Association of Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus with Tobacco-related and Other Malignancies[1]

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Abstract

Little is known about the etiology of esophageal and gastric cardia adenocarcinoma (EGA), a cancer with one of the fastest-rising incidences in the developed world. To explore the etiology of this cancer, we conducted a retrospective cohort analysis using data from the Surveillance, Epidemiology and End Results Program of the United States National Cancer Institute to study EGA and esophageal squamous cell carcinoma (ESC), in association with cancers of other sites. Standardized incidence ratios, adjusted for age, sex, and time period, were calculated as a measure of the relative risk (RR) of developing a second primary cancer (EGA or ESC) following a given first primary site. We found a moderately elevated risk of EGA following cancers of the lung (RR = 1.9 in men and RR = 2.0 in women) and of the head and neck (RR = 2.1 in men and RR = 6.3 in women) and a strongly elevated risk of ESC following cancers of the lung (RR = 2.8 in men and RR = 5.1 in women) and of the head and neck (RR = 9.6 in men and RR = 38.8 in women). A significantly elevated risk following breast cancer in women was observed for both EGA (RR = 2.6; 95% confidence interval, 1.8–3.7) and ESC (RR = 1.4; 95% confidence interval, 1.1–1.9). We also found a significantly elevated risk of EGA following bladder (RR = 2.0), colorectal (RR = 1.7), and prostate (RR = 1.4) cancer in men and of ESC following colorectal cancer (RR = 1.7) in women in this study. The strong association with tobacco-related malignancies in this study reinforces the role of tobacco in the etiology of esophageal cancers, which appears stronger for squamous cell carcinoma than for adenocarcinoma and stronger in women than in men. The study also suggests a possible shared etiology between esophageal adenocarcinoma and colorectal cancer in men and provides new evidence about the association of both adenocarcinoma and squamous cell carcinoma of the esophagus with breast cancer in women. Findings of this study provide clues to the etiology of EGA and ESC.

Introduction

One of the most dramatic recent trends in cancer incidence has been the rapid rise in the incidence of EGA[3], which has occurred over the past two decades in the Western world, including the United States (1, 2). The incidence rate of EGA, once rare, is now almost equal to the incidence rate of ESC, which has remained stable over the same period (3). Except for Barrett's esophagus (4, 5), little is known about the etiology of this rapidly increasing malignancy. It is only in recent years that a number of epidemiological studies, instigated by these dramatic changes, have started investigating risk factors for EGA as a separate entity (6–11) because the risk factors identified from previous studies of esophageal cancer pertain mostly to ESC.

The risk factors that have been identified for EGA from these recent studies are cigarette smoking, alcohol consumption, obesity, and gastroesophageal reflux disease (6–11). However, tobacco and alcohol, the strongest known risk factors for ESC, have not been found to be as important for EGA and cannot completely explain the recent rise in its incidence. The magnitude of the effect of tobacco and alcohol exposure for EGA ranges from a RR of 1 to 3 in different studies (6–9). Obesity, which is inversely associated with ESC, is found to be positively associated with EGA (7, 9, 10). The rising level of obesity of the United States population (12) may correlate with the rising incidence of EGA. These three factors together, as estimated in one study, can account for only about 50% of EGA cases (7). Other risk factors that have been associated with EGA are poor socioeconomic status, history of duodenal ulcer, low intake of fruits and vegetables, and high dietary fat (6, 8, 10).

Studies of multiple primary malignancies have been a useful tool for exploring risk factors by examining associations between different malignancies. An association between two cancers might suggest that those cancers share etiological risk factors. Other possible explanations for such an association would be hereditary predisposition to both cancers, treatment effects of one cancer on another, or a chance phenomenon (13). The association of esophageal cancers with tobacco-related cancers (lung and head and neck; Ref. 14) and with colorectal cancer (15) has been shown recently. In an effort to explore the etiology of EGA, we conducted a population-based retrospective cohort study to examine the occurrence of these cancers and esophageal squamous cell cancers in association with can-

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[3] The abbreviations used are: EGA, esophageal and gastric cardia adenocarcinoma; ESC, esophageal squamous cell carcinoma; RR, relative risk; SEER, Surveillance, Epidemiology and End Results; UGI, upper gastrointestinal; SIR, standardized incidence ratio; CI, confidence interval.

