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Esophageal Adenocarcinoma Incidence in Individuals With Gastroesophageal Reflux: Synthesis and Estimates From Population Studies

Joel H. Rubenstein, MD, MSc^{1,2}, James M. Scheiman, MD², Shahram Sadeghi, MD, PhD³, David Whiteman, BMedSc, MBBS, PhD³, and John M. Inadomi, MD⁴

¹Veterans Affairs Center of Excellence for Clinical Management Research, Ann Arbor, Michigan, USA

²Division of Gastroenterology, University of Michigan Medical School, Ann Arbor, Michigan, USA

³Cancer and Population Health, Queensland Institute of Medical Research, Brisbane, Australia

⁴Division of Gastroenterology, University of Washington, Seattle, Washington, USA

Abstract

Objectives—Recent advances in the management of Barrett's esophagus may kindle enthusiasm for screening for esophageal adenocarcinoma (EAC). Symptoms of gastroesophageal reflux disease (GERD) are recognized as *relative* risks for EAC. However, the *absolute* incidence of EAC in specific populations with GERD is unknown. We aimed to estimate the symptom-, age-, and sex-specific incidences of EAC, and place these incidences in the perspective of other cancers for which screening is endorsed.

Methods—A Markov computer model utilizing published and publicly available data was created to estimate the age- and sex-specific incidences of EAC in American white non-Hispanics with GERD symptoms.

Results—The incidence of EAC in men younger than 50 years with GERD symptoms is very low (for instance, at the age of 35 years, incidence = 1.0/100,000), and their incidence of colorectal cancer is relatively much higher (for instance, at the age of 35 years, incidence of colorectal cancer is 6.7-fold greater). The incidence of EAC in older men with weekly GERD symptoms is substantial (for instance, at the age of 70 years, incidence = 60.8/100,000 person-

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Correspondence: Joel H. Rubenstein, MD, MSc, Division of Gastroenterology, Veterans Affairs Center of Excellence for Clinical Management Research, VA Medical Center 111-D, 2215 Fuller Road, Ann Arbor, Michigan 48109, USA. jhr@umich.edu.

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Potential competing interests: James M. Scheiman has served as a consultant for AstraZeneca, Novartis, Pfizer, Bayer, Takeda, Pozen, and NiCox, and has received speaker's honoraria from Takeda and AstraZeneca. John M. Inadomi has served as a consultant to Takeda, AstraZeneca, and Ethicon Endo Surgery, and has received grant support from BARRX. Joel H. Rubenstein, Shahram Sadeghi, and David Whiteman have no relationships to disclose.

years), but their incidence of colorectal cancer is at least threefold greater. The incidence of EAC in women with GERD is extremely low, and similar to that of breast cancer in men (for instance, 3.9/100,000 person-years at the age of 60 years).

Conclusions—Screening for EAC should not be performed in men younger than 50 years or in women because of very low incidences of cancer, regardless of the frequency of GERD symptoms. In white men with weekly GERD over the age of 60 years, the incidence of EAC is substantial, and might warrant screening if that practice is particularly accurate, safe, effective, and inexpensive.

Introduction

Esophageal adenocarcinoma (EAC) is a particularly deadly neoplasm, and its incidence is rising rapidly (1,2). Symptoms of gastroesophageal reflux disease (GERD) are a major risk factor for EAC (3–7). As an endoscopically recognizable precancerous lesion, Barrett's esophagus, is associated with EAC (8), some subspecialty guidelines have advocated endoscopic screening of patients with GERD in an attempt to reduce mortality from EAC (9–11). Other guidelines have tempered such recommendations, citing the lack of proven efficacy of screening, and imprecision in estimating the risk of cancer in individual patients (12–14). The US Preventive Services Task Force has not published any guidelines for or against screening for EAC (15). Nonetheless, a recent survey of practicing American gastroenterologists found that 98 % would recommend screening a 55-year-old man with long-standing frequent GERD, and substantial proportions would screen other groups of patients with GERD (16). Recent advances in molecular and endoscopic markers predicting the risk of progression of Barrett's esophagus (17–19), and in the endoscopic treatment of neoplasia within Barrett's esophagus (20,21), will likely lead to greater enthusiasm for screening for EAC.

