarcinoma of the Esophagus and Gastric Cardia Continue to Rise in the Twenty-First Century?—a SEER Database Analysis

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Abstract
Background The rising incidence and histological change to adenocarcinoma in esophageal cancer over the past four decades has been among the most dramatic changes ever observed in human cancer. Recent reports have suggested that its increasing incidence may have plateaued over the past decade. Our aim was to examine the latest overall and stage-specific trends in the incidence of esophageal adenocarcinoma.
Patients and Methods We used the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute to identify all patients with adenocarcinoma of the esophagus and gastric cardia between 1973 and 2009. Both overall and stage-specific trends in incidence were analyzed using joinpoint regression analysis.
Results The overall incidence of adenocarcinoma of the esophagus and the gastric cardia increased from 13.4 per million in 1973 to 51.4 per million in 2009, a nearly 400 % increase. Jointpoint analysis demonstrated that the yearly increase in incidence has slowed somewhat from 1.27 per million before 1987 to 0.97 between 1987 and 1997 and 0.65 after 1997. Stage-specific analysis suggests that the incidence of noninvasive cancer has actually declined after 2003 with a yearly decrease of 0.22. The percentage of patients diagnosed with in situ cancer declined after 2000 and remained under 2.5 % through the study period.
Conclusions The incidence of esophageal adenocarcinoma continues to rise in the USA. The percentage of patients diagnosed with in situ cancer has declined in the twenty-first century.

Keywords Incidence · Adenocarcinoma of the esophagus · Epidemiology · Trends · Cardia · Esophagus

Background

The incidence of esophageal carcinoma has been rising rapidly during the past three decades, and it is the seventh leading cause of cancer-related death in males in the USA.[1] This is largely due to increasing numbers of adenocarcinoma cases, which are now 600 % higher than in the 1970s.[2] In fact, the absolute number of these cancers is even higher if adenocarcinoma of the cardia, often erroneously excluded from these analyses, is included. A similar trend has also been reported in other western countries.[3–5]

Previous studies have suggested that this trend in esophagus and the gastric cardia (EAC) incidence may be slowing and may even have plateaued over the past decade.[6] Reasons behind these changes are not completely understood, although several mechanisms, including dietary and environmental causes, have been suggested.[7]

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Given the poor survival rates of advanced EAC, detection and treatment in an early, potentially precancerous stage is paramount. On the other hand, since widely applicable, inexpensive screening techniques are not available, the population that would benefit the most from a screening program has to be defined.

The aim of this brief study was to update the latest trends and analyze the racial and gender differences in esophageal adenocarcinoma incidence in the USA. Data presented in this study could form the basis for the better allocation of resources in future esophageal cancer screening programs.

Methods

Surveillance Epidemiology and End Results (SEER) 9 database of the National Cancer Institute was queried for all cases of histologically verified primary adenocarcinomas of the EAC. SEER 9 has collected information on all newly diagnosed malignancies since 1973 among residents of the nine original SEER geographic areas (areas within the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the cities of Atlanta, Detroit, San Francisco, and Seattle) and represents approximately 10 % of the population from the USA.[8] Our analysis included data from all available years (1973–2009). EAC was defined by using tumor site codes C15.0–15.5, 15.8, 15.9, and 16.0 and ICD-O-3 histology codes 8140–8573. From this group, we excluded all patients that were diagnosed at autopsy or from death certificate data. The final study cohort comprised 26,334 patients with EAC. Information about age-adjusted incidence, sex, race, tumor stage, and population was obtained from SEER. Racial information was dichotomized into "white" and "nonwhite" categories. Stage-specific distribution was analyzed using the SEER historic stage A variable, which defines in situ stage as noninvasive cancer, localized stage as cancer limited to the primary organ, regional stage as disease extending beyond the primary organ into adjacent tissue or regional nodes, and distant stage as metastatic cancer detected. To evaluate time trends, we used joinpoint analysis[9] developed by the National Cancer Institute for the analysis of SEER