Table 1 Distribution of first and second primary esophageal and gastric cancers by sex[a]

Type of cancer	Men				Women			
	First primary		Second primary		First primary		Second primary	
	No.	%	No.	%	No.	%	No.	%
EGA	5,554	92.2	470	7.8	1,197	89.7	137	10.3
ESC	6,192	88.1	839	11.9	2,683	85.5	454	14.5
Distal gastric adenocarcinoma	11,455	92.1	987	7.9	7,485	90.0	835	10.0

[a] Ref. 16.

cers of other sites. We included distal gastric adenocarcinomas in our study for comparison purposes.

Materials and Methods

The SEER Program of the United States National Cancer Institute has been collecting information on cancers since 1973 through several population-based cancer registries. These registries together cover geographical areas containing about 10% of the United States population. We used data on about 1.6 million cancer cases diagnosed between 1973 and 1990 (16). For each case, SEER collects information on treatment, histology, survival, and occurrence of subsequent primary cancers, among other variables. A sequence number is assigned to an individual when a cancer is diagnosed for the first time, and for each subsequent diagnosis with a new primary, this sequence number is updated consecutively. Multiple primary cancers of the same individual registered in SEER can thus be linked through this sequence number. The information SEER collects is considered to be of high quality (17), and more than 90% of cases are microscopically confirmed (16).

This study investigated the occurrence of three different types of UGI cancers, EGA, ESC, and distal gastric adenocarcinoma, as second primary malignancies. Because UGI cancers, particularly esophageal cancers, have very poor survival rates, we could not investigate other cancers as second primary malignancies following UGI cancers. As in other studies (7–9), we analyzed esophageal adenocarcinoma and gastric cardia adenocarcinoma as a single entity in this study. Adopting a retrospective cohort design, we calculated the SIR, based on the general population incidence rates, as an estimate of RR of second primary malignancy following a given cancer of another site. We excluded from our analysis carcinomas *in situ*, cases diagnosed at autopsy or from death certificates, and second primary cancers for which the first primary occurred prior to 1973 or outside SEER areas. UGI cancers occurring as third or later primaries were also excluded.

We chose a number of first primary sites, following which the occurrence of second primary UGI cancers was studied. Our *a priori* expectation was that ESC would be strongly associated with tobacco-related malignancies, *e.g.*, lung and head and neck cancers, EGA would be less strongly associated with and distal gastric adenocarcinoma would be very weakly or unrelated to tobacco-related malignancies. Other associations that were examined in this study were mainly exploratory.

The methodology for calculating the SIR for second primary malignancy has been described previously (18) and is only briefly presented here. For each pair of cancers, first, the total number of second primary cancers diagnosed at least 3 months following the first primary site was calculated. Cases diagnosed within 3 months of the first primary were not included because these cases might not have been diagnosed had these patients not gone through the extra diagnostic work-up due to the first primary. We then estimated the sex-specific, age-specific (every 5 years), and period-specific (every 3 years) person-years of follow-up for the cases with that first primary site. We also calculated the sex-specific, age-specific (every 5 years), and period-specific (every 3 years) general population incidence rates for the second primary cancer types using SEER data. These category-specific incidence rates were then applied to the person-years of follow-up of the respective categories to estimate the expected number of second cancers following that particular first primary site. The ratio of the observed to the expected number of cases (incidence rate ratio) constituted the RR of a second primary cancer for a given first primary site. We calculated these RRs separately for all three second primary cancer types, following a number of different first primary sites. We also calculated the 95% CI around this RR using Byar's limits, assuming that the occurrence of the second primary malignancies followed a Poisson distribution (19).

Results

As shown in Table 1, ESC occurred more commonly as a second primary malignancy in both men and women than did EGA and distal gastric adenocarcinoma.

The RRs for a second primary UGI cancer are presented in Tables 2 and 3. As expected, the RR of ESC as a second primary was highly elevated, and that of EGA was moderately elevated following tobacco-related malignancies, particularly following lung cancer in women and head and neck cancers in both men and women. For both EGA and ESC, this association was stronger in women than in men with the RR for ESC following head and neck cancer in women reaching 38.8 (95% CI, 31.3–47.5). An association of EGA with bladder cancer and an association of distal gastric adenocarcinoma with lung cancer in men were the other associations observed between UGI cancers and tobacco-related malignancies in this study.

The associations of EGA and ESC with colorectal cancer followed a different pattern. Whereas the RR of a second primary EGA following colorectal cancer was elevated in men but not in women, the RR of a ESC was elevated in women but not in men. There was also a statistically significant elevation of RR of EGA following prostate cancer but not for ESC and distal gastric adenocarcinoma.