The US Institute of Medicine recently published a list of priorities for comparative-effectiveness research; within the top 25 priorities was to compare the effectiveness of upper endoscopy utilization in patients with GERD on the diagnosis of EAC (22). In addition to knowledge regarding the efficacy and adverse effects of a screening and endoscopic prevention strategy, assessing the net benefits of a screening strategy requires an understanding of the absolute risk of cancer in the screened population; in this case, patients with GERD. Although the *relative* risk of EAC is known to be increased by the presence of GERD, as well as by white race, male sex, and advancing age (14), the *absolute* age-, sex-, and race-specific incidences of EAC in patients with GERD has never been described in detail. We aimed to fill that gap by creating a computer model to estimate the incidence of EAC. To place our findings in context, we also compared the estimated absolute incidence of EAC with the observed incidence of colorectal and breast cancers, for which screening is recommended by the US Preventive Services Task Force (15).

Methods

The incidence of EAC in patients with GERD may be calculated using (i) the incidence in the baseline population (unstratified for the presence of GERD), (ii) the prevalence of GERD, and (iii) the standardized incidence ratio in people with GERD compared with those without GERD (see Supplementary Material online). We therefore created a Markov computer model using these three parameters. We obtained the incidence in the baseline population directly from the US Surveillance Epidemiology and End Results (SEER) cancer registry, the prevalence of GERD symptoms from a published systematic review (23), and the standardized incidence ratio in people with GERD compared with those without GERD from a meta-analysis of published studies (24). Derivation of each parameter is detailed

below. The study was exempted from review by the Institutional Review Board of the Ann Arbor Veterans Administration Medical Center.

Markov model of incidence of EAC

Using TreeAge Pro Suite 2009 software (TreeAge Software, Williamstown, MA), we created a Markov computer model of the development of EAC predicting the age- and sex-specific incidences of EAC in the general white non-Hispanic population, stratified by the presence or absence of clinically relevant GERD, and accounting for competing age-, sex-, and race-specific risk of death from all other causes (Figure 1) (25). We first defined GERD as occurring at least once weekly, and used the estimated standardized incidence ratio of EAC for men with weekly GERD compared with those without GERD or less frequent GERD. Therefore, the absolute incidences in both strata depended on the standardized incidence ratio of EAC for men without GERD (or less frequent GERD) compared with the general male, unstratified population. That standardized incidence ratio was calibrated such that the cumulative incidences of EAC in the Markov model summed across GERD strata was identical with the cumulative incidence of EAC expected in the general male white non-Hispanic population from SEER. We found that this also resulted in identical sums of age-specific incidences across GERD strata, with the expected age-specific incidences in the general male population. The validation of the model is reported in the Supplementary Materials.

The entire stratified model was then repeated for females, as well as with a threshold of GERD occurring at least daily compared with no GERD or less frequent symptoms for each sex. The incidence rates estimated from the Markov model were applied to the standard US population from 2005 in order to estimate absolute age-, sex-, and GERD-specific counts of EAC cases (26).

Data sources

Incidence of EAC—The US age- and sex-specific incidences of EAC for white non-Hispanics up to age 79 years were obtained using SEER*Stat software v.6.4.4 (The Surveillance Research Program of the Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD and Information Management Services, Silver Spring, MD) for the years 2000–2005, using an electronically available dataset from the SEER cancer registry (27). The set of International Classification of Diseases for Oncology, Third Edition codes used for EAC were 8140–8575, with a site of the esophagus. *In situ* cancers were excluded.