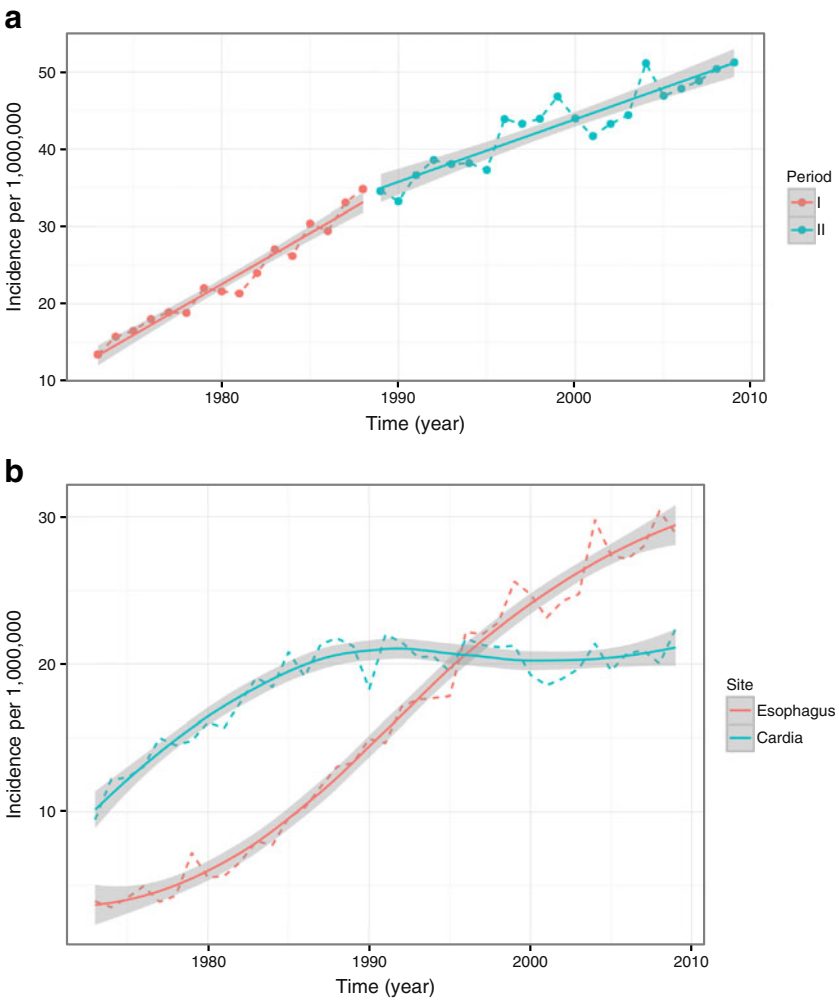

Fig. 1 **a** Incidence of adenocarcinoma of the esophagus and the gastric cardia. Using joinpoint analysis, a statistically significant change can be detected in the incidence trend between the two time periods (period I vs. period II). **b** Incidence of adenocarcinoma of the esophagus vs. incidence of adenocarcinoma of the gastric cardia

data. Joinpoint analysis identifies inflection points (so-called jointpoints) where a statistically significant change over time in linear slope of the trend occurred. The level of statistical significance was set at $p < 0.01$. All analyses were conducted using R 2.15.1 (R Development Core Team,[10] version 2.15.1).

Results

The overall incidence of adenocarcinoma of the esophagus and the gastric cardia increased from 13.4 per million in 1973 to 51.4 per million in 2009, a nearly 400 % increase (Fig. 1a). Figure 1b shows a significant change of slope in the incidence curve of adenocarcinoma of the gastric cardia. After a steep annual increase of 5.2 % since 1973, the incidence seems to have plateaued after 1985. During the same period, the incidence of esophageal adenocarcinoma changed from 3.9 per million in 1973 to 28.9 per million in 2009 surpassing the incidence of adenocarcinoma of the gastric cardia in 1996.

