

ORIGINAL CONTRIBUTIONS

Fundoplication and the Risk of Esophageal Cancer in Gastroesophageal Reflux Disease: A Veterans Affairs Cohort Study

Thomas Tran, M.D., Stuart J. Spechler, M.D., Peter Richardson, Ph.D., and Hashem B. El-Serag, M.D., M.P.H. *Department of Medicine, Baylor College of Medicine, Houston, Texas; Division of Gastroenterology, Dallas Veterans Affairs Medical Center, Texas; the Sections of Health Services Research at the Houston Department of Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas; and the Sections of Gastroenterology and Health Services Research at the Houston Department of Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas*

- BACKGROUND AND AIMS:** It has been proposed that fundoplication can reduce the risk of esophageal cancer in patients with gastroesophageal reflux disease (GERD). In this cohort study, we assessed the effect of fundoplication on the incidence of esophageal cancer.
- METHODS:** We identified all Veterans Affairs (VA) patients with GERD who had fundoplication between 1986 and 1990 and matched (1–2) to controls with GERD and no fundoplication and to controls with no GERD. We calculated incidence rates for esophageal cancer through October 2002 and examined the effect of fundoplication on the risk of esophageal cancer using Kaplan-Meier survival analysis and Cox proportional hazard analysis. We calculated and adjusted for the propensity score for receiving fundoplication.
- RESULTS:** We identified 946 patients who had fundoplication, 1,892 patients who had GERD without fundoplication, and 5,676 patients with no GERD. The mean age was 55 yr and 97.5% were men in all three groups. During a follow-up of 11,156 patient-years (PY), there were eight cases of esophageal cancer (72/100,000) in the fundoplication group. During a follow-up of 20,115 PY, there were eight cases of esophageal cancer (40/100,000) in the GERD without fundoplication group. During a follow-up of 59,439 PY, no patients in the group with no GERD developed esophageal cancer. The Kaplan-Meier analysis showed no significant difference in cumulative esophageal cancer rates between the fundoplication group and the GERD no-fundoplication group. The adjusted hazard ratio of esophageal cancer with fundoplication was 1.88 (95% CI: 0.70–5.03).
- CONCLUSIONS:** GERD is a risk factor for esophageal cancer, but there is insufficient evidence that fundoplication reduces that risk.

(Am J Gastroenterol 2005;100:1002–1008)

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common disorders of the gastrointestinal tract (1, 2). Surveys have shown that 10–20% of adults in western countries experience heartburn, the cardinal symptom of GERD, at least once a week (3, 4). It has been estimated that Americans spend \$9.3 billion each year for the evaluation and treatment of this chronic condition (5, 6). GERD can injure the stratified squamous epithelium that normally lines the distal esophagus and, in some patients, this injury heals through a metaplastic process in which the squamous epithelium is replaced by an abnormal, intestinal-type mucosa. This condition is called Barrett's esophagus, and the intestinal metaplasia of Barrett's esophagus predisposes to esophageal adenocarcinoma, a tu-

mor that has nearly quadrupled in frequency in the United States over the past two decades (7). A recent, well-publicized study has established that GERD is a strong risk factor for this tumor (8), and numerous reports on television and in the lay press have warned the public of the association between GERD and esophageal cancer.

Modern medical and surgical therapies for GERD are highly effective for healing the signs and symptoms of reflux esophagitis (9), but no antireflux therapy has been proved to decrease the risk of esophageal cancer (10). Nevertheless, it has been proposed that fundoplication surgery (which creates a barrier to the reflux of all gastric contents) might be more effective than medical therapy (which is directed primarily at decreasing gastric acid secretion) for preventing esophageal neoplasia (11–13). Some small,

methodologically flawed studies of patients with Barrett's esophagus who received medical and surgical therapies for GERD have supported this contention by describing fewer cases of dysplasia and cancer among surgically treated patients (14–16). Some authorities even have proposed that the medical treatment of GERD with histamine H₂-receptor antagonists and proton pump inhibitors (PPI) might predispose to esophageal cancer, perhaps by promoting bacterial colonization of the upper gastrointestinal tract (17, 18), and that the increasing use of antisecretory medications may be contributing to the rising frequency of esophageal cancer (19).