Standardized incidence ratio of GERD for EAC—The standardized incidence ratio of GERD for EAC was estimated from the random effects summary odds ratio of GERD symptoms for EAC from population-based studies with strict ascertainment of exposure and outcomes (24). For weekly GERD vs. less frequent or no GERD, the standardized incidence ratio was 4.92 (95 % confidence interval = 3.90, 6.22). For daily GERD vs. less frequent or no GERD, the standardized incidence ratio was 5.53 (95% confidence interval = 4.00, 7.65).

Prevalence of gastroesophageal reflux symptoms

Weekly GERD: A recently published systematic review of the prevalence of weekly GERD concluded that the prevalence has been rising in the United States by a 5% relative rate annually (23). Our base case prevalence of weekly GERD was therefore the most recently published estimate in a white population in the United States (28.2 % from a study published in 2004) (28). In sensitivity analysis, the upper limit utilized was the 95% upper confidence limit from that study (35.0%). The lower limit was the minimum of the prevalence found in that systematic review and in the control populations of the two American studies in the

meta-analysis of GERD symptoms and EAC risk (24), which resulted in a lower confidence limit of 11.6% (4).

Daily GERD: The published survey studies of the prevalence of GERD in the United States do not report the prevalence of daily symptoms. Instead, we used the weighted mean prevalence in the control populations of the two American studies in the meta-analysis of GERD symptoms and EAC risk (6.7%) (4,5). Since the symptoms reported in those two studies occurred around 1993, we applied a 5% annual increase (23) to estimate the prevalence in 2004 (the same year used in the base case for weekly GERD) at 11.5%. In the sensitivity analysis, the upper limit utilized the 95% upper confidence limit of the weighted mean prevalence (7.9%), and applied the 95% upper confidence limit of the annual increase in GERD (7.9%) (23), resulting in an upper estimate of daily GERD of 18.2% in 2004. The lower limit was directly obtained from the minimum of the estimates from the two American studies (6.0%).

Sensitivity analysis

The upper and lower confidence limits of the incidences of EAC in GERD were identified by simultaneously varying the prevalence of GERD and standardized incidence ratio of GERD for EAC, repeating this for each sex, and for both weekly and daily symptoms. The upper limit incidence scenario incorporated the upper limit of the standardized incidence ratio and the lower limit of the prevalence of GERD. The lower limit incidence scenario incorporated the lower limit of the standardized incidence ratio and the upper limit of the prevalence of GERD.

Comparisons to other cancers

In order to contextualize the symptom-specific incidence of EAC, we compared it with the age- and sex-specific incidences of colorectal and breast cancers in white non-Hispanics (unstratified with regards to GERD symptoms), because of the acceptance of screening for those cancers (15). The incidences of these cancers were obtained from the identical SEER data set from the identical time frame as the EAC incidence. We defined a benchmark as the minimum age- and sex-specific incidences of cancer at which screening has been endorsed for colorectal (incidence at the age of 50 years) or breast cancer (incidence at the age of 40 years) (15,29). As the current study does not assess the effectiveness of screening or the cost of such a policy, the data cannot support *positive* statements about which, if any, populations *should* be screened for EAC. Rather, by estimating the symptom-specific incidence of EAC, and comparing it to the incidence of cancers for which screening is believed to be effective and is endorsed, the data can support *negative* statements about which populations *should not* be screened, if the incidence of EAC in that population falls below the minimum incidences of colorectal or breast cancer for which screening is offered.

Outcomes

The primary outcomes of the study were the age- and sex-specific incidences of EAC in individuals with weekly or daily GERD symptoms. The secondary outcomes included the ages at which the incidence of EAC exceeded the benchmark minimum incidence of breast or colorectal cancer for which screening is endorsed. Another secondary outcome was the proportion of EAC arising from patients whose expected risk was greater than that benchmark.

Results

Incidence of EAC with weekly GERD symptoms

The incidence of EAC in women with weekly GERD was quite low at any age (Figure 2; Supplementary Table 1). For example, at 60 years, women with weekly GERD had an EAC incidence of 3.9/100,000 person-years. Furthermore, the EAC incidence in men *without* weekly GERD was greater than the EAC incidence in women with GERD at any age (Supplementary Table 1). The incidence of EAC in men with weekly GERD may be considered substantial over the age of 60 years. For example, at 70 years, such men are expected to have an annual incidence of EAC of 60.8/100,000. The incidences of EAC in men and women with daily GERD symptoms were only slightly greater than those with at least weekly symptoms (Figure 3; Supplementary Table 1).