Stage-Specific Trends

The incidence of noninvasive cancer (SEER stage A) decreased after 2003 with a yearly decrease of 0.22. The percentage of patients diagnosed with in situ carcinoma declined after 2000 and remained under 2.5 % through the study period. Yearly increase of incidence of localized cancer has slowed after 1999 and was 0.13 per million between 1999 and 2009. Similarly, from 1973 to 1985, the incidence of regional disease increased from 4.7 to 12.1 per million, an annual increase of 5.2 %. From 1985 to 2009, the incidence increased only with 0.16 per million/year (1.2 %), reflecting a significant decline in the slope of the incidence curve. During the study period, the incidence of metastatic disease has continued to rise and was slightly more than 20 per million in 2009.

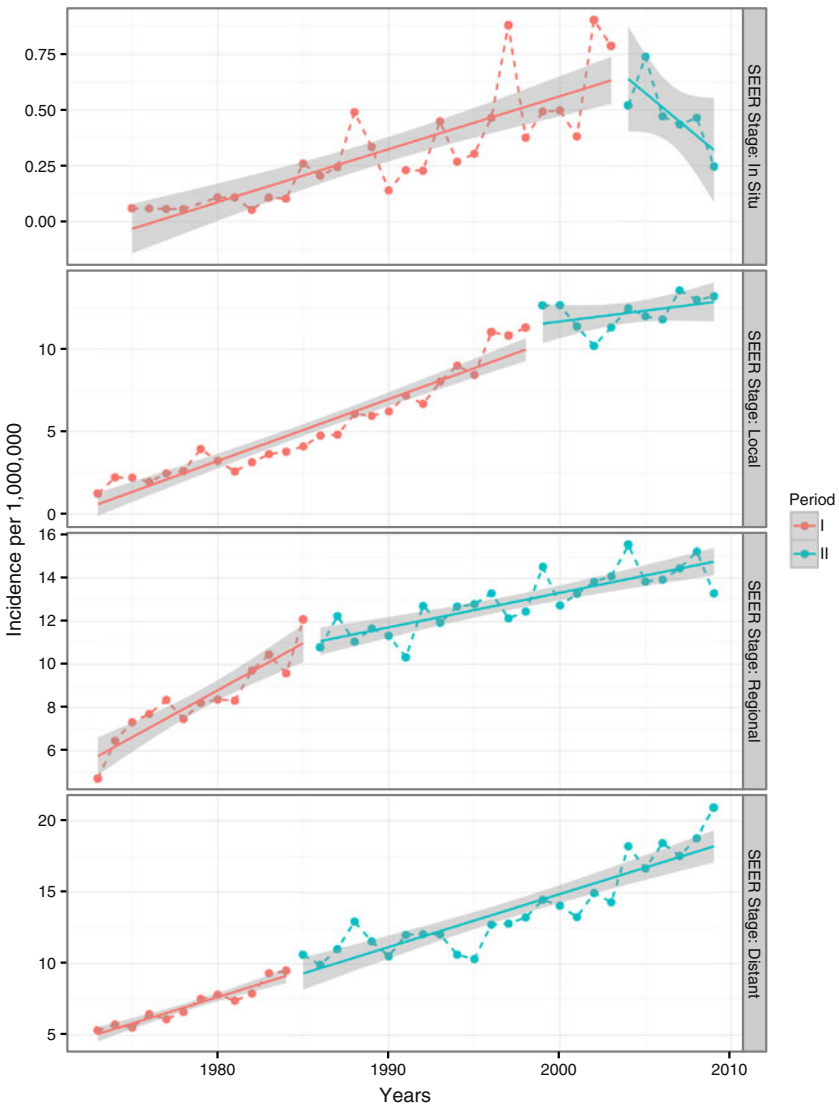

Fig. 2 Trends in stages of esophageal adenocarcinoma at diagnosis in 1973–2009. Using joinpoint analysis, a statistically significant change can be detected in the incidence trend between the two time periods (period I vs. period II)

Furthermore, 38 % of all patients were diagnosed in metastatic stage (Fig. 2).