Fueled by the development of minimally invasive (laparoscopic) surgical approaches and by public concern about esophageal cancer, fundoplication has become increasingly popular as an antireflux therapy. In New England, for example, the population-based rate of antireflux surgery more than doubled during the 1990s (20). However, several modern studies, including a recent metaanalysis, have found no significant cancer-preventive effect for fundoplication compared to medical antireflux therapy for patients with GERD and Barrett's esophagus (21–23). To explore this issue further, we utilized the computerized databases of the Department of Veterans Affairs (VA) Healthcare System to estimate the long-term incidence of esophageal cancer in patients who had medical and surgical treatments for GERD, and in control patients without GERD.

MATERIALS AND METHODS

Data Source

We used several computerized national VA databases for our analyses. The Patient Treatment File (PTF) contains inpatient records from all 172 VA hospitals in the United States. Discharge diagnoses are contained in the main files of the PTF. Procedures performed in the operating room are listed in the surgical procedural files of the PTF. The Outpatient Clinic (OPC) File contains records of outpatient diagnoses since October 1996. The ninth revision of the Clinical Modification of the International Classification of Diseases (ICD-9) is used to encode diagnoses and procedures (24). Lastly, the Beneficiary Identification and Records Locator Subsystem (BIRLS) Death File contains all deaths of veteran patients reported to the Veterans Benefits Administration. The BIRLS file is updated twice each month and is more than 90% complete as compared with the National Death Index. Causes of death are generally not available in the BIRLS file.

Study Subjects

All VA patients with a primary or secondary diagnosis of GERD (ICD-9 codes 530.1 for erosive esophagitis, 530.3 for esophageal stricture, 530.81 for gastroesophageal reflux, and 530.2 for esophageal ulcer) between 1986 and 1990 were eligible for enrollment. The year 1986 was chosen to be the starting point of enrollment because ICD-9 has been used by

the VA system since 1981, and we wanted to review clinical information for at least 5 yr prior to the index hospitalizations. The year 1990 was chosen as the ending point of the enrollment period to ensure that all surgical antireflux procedures were open fundoplications (laparoscopic fundoplication has been available since 1991) and that the follow-up period would be at least 10 yr. The sampling frame comprised unique patients and not hospitalization episodes. The date of discharge (alive) from the first hospitalization episode (in case of multiple episodes) was the index date for the inception of follow-up. The inpatient medical and surgical records were accumulated for each patient in the three cohort groups described below (5 yr prior and all years following the index hospitalization).

We excluded patients with a diagnosis of infectious, radiation-induced, or caustic esophagitis within 5 yr prior to index hospitalization to avoid including patients with nonreflux-related esophagitis. (These disorders were identified by: E864 for accidental poisoning by corrosives and caustics, E926 for exposure to radiation, E950 for suicide and self-inflicted poisoning by solid or liquid substances, E980 for poisoning by solid or liquid substances, undetermined whether accidentally or purposely inflicted, V15.3 for irradiation, V58.0 for radiotherapy, V67.1 for following radiotherapy, 054.79 for herpes simplex infection-other, 078.5 cytomegalovirus disease, 112.84 for candidal esophagitis, 112.89 for other candidiasis, 112.9 candidiasis of unspecified site, 279.06 for common variable immunodeficiency, 947.2 for esophageal burn, 947.3 for burn of gastrointestinal tract, and 990 for unspecified effects of radiation). We also excluded patients who had fundoplication before the time of enrollment and as far back as 1981. This was to avoid the index date being for reoperation. Lastly, we excluded patients with any diagnosis of malignancy, except basal cell skin cancer, 5 yr before or 1 yr after the index hospitalization (ICD-9 codes 199.1 for primary or secondary malignancy, 234.9 for carcinoma *in situ*, 238.9 for neoplasm of uncertain behavior, 239.9 for neoplasm of unspecified nature). We excluded these patients because they are unlikely to be treated with antireflux surgery and are likely to have a high mortality.

Study Cohorts

The study comprised three distinct cohorts.

1. The GERD fundoplication cohort included all patients who had a fundoplication during the enrollment period (ICD-9 code 44.66 for fundoplication, gastric cardioplasty, Nissen's fundoplication, and restoration of cardioesophageal angle).
2. The GERD medical cohort was selected based on a 2:1 ratio (2 GERD medical patients for 1 GERD fundoplication patient). We conducted frequency matching on 5-yr periods of age at index hospitalization.
3. The non-GERD cohort was assembled by randomly identifying 2 non-GERD patients (who had no primary or secondary GERD diagnoses by ICD-9 codes) for each GERD

patient. We also conducted frequency matching on 5-yr periods of age at index hospitalization.

