Original Article

Marked Increase in the Incidence Rate of Esophageal Adenocarcinoma in a High-risk Area for Esophageal Cancer

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Abstract

Background: Esophageal cancer (EC) is the eighth common cancer worldwide. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAD) are the most common histologic types of EC. Many recent reports showed an increasing trend in EAD and a decreasing trend in ESCC in many Western countries. Golestan Province in northeastern Iran has been known as a high-risk area for EC. The aim of this study was to describe the time trend of EAD in this area between 2000–2009.

Methods: Data on cancer cases were obtained from Golestan Population-based Cancer Registry. Analysis was done using Joinpoint software. To examine the incidence trends, the annual percent change was calculated. The possibilities of anatomic and histologic misclassification were considered by assessing the trend of ESCC and gastric adenocarcinoma.

Results: A total number of 1186 histologically-confirmed EC cases were recruited. The incidence rate of EAD showed a significant increasing trend. There was no significant trend in the incidence of ESCC during the study period. A significant increase in the incidence rate of gastric adenocarcinoma was observed during the period of 2000–2005, followed by a plateau during the period of 2005–2009.

Conclusions: We found a significant increasing trend in the incidence rate of EAD. We find no evidence to support an alternative explanation including anatomic and histologic misclassification. So, the observed rise in the incidence of EAD seems to be real. Therefore, designing and implementation of control programs, including control of preventable risk factors of EAD, should be considered in this high- risk area.

Keywords: Adenocarcinoma, epidemiology, esophagus, Golestan, Iran

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Introduction

Esophageal cancer (EC) is the eighth common cancer worldwide and was reported as the sixth most common cause of death from cancer.[1] Considerable variations were reported for the incidence of EC between different parts of the world. A geographic area extending from northern Iran to north-central China (Asian belt of EC) was considered as a high-risk area for EC.[2–4] Squamous cell carcinoma (SCC) and adenocarcinoma are the most common types of EC.[2–5] Reports in the 1960,s suggested that the morphologic diagnosis in about 90% of EC cases was esophageal SCC (ESCC).[3] ESCC is still more frequent than esophageal adenocarcinoma (EAD) worldwide, especially in the developing countries.[6,7] But, many recent reports showed an increasing trend in EAD and a decreasing trend in ESCC in many Western countries.[8–13] Age, male gender, tobacco smoking, gastroesophageal reflux disease (GERD), obesity, and hypertension[14–16] were proposed as possible risk factors of EAD.

Some reports suggested that the prevalence of some of these risk factors including hypertension and obesity is increasing in low- and middle-income countries.[17–20] This is partly due to rapid modernization and lifestyle changes including dietary changes, improved living conditions, and a decrease in physical activity.[21] So, it may be expected that the rate of EAD is also increasing in the developing world.

Golestan Province, located in northeast of Iran, has been known as a high-risk area for EC.[2,22] The results of a study in 2004 showed that ESCC included 91% of EC cases in GolestanProvince.[23] Recently, a high prevalence rate of some risk factors of EAD, including obesity, was reported from this region,[24] suggesting the possibility of an increase in the incidence rate of EDA in this high- risk area. The aim of this study was to describe the time trend of EAD in Golestan Province of Iran between 2000 – 2009.

Materials and Methods

Study population

This study was done in Golestan Province, located in northeast of Iran. Data on cancer cases during the period of 2000–2009 were obtained from Golestan Population-based Cancer Registry (GPCR) and Cancer Office of the Health Department of Golestan University of Medical Sciences. Esophageal and gastric cancer cases with histologic confirmation were recruited. Data on Golestan population were obtained from Provincial Census done by the Health Department of Golestan University of Medical Sciences.

Incidence Rates

Age-standardized incidence rates (ASRs) were calculated using direct standardization method. World standard population (18 groups) was considered and the rates were expressed per 1,000,000

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Table 1. Trend of age-standardized incidence rate of esophageal cancer, esophageal squamous cell carcinoma, and gastric adenocarcinoma (2000–2009).