Incidence Trends by Sex and Race

Further analysis revealed substantial differences in incidence trends according to race and gender (Fig. 3a–d). Between 1973 and 2009, EAC incidence in white males increased sharply with a yearly increase in incidence of 2.3 per million reaching 107.3 per million at the end of the study period. A markedly smaller and decreasing yearly increase in incidence is observed in white women (0.7 per million before 1988 to 0.4 per million after 1988). On the other hand, the incidence of adenocarcinoma of the esophagus and the gastric cardia in nonwhite males has been decreasing with −0.3 per million since 1992 reaching an incidence of 30 per million in 2009, less than a third of that of white males. EAC incidence in nonwhite females shows no trend and remains relatively constant between 7 and 17 per million.

Discussion

In this study, we provide an update on recent incidence changes through 2009 using the population-based SEER 9 registry. We have found that the incidence of esophageal adenocarcinoma continues to rise in the twenty-first century in the USA. Our results are in contrast with the findings of a previous report by Pohl et al.[6] and indicate that this increase involves all stages of invasive EAC. On the other hand, like other reports,[6] we have found that the slope of the incidence curve declines, which represents a significant change in trend. Furthermore, there seems to be a recent decrease in the incidence of noninvasive (in situ) disease, but this reduction has only a marginal effect on EAC incidence, since the proportion of patients diagnosed with in situ cancer remains only around 2 % of the total population.

Perhaps one of the more surprising findings of this study is the fact that, while adenocarcinoma rates are rising at a similar pace among both white men and women, the incidence of EAC remained stable in nonwhite women and actually declined in nonwhite men. We have also found that the previously reported significant epidemiological differences between adenocarcinoma of the esophageal body and that of the gastric cardia (GCA) persist in the first decade of the twenty-first century.[11] While the incidence of adenocarcinoma of the cardia remained stable between 1987 and 2009, the incidence of EAC continues to rise and surpassed the incidence of GCA already in the late 1990s.