Comorbidities of the three cohorts were identified during a 1-yr period preceding the index hospitalization, and were quantified using the Deyo's modification of the Charlson Comorbidity index. This index has been shown to be predictive of short-term mortality (25).

Outcomes

The patients' unique Social Security numbers were used to follow study subjects through the annual files of the PTF, OPC, and BIRLS Death starting from the day of enrollment until the end of the calendar year 2002. The primary outcome was new cases of esophageal cancer irrespective of site (ICD-9 codes 150.9, 150.2, 150.8, 150.5, 150.4, 150.1, 151.0) in the three study groups. The secondary outcome was the occurrence of death in the BIRLS Death File or the Main Files of the PTF.

Statistical Analysis

The three groups were compared with regard to variables obtained at the index hospitalization. χ^2 tests were employed for comparison of categorical variables, and analysis of variance (ANOVA) tests were used for comparison of continuous variables. The study outcomes (esophageal cancer and death) were examined in Kaplan-Meier survival analyses stratified by cohorts (GERD fundoplication, GERD medical, non-GERD). The inception point for follow-up was the date of fundoplication, or the date of index hospitalization for nonsurgical patients. Censoring was employed for death and at the end of follow-up (December 2002). Statistical significance was tested using the log-rank test. We conducted an adjusted analysis using the Cox proportional hazards (PH) model. Covariates included demographic features (age, gender, and ethnicity (White, Black, Other)), comorbidity index, and cohort status. Hazard ratios and 95% confidence intervals were calculated for each covariate. The PH assumption was tested using log-log calculations and was satisfied in all models (26).

To examine the robustness of the results, we calculated a propensity score for receiving fundoplication using age, gender, race, and comorbidity score as covariates (27, 28). We subsequently adjusted for the propensity score in the Cox PH model predicting esophageal cancer. We also performed a Cox PH analysis with a restricted group of patients who had GERD complications (ICD-9 codes 530.1 for erosive esophagitis, 530.3 for esophageal stricture, and 530.2 for esophageal ulcer).

RESULTS

Between 1986 and 1990, 63,199 patients with a primary or secondary diagnosis of GERD were identified. A total of 22,183 patients were excluded for the following reasons: previous hospitalization (6,868), age younger than 25 yr or

older than 75 yr (5,023), death during the index hospitalization (2,030), diagnosis of infectious, radiation-induced, or caustic esophagitis (2,492), any diagnosis of cancer (5,500), HIV (248), and previous funduplications (22). Among the remaining 41,016 patients, 946 (2.3%) had fundoplication, and 1,892 age-matched patients were randomly assigned as the GERD medical group. We also identified 5,676 patients with no GERD diagnoses who were randomly selected without replacement by a 2:1 frequency matching to GERD cases on 5-yr age groups. The baseline demographic characteristics of the three groups are shown in Table 1. There were no significant differences in age or gender among the groups. There was a significantly greater proportion of White patients in the GERD fundoplication group compared to the GERD medical group; both GERD groups had a significantly greater proportion of White patients than the non-GERD group.

Esophageal Cancer

We analyzed the occurrence of new cases of esophageal cancer in the three study groups starting 1 yr following the index hospitalization until death or until December 31, 2002. During a follow-up period of 59,439 patient-years (PY) and a mean duration of 10.5 yr, no patients in the non-GERD group were diagnosed with esophageal cancer. During a follow-up period of 20,115 patient-years and a mean duration of 10.6 yr, there were eight cases of esophageal cancer (40/100,000 PY) in the GERD medical group. During a follow-up period of 11,156 patient-years and a mean duration of 11.8 yr, there were eight cases of esophageal cancer (72/100,000 PY) in the GERD fundoplication group. The difference in esophageal cancer incidence rates between the two GERD groups was not statistically significant. In the fundoplication group, there were four in lower third and four unspecified site; in the non-fundoplication (8 total), there was one in lower third, one in middle and lower thirds, and six unspecified site.