		Trend I		Trend II	
	APC 2000–2009(95% CI)	**Year**	**APC (95% CI)**	**Year**	**APC (95% CI)**
Esophageal cancer	4.6 (-6.1–16.5)	2000–2007	6.1 (-2.6–15.5)	2007–2009	-0.3 (-43.1–74.6)
Esophageal squamous cell carcinoma	3.4 (-7.7–15.8)	2000–2007	5.2 (-3.6–14.9)	2007–2009	-2.8 (-46.4–76.3)
Gastric adenocarcinoma	10.4* (2.8–18.5)	2000–2005	19.3* (5.1–35.4)	2005–2009	0.2 (-12.7–15.0)

APC= annual percent change; *The APC is significantly different from zero ($P < 0.05$).

person-years. At first, the overall trend of EC incidence was examined. Then, the incidence trends of EAD were provided for total studied population as well as for males and females, separately.

To assess the possibility of histologic misclassification (if what was once called SCC of the esophagus is now called adenocarcinoma of the esophagus), we examined the trend of ESCC. The incidence trend of gastric adenocarcinoma was examined to determine if anatomic misclassification was occurred (if what was once called adenocarcinoma of the stomach is now called adenocarcinoma of the esophagus). In order to assess the possibility of anatomic misclassification precisely, we needed the data on adenocarcinoma of the gastric cardia. As these data were not available in GPCR, we used the data from Atrak Clinic, which is a research, diagnostic, and therapeutic center located in Gonbad City, eastern part of Golestan Province. It provides medical services to patients with upper gastrointestinal (GI) problems in the region. Recent reports suggest that about 70% of upper GI cancer cases in eastern parts of Golestan Province refer to Atrak Clinic. Detailed information about anatomic sub-site and histologic sub-type of upper GI cancers is routinely recorded for all patients referred to this center. Data on esophageal and gastric cancer cases diagnosed during the period of 2002–2009 were obtained from Atrak Clinic. The population from which Atrak cases came could not be clearly defined. So, we could not calculate the ASR of adenocarcinoma of the gastric cardia. Instead, we considered the proportion of cases with adenocarcinoma of the gastric cardia to total cases of adenocarcinoma in Atrak Clinic (CAD/TAD) for each year. The trend of CAD/TAD proportion during the period of 2002–2009 was examined. To make a comparison, the proportion of cases with adenocarcinoma of the esophagus to total cases of adenocarcinoma in Atrak Clinic (EAD/TAD) was also calculated.

Statistical analysis

Analysis was done using a Joinpoint software version 3.5.4.[25] To examine the incidence trends, the annual percent change (APC) was calculated by generalized linear models assuming a Poisson distribution. A weighted least-squares regression was performed, in which the independent variable was the year and the dependent variable was the natural logarithm of the incidence rate or proportion. Heteroscedastic errors were assessed based on the number of cases in each year using a Poisson model and used for calculating 95% confidence intervals (95% CI) of APC. Joinpoint regression analysis[26] was used to choose the best-fitting points (the 'joinpoints'), where the magnitude and/or direction of rate significantly changed. The Joinpoint permutation test was performed to identify significant differences.[26] Regarding the number of observations in our study (lower than 12), a maximum number of one joinpoint was allowed for estimations. APCs were separately determined for each segment (from start to jointpoint and from jointpoint to the end of observation) as well as across the entire range of data (from start to the end of observation). The trend was considered as significant if the 95% CI of APC did not include zero. A *P*-value of less than 0.05 was considered as significant.

Results

A total number of 1186 histologically-confirmed EC cases were diagnosed in Golestan Province during the period of 2000–2009. About 56% of these cases were males. We found no significant trend in the incidence rate of EC during the study period (Table 1). The incidence rate of EAD showed a significant increasing trend (Figure 1). Our results suggested a significant increasing trend of EAD in man, but no significant change was seen in the incidence rate of EAD during the study period in women (Figure 2).

There was no significant trend in the ASR of ESCC during the study period (Table 1). A significant increase was observed in the incidence rate of gastric adenocarcinoma during the period of 2000–2005, followed by a plateau during the period of 2005–2009 (Table 1). Both of EAD/TAD and CAD/TAD proportions showed an increasing trend during the period of 2002–2009. The trend of CAD/TAD proportion was significant, but no significant change was found in the proportion of EAD/TAD (Figure 3).