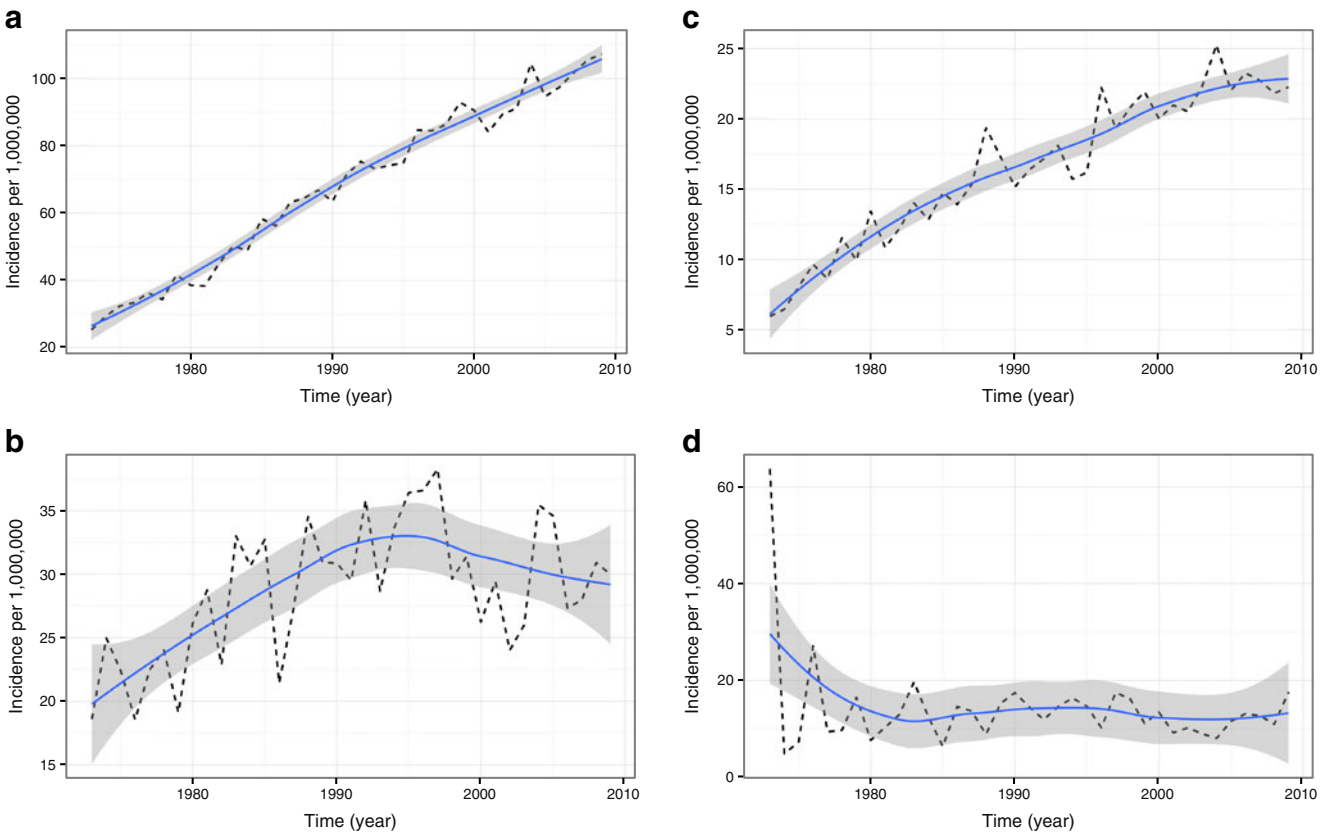

Fig. 3 Incidence of EAC according to race and sex between 1973 and 2009. **a** White males. **b** Nonwhite males. **c** White females. **d** Nonwhite females

Similar trends have been observed in other countries.[3–5,12] In contrast, Lagergren et al. reported that after decades of rising incidence in Sweden, the rate of EAC was stabilizing after 2001 and was showing a decreasing trend after 2005.[13]

Reasons for the initial dramatic rise in the incidence of EAC are largely unknown; rising prevalence of smoking, gastroesophageal reflux, and obesity have all been discussed as possible explanations. On the other hand, it is also possible that these risk factors might have already exerted their maximal effect, thus resulting in the contemporary decline in the slope of the incidence curve. Additionally, the decline in the incidence of in situ disease might be a result of recent progress in Barrett screening and possibly of an increased access to ablation therapy.[14]

Based on the natural history of esophageal cancer, a change in local or systemic exposures must have predated this rise in EAC incidence by several years. However, according to results from the National Health and Nutrition Examination Survey (NHANES), a significant increase in the prevalence of obesity in the USA was not observed until 1976–1980.[14] Although SEER data is available since 1973 only, analysis of the Connecticut Tumor Registry Database (the oldest population-based tumor registry in the USA) indicates that the incidence of EAC has already begun to rise in the late 1960s; therefore, obesity could not have played a deciding role in the initial phase.[15] Furthermore, despite the higher documented prevalence of obesity among African–Americans,[16,17] the incidence of EAC remained stable in nonwhite women and declined in nonwhite men in the last 20 years in the USA.