The Kaplan-Meier survival analysis for esophageal cancer of the GERD medical *versus* the GERD fundoplication groups is shown in Figure 1. There was no statistically significant difference between the cumulative rates of esophageal cancer in the GERD fundoplication group *versus* the GERD medical group (p for log-rank test = 0.15). Separate Cox PH models adjusted for each of age, ethnicity, gender, and Deyo comorbidity index showed that the hazard ratio of developing esophageal cancer among fundoplication patients was between 1.83 and 2.11 (all $p > 0.05$). The hazard ratios of developing esophageal cancer for these covariates in four separate models are shown in Table 2. We limited the number of predictor variables to two in each model to avoid overfitting the model given the low number of outcome events. Using a logistic regression model, we calculated a propensity score for receiving fundoplication using age, gender, race, and comorbidity score as covariates. Subsequently, we examined the effect of fundoplication on esophageal cancer in a Cox PH model that adjusted for propensity score. The hazard ratio associated with fundoplication in that model was not different from previous models (Table 2).

Table 1. Baseline Demographic Characteristics of the Three Study Groups

| Characteristics | GERD Fundoplication (n = 946) | GERD Medical (n = 1,892) | Non-GERD (n = 5,676) | p-Values |
|----------------------------|-------------------------------|--------------------------|----------------------|----------|
| Age at index (yr) \pm SD | 54.9 \pm 11.9 | 55.0 \pm 11.8 | 54.9 \pm 11.9 | 0.99 |
| Male sex (%) | 922 (97.5) | 1847 (97.6) | 5545 (97.7) | 0.16 |
| White race (%) | 874 (92.4) | 1533 (81.0) | 4302 (75.8) | <0.0001 |

Given that Barrett's esophagus is likely to be associated with severe erosive esophagitis, strictures, or ulcers (complicated GERD), we also restricted the Cox PH analysis to patients with GERD complications; the adjusted hazard ratio of developing esophageal cancer among fundoplication patients was 1.84 (95% CI: 0.68–4.93, $p = 0.23$). Similarly, we restricted the analysis to Caucasian patients, and fundoplication was associated with an adjusted hazard ratio of 1.56 (95% CI: 0.71–3.91, $p = 0.33$).

Mortality

We analyzed the occurrence of deaths recorded in the BIRLS files following the index hospitalization until December 31, 2002 in the three groups. In the non-GERD group, 2,676 of 5,676 patients (47.15%) died during a follow-up period of 59,439 patient-years. The mean duration of follow-up was 10.5 yr. In the GERD medical group, 887 of 1,892 patients

(46.88%) died during a follow-up period of 20,115 patient-years and a mean duration of 10.6 yr. During a follow-up period of 11,156 patient-years and a mean duration of follow-up of 11.8 yr, 348 of 946 patients (36.79%) died in the GERD fundoplication group.

The cumulative mortality rate was greater in the non-GERD and the GERD medical groups than in the GERD fundoplication group (p for log-rank test < 0.0001). Patients in the GERD medical group were significantly sicker than those in the GERD fundoplication group; the mean Deyo score was 0.90 for the medical group compared to 0.44 for the fundoplication group ($p < 0.0001$). Further analyses were performed in the two GERD groups to evaluate the mortality rate difference. A Deyo comorbidity of zero suggests that the patient has no significant chronic illnesses. When data were analyzed for patients with a Deyo comorbidity index of zero only, the mortality rate difference became statistically