Discussion

We found a marked increase in the ASR of EAD in Golestan Province of Iran from 1.9 per 1000000 person-years in 2000 to 19.94 per 1000000 person-years in 2009. Such an increasing trend in the incidence rate of EAD was initially reported from Western countries.[11,12,14,27,28] Change in the prevalence of some risk factors including GERD,[29] obesity,[30] smoking,[31] and *Helicobacter pylori* infection[32] were suggested as possible explanations for increasing trend of EAD. A number of recent reports also showed a high prevalence of such risk factors in developing countries.[17,18,20] So, it may be expected that the incidence rate of EAD is increasing in the developing world. A high prevalence of the risk factors of EAD in Iran[19,24,33,34] may explain a high incidence of EAD in our area. Therefore, it seems that our findings reflect a true rise in the incidence rate of EAD in Golestan Province of Iran during the last decade. An increase in the prevalence of EAD in Golestan Province, a high-risk area for ESCC,[7] seems to be an important health issue. Therefore, designing and implementation of control programs, including control of preventable risk factors of EAD, should be considered as a priority of health policy making in this area.

Figure 2 shows that the increasing trend of EAD was observed only in males, while the rate of this cancer in females remained constant (with a slight increase) during the study period. The results of previous studies suggested a considerable gender difference in the incidence of EAD with a sex ratio of 8 – 9: 1 in favor of males. Protective effect of estrogen in females has been proposed as possible explanation for such difference.[35] So, the impact of in-

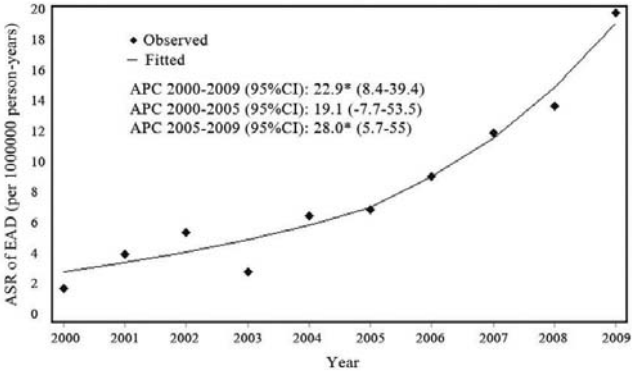

Figure 1. Trend of age- standardized incidence rate of EAD in Golestan Province, Iran (2000 – 2009). (APC= annual percent change; *The APC is significantly difference from zero at alpha = 0.05.)

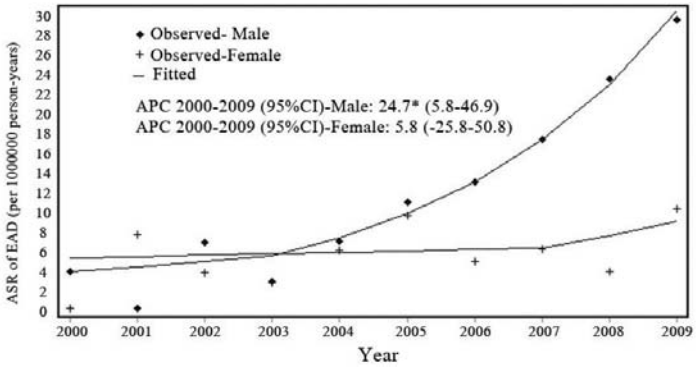

Figure 2. Trend of age- standardized incidence rate of EAD in males and females, Golestan Province, Iran (2000 – 2009). (APC= annual percent change; *The APC is significantly difference from zero at alpha = 0.05.)