The roles of gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE) in the development of EAC are well established, but their contribution to the rising incidence of EAC is uncertain since there is no incident data available on these risk factors. In a review of 45 population-based studies, El Serag found a significant increase in the prevalence of GERD between 1982 and 2005, and it seems likely that an increase in prevalence is a reflection of increase over time in the incidence of GERD.[18] Additionally, a study of Olmsted County, Minnesota, residents found that the incidence of BE increased 28-fold during a period of three decades, and a study of endoscopy and histology reports between 1977 and 1996 found that frequency of BE increased from 0.2 to 1.6 % of all endoscopies in the UK.[19,20]

Tobacco smoking is an established risk factor for EAC, and the prevalence of smoking rose markedly during the first half of the twentieth century.[21] Two large population-based studies found moderately increased risk of adenocarcinoma of the esophagus among cigarette smokers, but no significant association was identified in a Swedish study.[22–24] Furthermore, it is unlikely that smoking was a major contributor in the dramatic rise in incidence of EAC since similar temporal trends were not observed in the incidence of other malignancies associated with tobacco use such as noncardia gastric cancer and esophageal squamous cell cancer.[25]

Our study shares the limitations of all investigations using a population-based dataset. First, despite being the most representative cancer database in the USA, the SEER 9 regions represent approximately only 10 % of the US population.[8] Second, although SEER conducts regular audits to evaluate both the quality and completeness of data, a possible misclassification of patient information particularly regarding tumor site must always be considered when using a population-based database. Studies evaluating the role of misclassification in incidence trends of esophageal and cardia cancer have shown that a possible substantial misclassification of anatomic site exists, yet this does not explain the observed incidence trends.[2,26]

Despite these limitations, we can conclude that our results strongly indicate that the incidence of esophageal adenocarcinoma continues to rise in the twenty-first century in the USA, most dramatically among white males, while its incidence in nonwhite males is decreasing. The significant epidemiological differences between adenocarcinoma of the esophageal body and that of the gastric cardia persist.

Conflict of Interest The authors have nothing to disclose.

References

1. American Cancer Society. Cancer Facts & Figures 2012. Atlanta: American Cancer Society; 2012
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005 Jan 19;97(2):142-6.
3. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. Eur J Cancer Prev. 1992 Apr;1(3):265-9.
4. Hansen S, Wiig JN, Giercksky KE et al. Esophageal and gastric carcinoma in Norway 1958-1992: incidence time trend variability according to morphological subtypes and organ subsites. Int J Cancer. 1997 May 2;71(3):340-4.
5. Armstrong RW, Borman B. Trends in incidence rates of adenocarcinoma of the oesophagus and gastric cardia in New Zealand, 1978-1992. Int J Epidemiol. 1996 Oct;25(5):941-7.
6. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? Cancer Epidemiol Biomarkers Prev. 2010 Jun;19(6):1468-70.
7. Lagergren J, Lagergren P. Oesophageal cancer. BMJ. 2010 Nov 26;341:c6280.
8. NCI (2013) Number of Persons by Race and Hispanic Ethnicity for SEER Participants, http://seer.cancer.gov/registries/data.html. Accessed on 05.08.2013
9. Kim HJ, Fay MP, Feuer EJ et al. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–51.
10. R Development Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/
11. El-Serag HB, Mason AC, Petersen N et al. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut. 2002 Mar;50(3):368-72.
12. Bollschweiler E, Wolfgarten E, Gutschow C et al. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer. 2001 Aug 1;92(3):549-55.