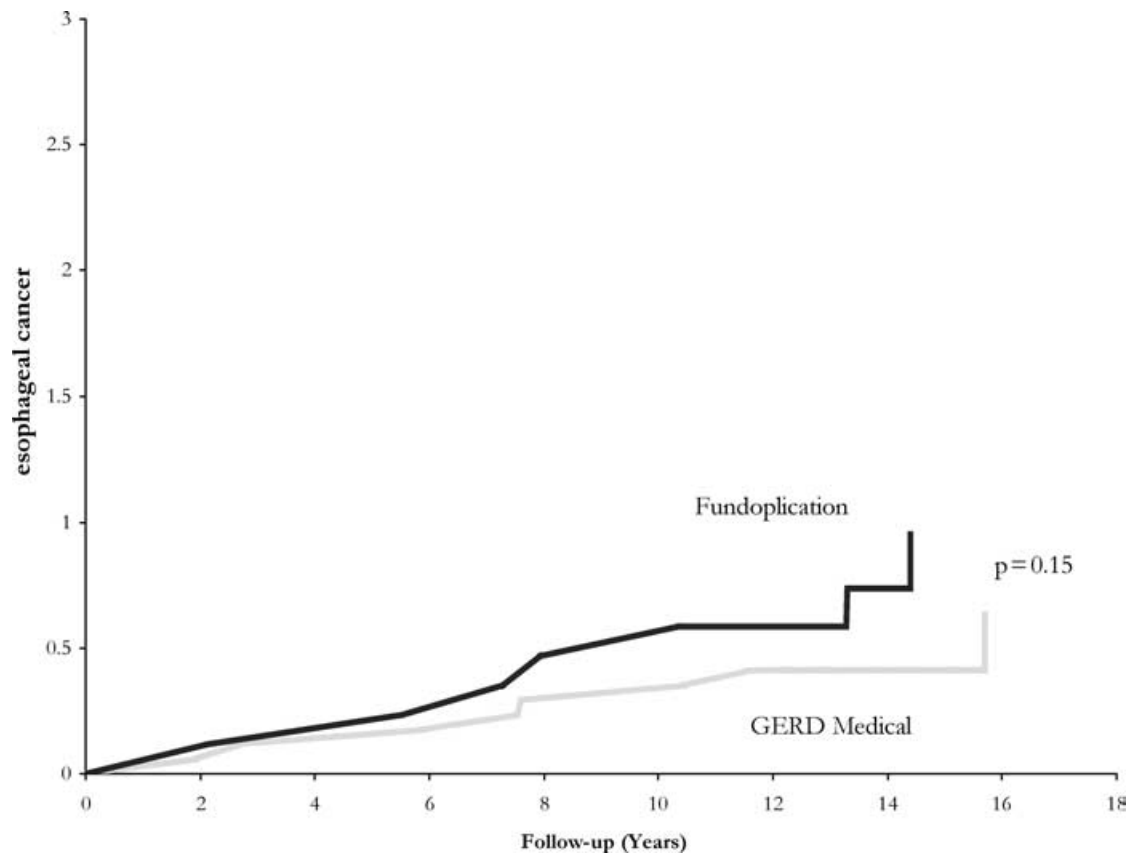


Figure 1. Kaplan-Meier graph for the cumulative incidence rates of esophageal cancer between the GERD medical and the GERD fundoplication groups. The difference between the incidence rates was not statistically different. There were no recorded cases of esophageal cancer in the non-GERD group, which is not shown.

Table 2. Potential Risk Factors for Developing Esophageal Cancer (n = 16). Results of Cox Proportional Hazard Analysis. Four Separate Models were Constructed each Examining Fundoplication to only One Variable

| Variables | Hazard Ratio | 95% Confidence Limits | p-Values |
|--|--------------|-----------------------|----------|
| Fundoplication adjusted for: | | | |
| Age | 2.02 | 0.76–5.40 | 0.16 |
| Female gender | 2.04 | 0.76–5.42 | 0.16 |
| Race | 1.83 | 0.69–4.88 | 0.23 |
| Deyo comorbidity | 2.11 | 0.77–3.54 | 0.15 |
| *Propensity score | 1.51 | 0.45–2.97 | 0.09 |
| Age (for each additional year) | 1.04 | 0.99–1.10 | 0.11 |
| White race | 1.85 | 0.24–14.18 | 0.69 |
| Female gender | 2.32 | 0.31–17.53 | 0.42 |
| Deyo comorbidity index score (for each additional point) | 1.10 | 0.70–1.72 | 1.10 |

*Propensity score (for receiving fundoplication) was calculated for each individual using age, gender, race, and comorbidity score as covariates.

nonsignificant. For example, when the Cox analysis was limited to patients with Deyo comorbidity score of zero only, the relative risk of mortality among fundoplication patients was 0.84 (95% CI: 0.71–1.00, $p = 0.05$). Similarly, when the analysis was repeated for deaths occurring after the first year of follow-up in those with comorbidity score 0, the hazard ratio was 0.86 (95% CI: 0.72–1.02, $p = 0.09$).

DISCUSSION

Several small studies of medical and surgical treatments for patients with Barrett's esophagus have found that the surgically treated group developed fewer cases of esophageal dysplasia or cancer (14–16). In addition, at least one meta-analysis has concluded that surgery appears to be superior to medical therapy in reducing the incidence of cancer in Barrett's esophagus (29). However, a more recent meta-analysis found no significant difference in the incidence of cancer in Barrett's esophagus between medically- and surgically treated patients (23). Furthermore, the authors pointed out serious deficiencies in the other metaanalysis. For example, the metaanalysis that found a cancer-protective effect for surgery included studies whose follow-up was less than 1 yr (29). Such studies should have been excluded because cancers found within 1 yr of treatment likely were present when the treatment was initiated. For reasons that are not clear, the earlier report also did not consider a number of key studies included in the more recent metaanalysis, studies that may well have altered the conclusions of the earlier investigation.