Another interesting finding in this study was the association of UGI cancers with breast cancer among women. Although the RRs of all these second primary cancers were elevated following breast cancer, the strongest association was for EGA (RR = 2.64; 95% CI, 1.82–3.68).

Discussion

Here, we found associations of varied strength for EGA, ESC, and distal gastric adenocarcinoma with cancers of other sites. However, the limitations of this study should be kept in mind while these associations are being interpreted. As mentioned

Table 2 RR of second primary esophageal and gastric cancers following first primary cancers of other sites in men

First primary cancer	Second primary cancer	No. of observed cases	No. of expected cases	RR[a]	95% CI
Bladder	EGA	37	18.8	1.97	1.39–2.71
	ESC	22	30.9	0.71	0.45–1.08
	DGA[b]	72	70.5	1.02	0.80–1.29
Colon and rectum	EGA	52	30.3	1.72	1.28–2.25
	ESC	43	48.5	0.89	0.64–1.19
	DGA	107	111.4	0.96	0.79–1.16
Head and neck	EGA	28	13.2	2.12	1.41–3.07
	ESC	214	22.4	9.55	8.32–10.92
	DGA	48	44.2	1.09	0.80–1.44
Kidney	EGA	8	4.9	1.63	0.70–3.22
	ESC	4	8.0	0.50	0.13–1.28
	DGA	12	16.4	0.73	0.38–1.28
Leukemia	EGA	5	3.6	1.39	0.45–3.24
	ESC	3	5.7	0.53	0.11–1.54
	DGA	14	12.5	1.12	0.61–1.88
Lung	EGA	29	15.6	1.86	1.24–2.67
	ESC	66	23.3	2.83	2.19–3.60
	DGA	60	44.9	1.34	1.02–1.72
Malignant lymphoma	EGA	5	4.1	1.22	0.39–2.85
	ESC	6	5.9	1.02	0.37–2.21
	DGA	7	11.8	0.59	0.24–1.22
Prostate	EGA	83	60.0	1.38	1.10–1.71
	ESC	107	91.4	1.17	0.96–1.41
	DGA	183	233.6	0.78	0.67–0.91

[a] Adjusted for age and calendar period.
[b] DGA, distal gastric adenocarcinoma.

Table 3 RR of second primary esophageal and gastric cancers following first primary cancers of other sites in women

First primary cancer	Second primary cancer	No. of observed cases	No. of expected cases	RR[a]	95% CI
Breast	EGA	34	12.9	2.64	1.82–3.68
	ESC	55	38.1	1.44	1.08–1.88
	DGA[b]	149	119.5	1.24	1.05–1.46
Bladder	EGA	3	1.3	2.31	0.46–6.74
	ESC	5	3.4	1.47	0.47–3.43
	DGA	16	12.5	1.28	0.73–2.08
Colon and rectum	EGA	4	6.6	0.61	0.16–1.55
	ESC	28	16.1	1.74	1.16–2.51
	DGA	66	60.9	1.08	0.84–1.38
Head and neck	EGA	5	0.8	6.25	2.01–14.59
	ESC	93	2.4	38.75	31.28–47.47
	DGA	9	7.2	1.25	0.57–2.37
Kidney	EGA	1	0.5	2.00	0.03–11.13
	ESC	3	1.5	2.00	0.40–5.84
	DGA	5	4.9	1.02	0.33–2.38
Leukemia	EGA	2	0.6	3.33	0.37–12.03
	ESC	1	1.5	0.67	0.01–3.71
	DGA	8	5.4	1.48	0.64–2.92
Lung	EGA	3	1.5	2.00	0.40–5.84
	ESC	21	4.1	5.12	3.20–7.83
	DGA	9	11.3	0.80	0.36–1.51
Malignant lymphoma	EGA	1	0.8	1.25	0.02–6.95
	ESC	1	1.9	0.53	0.01–2.93
	DGA	9	6.2	1.45	0.66–2.76

[a] Adjusted for age and calendar period.
[b] DGA, distal gastric adenocarcinoma.

previously, most of the associations examined in this study, except for those of ESC and EGA with tobacco-related malignancies, were not *a priori* hypothesized. Moreover, multiple comparisons were made, with several first primary sites and three different second primary sites. The design of this study also restricted the scope of adjustment for many confounding variables. So, a chance phenomenon or unadjusted confounders may be responsible for some of the observed associations, particularly the weak ones.