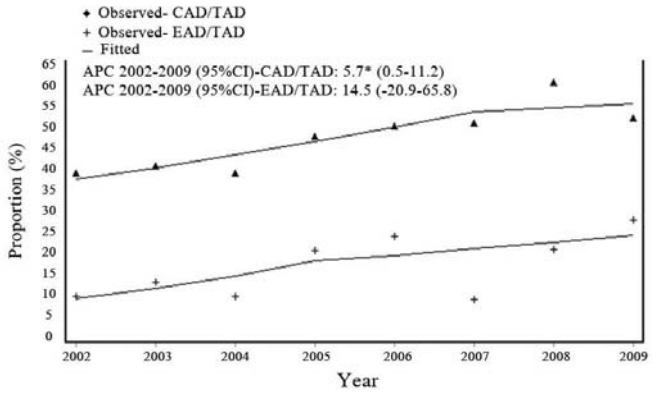

Figure 3. Trend of the proportion of EAD and gastric cardia adenocarcinoma (CAD) to total cases of adenocarcinoma (TAD), in Atrak Clinic, Golestan Province, Iran (2000–2009). (APC = Annual percent change; *The APC is significantly difference from zero at alpha = 0.05.)

crease in the incidence of EAD is obviously more prominent in male gender.

Beside the real increase in the incidence of EAD, other possibilities including over-diagnosis, histologic misclassification, and anatomic misclassification may be proposed as possible explanations for the observed increasing trend in our study.

Over-diagnosis may occur when a screening program is implemented in a population[36] or when the diagnostic intensity is increased. No screening program has been implemented for EC in this region and other parts of Iran. But, it seems that the diagnostic intensity has been increased during the last decade. In other words, the number of gastroenterologists as well as diagnostic facilities including endoscope sets has been considerably increased in Golestan Province. Such change may result in over-diagnosis of EAD and explain the observed rise in the incidence of EAD. But, if that was correct, the incidence of ESCC would be expected to similarly have increased. But, our results suggested no increase and even a slight decrease in the incidence of ESCC during the same period (Table 1). So, over-diagnosis may not be considered as a serious explanation for the increasing trend of EAD in Golestan Province.

Another possible explanation of the observed rise in the incidence of EAD is histologic misclassification. It may be proposed that some of EAD cases had been wrongly classified as ESCC and are now correctly identified, resulting in such non-real increase in the incidence of EAD. If we are going to accept that, a significant decrease would also be expected in the incidence of ESCC. But, we found that the ESCC rate remained constant between 2000–2009 (Table 1). So, histologic misclassification may not explain the increasing trend of EAD in our area.

Anatomic misclassification was also considered as a possible explanation for the rising incidence of EAD. That means some of EAD cases might be wrongly diagnosed as adenocarcinoma of the stomach and are now correctly classified as EAD. Such change in classification may be proposed to cause a false increase in the incidence of EAD. But, if that explanation was correct, we might not expect a major increase in the incidence of adenocarcinoma of the stomach, specifically of CAD, during the study period. We found an increasing trend in the proportion of CAD/TAD (Figure 3). Furthermore, we found that the incidence of gastric adenocarcinoma was approximately doubled in this period (10.4 to 19.3 per 100,000). If we assume that all of the excess cases of EAD in 2005–2009 compared to 2000–2005 (28.0–19.1= 8.9 per 100,000), were in fact CAD cases, then we would expect a triple increase in the incidence of adenocarcinoma of the stomach in 2000–2009. Such a high increase in the incidence of CAD in a relatively short time and no increase in the EAD incidence may be less likely than a real increase in the incidence of both cancers. Therefore, anatomic misclassification is unlikely to explain all of the increase in the incidence of EAD in our study.

The results of similar studies from other parts of the world also

showed that the increasing trend of EAD could not be explained by misclassification or over-diagnosis. As in our study, they also found a real rise in the incidence of EAD and concluded that an increase in the prevalence of risk factors including smoking, obesity, and GERD is the most appropriate explanation for such an increasing trend.[37,38]

In conclusion, we found a significant increasing trend in the incidence rate of EAD in a high ESCC-risk area in northeastern Iran during the last decade. We find no evidence to support alternative explanation including over-diagnosis or anatomic misclassification of adenocarcinoma of the gastric cardia or histologic misclassification of ESCC. So, the observed rise in the incidence of EAD seems to be real. Therefore, designing and implementation of control programs, including control of preventable risk factors of EAD, should be considered in this high-risk area.

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