Comparison to other cancers

At the ages that screening for cancer has been endorsed to commence in the United States, the incidence of breast cancer in women was 100.5/100,000 cases at the age of 40 years, the incidence of colorectal cancer in men was 47.2/100,000 at the age of 50 years, and the incidence of colorectal cancer in women was 35.6/100,000 at the age of 50 years. Therefore, we defined the benchmark incidence of cancer below which screening has not been recommended despite the availability of effective screening modalities, and this was found to be 35.6/100,000.

The incidence of EAC in women with weekly GERD was not expected to breach the benchmark incidence for screening at any age (Figure 2; Supplementary Table 1). For instance, at the age of 50 years, the incidence of EAC in a woman with GERD is expected to be an order of magnitude lower than her incidence of colorectal cancer. In fact, women with weekly GERD have a similar incidence of EAC as the incidence of breast cancer in men. Men with weekly GERD were expected to exceed the benchmark incidence at 61 years (Figure 2; Supplementary Table 1). However, at any age, the incidence of colorectal cancer was at least three times greater than the expected incidence of EAC in men with weekly GERD. For example, at the age of 70 years, men with weekly GERD had an expected incidence of EAC of 60.8/100,000 and an incidence of colorectal cancer of 265.6/100,000. This relative risk of colorectal cancer was even greater at younger ages. At 35 years, men with weekly GERD had an expected incidence of colorectal cancer that was 6.7 times that their expected incidence of EAC. In sensitivity analysis, men with weekly GERD breached the benchmark incidence between ages 55 and 64 years. Even in the upper limit sensitivity analysis, the incidence in women of any age did not exceed the benchmark.

In individuals with daily GERD symptoms, at all ages the incidence of EAC in women was lower than the benchmark incidence, including in sensitivity analyses (Figure 3; Supplementary Table 1). Men with daily GERD were expected to exceed the benchmark at the age of 55 years, and in sensitivity analyses, it ranged from ages 52 to 59 years (Figure 3; Supplementary Table 1).

Proportions of EAC cases arising from specific groups

Applying the incidences from the base case analysis to the US standard population from 2005 produced absolute counts of EAC cases. Among white non-Hispanics younger than the age of 80 years, there were 5,920 cases of EAC in 2005. The proportion of EAC cases arising from specific groups is shown in Figure 4. Men with weekly GERD > 60 years of age account for 36% of these EAC cases. Women account for only 12% of EAC cases, including all ages and regardless of GERD. Individuals without weekly GERD account for

34% of EAC cases. Men aged 55–60 years with daily GERD accounted for 7% of EAC cases (a stratum not shown in Figure 4).

Discussion

We synthesized data from multiple sources to estimate the age-, sex-, and symptom-specific incidences of EAC, and compared these incidences with those of cancers for which screening is recommended. A number of important observations arise from this study. First, we conclude that women of any age with GERD have a very low risk of developing EAC. This is due to the exceedingly low baseline incidence of EAC among women. Second, we conclude that the risk of EAC in men with GERD younger than 61 years (or younger than 55 years if GERD occurs daily) is relatively low; people with a similar risk for colorectal or breast cancer are not offered screening despite the accepted effectiveness of screening for those cancers. If we are to recommend screening for EAC among these younger men with GERD, then we should likewise be prepared to recommend average risk people younger than 50 years to undergo colon cancer screening. Finally, we conclude that the incidence of EAC is substantial in white men with at least weekly GERD who are above the age of 60 years, and in white men with at least daily GERD who are at least 55 years of age. Screening for EAC in these groups of men might be reasonable if the practice were effective; however, there is no high-quality evidence to support the contention that screening is effective for reducing mortality from EAC (13,14,30–34). Furthermore, the risk of colorectal cancer in these men is expected to be at least three times greater than their risk of EAC. Therefore, the highest yielding screening test in a 65-year-old man with GERD is one for colon cancer, not a test for EAC as many providers and patients may believe.