A recent report describing the long-term outcome of a randomized trial of medical and surgical therapies for 247 veteran patients with complicated GERD (including 108 with Barrett's esophagus) provides little support for the contention that fundoplication prevents esophageal cancer better than antisecretory therapy (21). During 10–13 yr of follow-up, 4 of 165 patients (2.4%) in the medical group and 1 of 82 (1.2%) in the surgical group developed an esophageal adenocarcinoma. The difference between the treatment groups in the incidence of this tumor was not statistically significant but, with such a low observed rate of cancer development, the study did not have sufficient statistical power to detect small

differences in the incidence of esophageal cancer. However, any potential cancer-preventive benefit of surgery was offset by an unexplained, but significant, decrease in survival for the surgical patients due to excess deaths from heart disease.

Although GERD and Barrett's esophagus are strong risk factors for esophageal adenocarcinoma, the incidence of the tumor in individuals with those conditions is low nevertheless. Recent estimates suggest that patients with Barrett's esophagus develop adenocarcinoma at the rate of 0.5% per year (30), whereas the cancer incidence is less than 0.1% per year for those who have GERD without Barrett's esophagus (21). With such low cancer incidence rates, meaningful studies on the cancer-protective effects of treatments require large numbers of patients and long durations of follow-up. In a Swedish, population-based cohort study in which patients with GERD were followed for up to 32 yr, the relative risk for developing esophageal adenocarcinoma (compared to the general population) among 35,274 men who received medical antireflux therapy was 6.3 (95% CI: 4.5–8.7), whereas the relative risk for 6,406 men treated with fundoplication was 14.1 (95% CI: 8.0–22.8) (22). No comparable study has been conducted in the United States.

We have conducted a large, retrospective, cohort study using the computerized databases of the VA Healthcare System to explore the long-term incidence of esophageal cancer among veteran patients who had medical and surgical treatments for GERD. Among 946 patients with fundoplications who were followed for a mean duration of 11.8 yr, the incidence of esophageal cancer was 0.072%, whereas the incidence of this cancer in 1,892 age-matched, medically treated patients with GERD who were followed for a mean duration of 10.6 yr was 0.04% (NS). Thus, we found no cancer-protective effect for antireflux surgery. Interestingly, none of the 5,676 control patients who had no GERD diagnoses developed an esophageal cancer during a mean follow-up period of 10.5 yr. Apparently, the incidence of esophageal cancer is extremely small in patients without GERD. The findings persisted in sensitivity analyses restricted to Caucasians only or to those with complicated GERD only.

The major strengths of our investigation include the large sample size, the long durations of follow-up, the use of two

control groups, matching for age to increase the comparability of these groups, and near complete ascertainment of deaths. We examined cases of esophageal cancer reported after 1 yr of follow-up thus minimizing the likelihood of including prevalent cases of cancer; this reduces the possibility of a selection bias where patients with complications related to esophageal cancer get preferentially enrolled in the study. Even though the number of events is relatively small, our study still has the largest number of esophageal cancer cases among similar studies to date. A recent metaanalysis found only 44 cases of esophageal cancer in 34 studies (23). One might argue that our study as well as the Swedish study did not have sufficient power to detect differences due to the very small number of cases with esophageal cancer. Given the very small number of cases of esophageal cancer, it will take almost double the size of the current study to identify statistically significant reduction in esophageal cancer with fundoplication. Lastly, the calculation of a propensity score for receiving fundoplication is an attempt to adjust for baseline differences between the groups receiving therapy (quasi-randomization) (27, 28). More importantly, in this study, having a propensity score allowed for more efficient modeling of the risk of esophageal cancer in the presence of few outcome events; we used one variable (propensity score) that encompassed four variables (age, gender, race, comorbidity score).