The finding of a strong association between ESC and lung and head and neck cancers suggests a shared etiology, *i.e.*, cigarette smoking. A weaker association between EGA and these strongly tobacco-related malignancies is consistent with the moderate association of EGA with smoking, which was observed in other studies (6–9). For both ESC and EGA, the finding of a stronger association in women than in men is also consistent with the stronger carcinogenic effect of tobacco in women found in some recent studies (14, 20–22). Zang and Wynder (22) have suggested that women are biologically more susceptible to tobacco carcinogens than men, and this increased susceptibility results from a higher level of activation of tobacco procarcinogens by certain cytochrome P-450 enzymes, a slower metabolism of nicotine, or the role of female sex hormones on the tumor development. Begg *et al.* (14) have demonstrated that associations between tobacco-related malignancies estimated through SIR can be overestimated, particularly within 1 year of the diagnosis of first cancer, mainly due to diagnostic bias (14). Although we excluded second cancers diagnosed within 3 months of the diagnosis of first primary cancers, it is possible that the associations between UGI cancers and lung and head and neck cancers in this study may have been overestimated to some extent. This is particularly possible because the anatomical proximity of these cancer sites might have led to an increased detection of esophageal cancers during the endoscopic or radiographic (UGI series or computed tomography scan) work-ups due to symptoms or complications resulting from the first primary lung or laryngeal cancers or a misdiagnosis of local spread of the first primary site to esophagus as a new primary.

We also found an association of EGA with bladder cancer, particularly in men. Because we did not find such an association for ESC and the association is less susceptible to diagnostic bias, we considered that it may reflect a possible effect of occupational exposures (chemicals and dyes), the major bladder cancer risk factors other than tobacco.

The positive association between EGA and colorectal cancer in men that was found in this study is consistent with the finding of a previous study in which the association of EGA with colorectal cancer was assessed in SEER data using a case-control design with ESC patients serving as controls (15). This association between EGA and colorectal cancer may indicate that both conditions share etiological risk factors. In several clinical series (23–25), colorectal cancers have been shown to be associated with Barrett's esophagus, a condition that is known to be a precursor lesion for EGA. Also, dietary fat, an established risk factor for colorectal cancer, has been shown to be associated with EGA (8). Apart from these epidemiological observations, a shared etiology of EGA and colorectal cancer is also supported by their similarity in some molecular genetic alterations. The tumor suppressor gene *p53* has been shown to be mutated in different stages of carcinogenesis of both EGA (26, 27) and colorectal cancer (28, 29). Another common molecular genetic alteration found in both hereditary (hereditary nonpolyposis colon cancer) and sporadic colorectal cancer, the microsatellite instability (30–32), has also recently been found to be present in EGA, particularly Barrett's-associated EGA (33, 34).

We also found a positive association of ESC with colo-

rectal cancer in women in our study. Because tobacco is generally not considered to be a risk factor for colorectal cancer, this association is unlikely to be due to smoking. In fact, the finding can partly explain the significant negative association of EGA with colorectal cancer in women found in a previous study because ESC cases were used as the control group in that study (15). However, the absence of this association in men makes it more likely to be a chance finding.

The positive association of EGA with prostate cancer and a negative association between distal gastric adenocarcinoma and prostate cancer that was found in this study may be due to chance. Interestingly, however, these associations are somewhat consistent with the descriptive epidemiology of these cancers because the incidence of EGA and prostate cancer has been rapidly rising and that of gastric adenocarcinoma has been falling. The positive association between EGA and prostate cancer may also be due, in part, to the effect of high dietary fat intake.

The positive association of all three UGI cancers (EGA, ESC, and distal gastric adenocarcinoma) with breast cancer among women in this study is interesting. It is most likely that each individual association involves a different etiological pathway rather than one general explanation for all. Effect of treatments for breast cancer could be one of the possible explanations.

In conclusion, we have found a very strong association of ESC and a moderately strong association of EGA with tobacco-related malignancies, particularly with the cancers of lung and head and neck. These findings reinforce the association of esophageal malignancies with tobacco, which is stronger for squamous cell carcinomas than for adenocarcinomas and stronger in women than in men. The study also supports association of EGA with colorectal cancer in men and breast cancer in women. Other findings, including the association of EGA with cancers of bladder and prostate in men in this study, have not been described previously and need to be examined in future studies.

Overall, the observed associations in this study may provide new clues to the etiology of the EGA and ESC and may also provide useful information for developing appropriate surveillance strategies for second malignancies of the esophagus among individuals with certain cancers.

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