13. Lagergren J, Mattsson F. No further increase in the incidence of esophageal adenocarcinoma in Sweden. Int J Cancer. 2011 Jul 15;129(2):513-6.
14. CDC (2011) Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1960–1962 Through 2007–2008, http://www.cdc.gov/nchs/data/hestat/obesity_adult_07_08/obesity_adult_07_08.htm, Accessed on 05.08.2013
15. Abrams JA, Sharaiha RZ, Gonsalves L et al. Dating the rise of esophageal adenocarcinoma: analysis of Connecticut Tumor Registry data, 1940-2007. Cancer Epidemiol Biomarkers Prev. 2011 Jan;20(1): 183-6.
16. CDC (2009) Differences in Prevalence of Obesity Among Black, White, and Hispanic Adults—United States, 2006—2008, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5827a2.htm, Accessed on 05.08.2013
17. Li C, Ford ES, McGuire LC, Mokdad AH. Increasing trends in waist circumference and abdominal obesity among US adults. Obesity (Silver Spring) 2007;15(1): 216-24.
18. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. Clin Gastroenterol Hepatol. 2007 Jan;5(1):17-26.
19. Locke GR 3rd, Talley NJ, Fett SL et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology. 1997 May;112(5):1448-56.
20. Caygill CP, Reed PI, Johnston BJ et al. A single centre's 20 years' experience of columnar-lined (Barrett's) oesophagus diagnosis. Eur J Gastroenterol Hepatol. 1999 Dec;11(12):1355-8.
21. U.S. Department of Health and Human Services. Reducing tobacco use: A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Office on Smoking and Health; 2000.
22. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control. 2001 Oct;12(8):721-32.
23. Gammon MD, Schoenberg JB, Ahsan H et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst. 1997 Sep 3;89(17):1277-84.
24. Lagergren J, Bergström R, Lindgren A et al. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer. 2000 Feb 1;85(3):340-6.
25. Anderson WF, Camargo MC, Fraumeni JF, et al. Age-specific trends in incidence of noncardia gastric cancer in U.S. adults. JAMA 2010; 303(17):1723–1728.
26. Lindblad M, Ye W, Lindgren A et al. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg. 2006 Apr;243(4):479-85.

Discussant

Dr. Selwyn Vickers (Minneapolis, Minnesota): The study "Does the Incidence of Adenocarcinoma of the Esophagus and Gastric Cardia Continue to Rise in the 21st Century?" is a well-written paper by Dr. Dubecz and Dr. Peters of the University of Rochester. The study documents what appears to be a continued astronomic rise of the incidence of adenocarcinoma of the esophagus and gastric cardia. Using the SEER database from the National Cancer Institute, they outline the incidence of this disease from 1973 to 2009. This study demonstrated that there is nearly a 400 % increase in the incidence of these tumors. The questions that I believe are relevant as I reviewed this are the following:

1. Do the authors see any significant correlate of this rise in esophageal adenocarcinoma to the increased incidence of H_2 blockers as well as proton pump inhibitors? That is, does the process of achlohydria create an increased level of carcinogenesis in the distal esophagus and the cardia of the stomach?
2. Is there potential risk of misdiagnosis of tumors of the esophagus and the gastric cardia in the SEER database which could accumulate to this large increase of incidence that we're seeing?
3. Has there been a correlate increase in survival with this earlier detection and increased incidence in the last 20 years?

Thank you for the opportunity to review this paper and the outstanding work done by this group under the leadership of Dr. Jeff Peters.

Closing Discussant

Dr. Attila Dubecz: Dr Vickers, thank you for your kind comments and questions. To answer your first question, there is a good deal of experimental evidence supporting the cause-and-effect relationship between alkaline reflux and adenocarcinoma of the distal esophagus. Furthermore, acidic gastric juice seems to have a protective effect against esophageal carcinogenesis in a rat tumor model. On the other hand, according to the results of our study, the incidence of esophageal adenocarcinoma has been on the rise since the early 1970s, but the first H_2 blockers were introduced on the US market in the late 1970s, and omeprazole was marketed only in 1989. Therefore, these drugs could not have played a deciding role in the initial rise in the incidence of adenocarcinoma of the esophagus and the gastric cardia.

Secondly, a possible misclassification of any patient information must always be considered when analyzing a population-based database. Studies evaluating the role of misclassification of the tumor site in incidence trends of esophageal and cardia cancer have shown that the incidence of subsite unspecified gastric cancer has fallen during the last 40 years which could eventually result in an artificially increased incidence of cardia cancer, yet this cannot fully explain the observed temporal trends in esophageal adenocarcinoma.

Lastly, this increase in incidence seems to be a true change since the percentage of patients diagnosed with in situ disease has actually been declining, and the incidence of all invasive stages has been increasing during the study period. Despite these facts, long-term survival of patients with carcinoma of the gastric cardia and the esophagus seems to be improving probably due to therapeutic advances in the treatment of this malignancy.