

Editorial

Esophageal Cancer Incidence Trends in Northeastern Iran: Comparing Rates Over 36 Years

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In this issue of the Journal, Roshandel and colleagues present the results of a population-based cancer registry in Golestan Province, in northeastern Iran.¹ The authors should be praised for establishing a population-based cancer registry with high standards in Iran, where there is relatively scant reliable information from comprehensive registries, thus adding to our current knowledge of cancer epidemiology in Iran and the Middle-East. In a matter of a few years, these investigators were able to improve the methods of cancer registry from retrospective to prospective registry, substantially increase the proportion of cases that are verified microscopically, and reduce the number of cases that are classified solely based on death certificates.

What makes the results of this cancer registry of even more interest is that Golestan Province has long been known to have exceptionally high rates of esophageal cancer (EC). Based on anecdotal reports of such high rates, Janiz Kmet from the International Agency for Research on Cancer (IARC) and Ezzatollah Mahboubi from the Institute of Public Health Research (IPHR) of Tehran University established a cancer registry in Golestan Province – then the eastern part of Mazandaran Province -- and neighboring areas from 1968 to 1971, the results of which were published in 1973.² This cancer registry, the first of its kind in Iran, showed very high EC incidence rates, with annual age-standardized rates (ASRs) up to 165 per 100,000 in men and 195 per 100,000 in women, in certain parts of the Golestan Province (Table 4 in Roshandel's study). Rates were high in other parts of the Province too, though not as high. These findings led to the establishment and completion of several etiologic and early detection studies in the 1970s. These studies were terminated in 1979, but in the late 1990s and early 2000s a new international collaboration resumed investigations into the etiology of EC in the Golestan Province (reviewed in Kamangar et al³, and Islami et al⁴). These new collaborations have thus far led to the completion of a case-control study and an ongoing cohort study.^{3,5} The results of the cancer registry by Roshandel et al. complement the results of the case-control and cohort studies and help in more accurate diagnosis of cases in the cohort. Furthermore, they allow us to compare rates of various cancers, including EC rates between now and those found by Mahboubi and Kmet 36 years earlier.

Roshandel's results suggest that EC rates are still high in Golestan. However, compared to 36 years ago, ASRs of EC in this Province have decreased between 57% and 82%, respectively. Facing such dramatic reductions, two questions come to mind. First, are the reductions real? Or are they due to other explanations, such as overestimation of the rates in 1970s? Second, if the declines are real, what could be the possible cause?

We believe that the reductions are real. Although Mahboubi and Kmet's case diagnoses were mostly based on clinical and/or radiologic features, rather than microscopic verification,² clinical features of EC – i.e., progressive dysphagia in older patients followed by emaciation and death – make it easily distinguishable from most other malignant or non-malignant conditions. One exception, however, is gastric cardia adenocarcinoma, which has similar clinical presentations. Results from recent studies show that this cancer is rather common in Golestan Province, suggesting some of the EC cases diagnosed in the 1970s might have been gastric cardia cancers; though this cannot explain the observed differences between now and then. The sum of the ASRs for female esophageal and gastric (both cardia and noncardia) cancers shown in Table 3 of Roshandel is 31.5 / 10⁵ (19.1 for EC and 12.4 for gastric cancer). This number is lower than the rates observed in the region with the lowest incidence in the 1970s (38.7 / 10⁵) and far lower than those seen in the region with the highest incidence (195 / 10⁵). The real difference is perhaps much more, as only half the gastric cancers in this area are cardia cancers, and it is unlikely that all of them would have been misclassified as EC, considering that in the 1970s gastric cancer itself was the second highest reported cancer in the area. Similar, but not quite as striking reductions, have been seen in men too. Also, one has to note that the 1970s rates were adjusted to the World Population in 1960, whereas Roshandel's rates were adjusted to the standard World Population in 2000.¹ Given that in 1960 World Population was younger, if Roshandel et al. were to adjust their rates to 1960, they would have been even lower.

So what is the cause of such a decline? One could only make educated guesses, as reliable information on the etiology of EC in Golestan Province is relatively scant. Genetic risk factors are not suspect, as gene pool, at least at the nucleotide level, takes millions of years to change. No major immigration or emigration has happened in this area in the past 40 years. So what about environmental factors? Approximately 90% of the EC cases in this area are esophageal squamous cell carcinomas (ESCCs)⁶ but in Golestan – unlike that seen in the United States and Europe -- cigarette smoking and alcohol consumption are not major causes of ESCC.⁷⁻⁹ Early publications in the 1970s, mostly based on ecological studies,⁹ suggested a host of factors as potential risk factors for ESCC in this area. However, future case-control studies examined only a number of these factors and provided support to only a few of them – i.e., low socioeconomic status,^{7,10} low intake of fruit and vegetables,^{9,11} opium use,^{8,9,12} and drinking very hot tea^{9,13} – to be risk factors. The putative risk effects of low intake of vitamins and/or essential metals and minerals, such as zinc,^{14,15}

and also wheat seed contamination^{4,9} by carcinogens, fungi, or unknown foreign seeds are still open questions. None of the suggested risk factors were very strong, and none has yet been shown to be a risk factor for ESCC in a prospective study. But if we assume that these are causal, one might be able to suggest why rates have reduced.

Socioeconomic status of the society overall has improved dramatically over the past few decades. As discussed elsewhere,¹⁰ there has been substantial improvement in access to education, electricity, safe drinking water, telephone communications and roads. For example, the number of people aged 7 to 29 years in the study area who had no formal education decreased from 75% in 1966 to 7% in 1996, and the percentage of households with access to electricity increased from 11% in 1966 to 95% in 1996. As a result of improvement in the roads and availability of refrigerators, access to fresh fruit and vegetables has increased. Additionally, introduction of industrialized farming to the area has resulted in significant improvements in both storage and winnowing of wheat seed, thus decreasing the possibility of contamination to the lowest achievable levels.

Opium use has also declined. A study of 1590 rural individuals in the 1970s showed that the prevalence of opium use in areas with high or very high risk for EC was 54% in men over 50 years of age and 30% in women in that age range.¹² Recent data from Golestan Cohort Study (unpublished), however, show that the prevalence of opium use in rural men and women over 50 years of age is 32% and 12%, respectively. Perhaps such a substantial decrease can partly explain reduced rates.

These factors, alone or interacting with each other, might have resulted in reduced risks. In addition, it has been suggested that a very strong risk factor, yet unidentified, may exist in Golestan Province that has led to the extremely high rates of EC.³ If such factor exists, though yet entirely speculative, its prevalence may be on the decline because of the substantial changes in the environment observed over the past few decades.

Declining rate of EC in Golestan, due to any reason, is good news. Establishing an excellent registry in Golestan, which helps health authorities as well as ongoing studies, is also good news. We look forward to future reports from this registry, hoping that even further declines would be reported. In the meantime, further epidemiological studies are needed to increase our knowledge of the causes of EC in this region.

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