Potential weaknesses are the retrospective nature of the study and the inclusion of only veteran patients who are predominantly White men. However, adenocarcinoma of the esophagus is predominantly a disease of White men, and it can be argued that our patients are exceptionally well suited for a study designed to demonstrate a cancer-protective effect of antireflux therapy. There was a concern that Caucasian patients were overrepresented in the fundoplication group. However, similar findings were obtained when the analyses were restricted to Caucasian patients only; fundoplication was associated with an adjusted hazard ratio of 1.56 (95% CI: 0.71–3.91, $p = 0.33$). The sampling frame of hospitalized patients with GERD and no fundoplication may have resulted in the inclusion of patients with severe GERD (as compared to ambulatory patients). This could have resulted in conservative estimates of hazard ratios. Another potential weakness is that patients were identified on the basis of ICD-9 codes whose completeness and validity have not been formally tested. It also was not possible to examine the integrity of fundoplication or the type of medical therapy. There was a concern that a diagnosis of GERD based only on symptoms may or may not represent GERD. Therefore, we performed a Cox PH analysis on patients with a diagnosis of GERD complications (which required at least one diagnostic test to make the diagnosis). The results were similar to those using the more general definition of GERD, thus confirming the validity of our method. Another potential limitation is the use of hospitalization as baseline markers because GERD is usually diagnosed during outpatient clinic visits. However, the VA Outpatient Clinic File was not available

until October 1996, which was after our enrollment period. While the study cohort may not be representative of the entire GERD population in VA, it is likely to include those with severe GERD (severe enough to be recorded during hospitalization) and therefore more likely to develop esophageal cancer. The use of hospitalization also offers an opportunity to capture and therefore adjust for comorbidity. Lastly, the prevalence of Barrett's esophagus could not be ascertained in either group; it is conceivable but unknown if the surgical group had a higher prevalence of Barrett's esophagus. This limitation applies also to the previously conducted Swedish study (22). This could have led to relative increase in the risk of esophageal adenocarcinoma in the fundoplication group thus masking a potential beneficial effect. However, this is not a high probability given the relatively young age (54 yr) as compared to median age of 61 for Barrett's esophagus, and that the prevalence of Barrett's esophagus in surgical series contemporary to our study had ranged between 10% and 18% (29). Moreover, this effect is counteracted by the fact that medical patients were unlikely to be treated with effective therapy (PPI) during the first several years of follow-up. Even if Barrett's esophagus is twice as common in the surgical group compared to the medical group (for example 20% vs 10%), one can show by a back of the envelope calculation (and assuming 0.5% annual risk of cancer in Barrett's and the same PY follow-up observed in this study) that there will be six cases in the surgical group as compared with five cases in the medical group. Thus, we believe that our study design was reasonable, and that our conclusions are likely to be valid.

Fundoplication has been largely changed to laparoscopic and medical treatment for GERD has changed to proton pump inhibitors during the last 10 yr; these changes are likely to favor medical therapy since the open and laparoscopic operation have similar efficacy in controlling reflux. Thus, this study is as relevant to patient care now as in the past.

Unlike the VA Cooperative Study on GERD (21), we did not find that antireflux surgery adversely affected survival. Indeed, the cumulative mortality rate was greater in the control and GERD-medical groups than in the GERD-fundoplication group (p for log-rank test < 0.0001). There are a number of potential explanations for this disparity. First, it is possible that the significant difference in mortality between the medical and surgical groups in the VA Cooperative Study was merely a statistical aberration, and that surgery had no true adverse affect on survival. Alternatively, it is possible that antireflux surgery does affect survival in truly comparable patients, but that this effect is masked in our study because only healthier patients are likely to be referred for fundoplication. To explore this possibility, we identified and quantified comorbidities in our patients using the Deyo's modification of the Charlson Comorbidity index, which has been shown to be predictive of short-term mortality (25). The Deyo comorbidity index was 0.90 for the GERD-medical group compared to only 0.44 for the GERD-fundoplication group ($p < 0.0001$), indicating that the medically treated patients had significantly greater comorbidities. Nevertheless, the question of

whether fundoplication affects survival from diseases other than esophageal cancer remains an open issue that would be best resolved by prospective, randomized studies of comparable patients.

In conclusion, we have found insufficient data to support the cancer-protective effect for antireflux surgery in a large, retrospective, cohort study that used the computerized databases of the VA Healthcare System. Although fundoplication can be highly effective at eliminating the peptic complications of GERD, there is not enough evidence to support the use of this operation for esophageal cancer prophylaxis.

ACKNOWLEDGMENT

Dr. El-Serag is a VA HSR&D Awardee (RCD00-013-2).

Reprint requests and correspondence: Hashem B. El-Serag, M.D., M.P.H., The Houston Veterans Affairs Medical Center (152), 2002 Holcombe Blvd., Houston, TX 77030.

Received June 19, 2004; accepted October 29, 2004.

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