These findings contrast with the results of a survey of practicing American gastroenterologists (16). In that survey, 73% reported they would recommend screening for a 35-year-old man with GERD, but the current study estimates that such a patient has a risk of colorectal cancer that is over fivefold greater than his risk of EAC, and yet the patient would be very unlikely to be offered colorectal cancer screening. In the same survey, 42% of gastroenterologists would recommend screening for a 55-year-old woman with GERD, but the current study estimates that her risk of EAC is similar to a man's risk of developing breast cancer—not zero, but exceedingly small. Finally, the survey found that 16% would recommend screening for a 35-year-old woman with GERD; the current study estimates that her annual incidence of EAC is less than 1 per 1 million. Those providers' recommendations are likely in part due to too much attention assigned to the *relative* risk of GERD and too little to the baseline incidence of EAC (35). We hope that the current study can assist providers in recognizing the *absolute* risk of EAC in individual patients with GERD within the context of the risk of other more familiar cancers, and enable them to communicate these risks to patients to guide them in making rational decisions against screening for EAC.

Paradoxically, we found that despite the substantial incidence of EAC in older men with GERD, they only account for 43% of all EAC cases presenting under the age of 80 years. Therefore, any screening program directed at older men with GERD would be destined to have limited impact on reducing the mortality burden from this cancer, regardless of the efficacy of screening and patient and provider adherence to the screening program. A screening program might be applied to wider populations such as women or younger men with GERD, but the incremental resource utilization required to screen those populations would be in great excess to the incremental benefit. The conundrum might be resolved if additional factors were identified that could further stratify risk for EAC among the lower risk groups (women and younger men with GERD, or older men without GERD) and were incorporated in the model. Candidate factors would include obesity and tobacco use (7), but

incorporating them would require detailed recent data regarding the covariance of GERD, obesity, and tobacco use in Western populations.

To our knowledge, the only prior study on this topic was a letter describing the absolute incidence of EAC in the Swedish population limited to overweight men with GERD over the age of 50 years, and it did not provide the age-specific incidence (36). The current study estimates age-specific incidences for both American men and American women with GERD. We utilized a recursive Markov model design to estimate these incidences, validated by comparing the predicted age-specific incidence in the general population to that observed in two countries, and compared the predicted symptom-specific incidences with those predicted by a static mathematical model. We find that these redundant methods of validation are re-assuring.

Nonetheless, the current study is limited by available data. Although the first population-based study estimating the effect of duration of GERD symptoms on the incidence of EAC found a dramatic threshold effect at 20 years duration, the subsequent studies have found little or no effect of longer duration beyond the effect of frequency of GERD symptoms (3–7). Because of those heterogeneous findings, it is not clear if duration of GERD adds important information beyond frequency of GERD, and the model did not account for GERD duration. Another important limitation is that there were no recent estimates of the prevalence of daily GERD. The standardized incidence ratio of GERD for EAC was based on the summary odds ratio of published studies, and assumed to be the same at any age and for both sexes. Similarly, the prevalence of GERD was assumed to be the same at any age and for both sexes. The assumption regarding sex is generally supported, but the prevalence of GERD may actually peak in middle age (37–39). If we had used age-specific prevalences of GERD with a peak in middle age, the effect would have been to decrease the estimate of the incidence of EAC in middle age, and/or increase the incidence in older ages without altering the general conclusions (data not shown).

Finally, the benchmark incidence of cancer was implied by the observed incidences at which screening is offered for colorectal and breast cancer, but to our knowledge, the US Preventive Task Force does not utilize a specific threshold of cancer incidence for determining the age at which screening should be initiated. Other factors should also influence those guidelines, including the accuracy of screening, the fatality associated with the cancer, the biology of the cancer, and the safety and effectiveness of early treatment or preventive intervention (40). If screening for EAC were particularly inexpensive, accurate, safe, and effective in comparison to screening for breast and colorectal cancers, then it might be reasonable to screen at incidences lower than the identified benchmark. As it stands currently, however, screening for EAC would not appear to fit any of those criteria (31). Therefore, screening should not be endorsed for individuals with predicted incidences of EAC lower than this benchmark. Whether screening should be offered to individuals with predicted incidences greater than this benchmark (e.g., white men greater than 60 years of age with weekly GERD) cannot be directly addressed by the current study, but should also reflect the other factors important in determining screening policy listed above.

In conclusion, we synthesized available data to estimate the absolute age-, sex-, and symptom-specific incidences of EAC, finding that the incidence is substantial in older white men with GERD, but when compared with the risk of other screened cancers, their risk of EAC is much lower. In other groups, such as younger men with GERD, or in women of any age with those symptoms, the absolute risk is very low, and does not warrant screening. While a group that is at reasonably elevated risk for EAC has been identified, it still remains to be proven whether a screening program is effective and safe.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

What Is Current Knowledge

- Gastroesophageal reflux disease (GERD) symptoms are a relative risk factor for esophageal adenocarcinoma (EAC).
- The absolute risk of EAC in individuals with GERD is not known.
- Male sex, white race, and advancing age are also risk factors for EAC.

What is New Here

- Women with gastroesophageal reflux disease (GERD) likely have an incidence of esophageal adenocarcinoma (EAC) that is extremely low, and similar to the incidence of breast cancer in men.
- The incidence of EAC in white men older than 60 years of age with weekly GERD is substantial, but is one third of their incidence of colorectal cancer.
- The incidence of EAC in younger white men with GERD is less than one third of their incidence of colorectal cancer.

Figure 1.

Markov model. The Markov model stratifies the population into those with at least weekly gastroesophageal reflux disease (GERD) symptoms and those without GERD symptoms (or less frequent symptoms). In each stratum, there is an annual chance of developing esophageal adenocarcinoma (EAC) and dying from other causes. Those alive without EAC at the end of a year cycle again through the model. The annual incidence of EAC in those with GERD is determined by applying the standardized incidence ratio to the incidence in the stratum without GERD. The incidence in the stratum without GERD is determined by calibrating the standardized incidence ratio in that group compared with the unstratified population such that the summed incidence across strata is identical to the age- and sex-specific incidences obtained from SEER for the unstratified population. The model and calibration is repeated for a threshold of daily GERD symptoms, and for each sex.

Figure 2.

Estimated incidence of esophageal adenocarcinoma (EAC) with weekly gastroesophageal reflux disease (GERD) symptoms. Incidences of colorectal cancer (CRC) and breast cancer (BrCa) are displayed for context. The benchmark incidence of cancer for endorsed screening is demonstrated by the horizontal line. The incidences of BrCa in men and EAC in women with weekly GERD overlap in the figure. Thick lines represent EAC, thin lines represent CRC, and dotted lines represent BrCa. Thin dashed lines represent the upper and lower confidence limits of the incidence of EAC in men with weekly GERD, and the upper confidence limit of EAC in women with weekly GERD. The lower confidence limit for women with GERD overlap the point estimate incidence of EAC in women and are not visible on the figure.

Figure 3.

Estimated incidence of esophageal adenocarcinoma (EAC) in populations with daily gastroesophageal reflux disease (GERD) symptoms. This figure contrasts with Figure 2 in that GERD here is defined as occurring daily, and in Figure 2 it is defined as occurring at least weekly. BrCa, breast cancer; CRC, colorectal cancer.

Figure 4.

Proportion of esophageal adenocarcinomas (EACs) arising from specific populations. There were 5,920 estimated annual cases of EAC in the United States among white non-Hispanics younger than 80 years. This chart displays the estimated proportions of those cancers arising from specific populations, stratified by sex, age, and weekly gastroesophageal reflux disease (GERD).