

Quality of Drinking Water and High Incidence Rate of Esophageal Cancer in Golestan Province of Iran: A Probable Link

Summary: Golestan Province in northern Iran is known to be a high-risk area for esophageal cancer (EC). Of a long list of multiple risk factors, this study focuses on a possible link between the epidemiologic patterns of EC and the anomalous concentration of some ions and elements in the drinking water sources. A total of 183 samples from 45 villages covering a wide range of EC mortality rates are collected and analyzed. The results demonstrate that NO_3^- , SO_4^{2-} , Sb, and Sr exceed the recommended maximum concentration level (MCL) in drinking water. This is more prominent in the villages with high esophageal cancer mortality rate, suggesting a possible link between EC incidence and water quality. Se concentration in drinking water increases from low to the high EC areas, a finding contrary to the expected trend. It is concluded that Se deficiency does not play a major role in the etiology of EC in the Golestan Province. The statistical results obtained from Mann-Whitney and Kruskal-Wallis tests along with cluster analysis are consistent with the observed trend of EC mortality rate in Golestan Province.

Source: Keshavarzi B, Moore F, Najmeddin A, Rahmani F, Malekzadeh A. *Environ Geochem Health*. 2011 March 19 [Epub ahead of print]

Comment: The study by Keshavarzi and colleagues¹ provides indirect evidence for lack of implication of selenium deficiency in unusually high rates of esophageal cancer in Golestan. Due to high nitrate content and as some ions/trace elements exceed the recommended maximum concentration level in drinking water, the authors suggest that high incidence of EC in the region may have an association with poor-quality drinking water.

In areas with low to moderate incidence of esophageal squamous cell carcinoma (ESCC), tobacco and heavy alcohol use are major risk factors for the disease.² ESCC is usually much more common in men than in women in those population because tobacco and alcohol use are more common among men.² On the other hand, the incidence rates in high-risk areas for ESCC, including Golestan Province in northern Iran and Linxian in China, tobacco and alcohol use are not as strong risk factors for ESCC as in low-incidence areas.² In Golestan, alcohol use is rare and tobacco use is not a common habit, particularly among women,³ so some other factors should be responsible for the high incidence of ESCC. Furthermore, incidence rates of ESCC in high-incidence areas are similar in both sexes, suggesting that some common factors affecting both sexes equally may be involved in the carcinogenesis of ESCC in those areas.⁴⁻⁶ The incidence of esophageal cancer in Golestan has been nearly halved during the past 3 – 4 decades,⁷ a finding that suggests environmental exposures are the major factors that lead to development of ESCC in the region. Exposure to carcinogens through drinking water may be one of those factors.

Role of drinking water quality in EC incidence or mortality have been reported in several ecological, case-control, and retrospective cohort studies from high incidence areas, mainly from Linxian.⁸⁻¹⁵ Drinking of ground water was associated with an increased risk of EC in several of those studies.¹³⁻¹⁵ Such an association has

been reported in a prospective study on preneoplastic lesions of the esophagus.¹⁶ A prospective study in Linxian has also reported an inverse association between drinking water piped into the home, compared to other sources, and EC.¹⁷ The association between quality of drinking water and risk of EC has been attributed to several factors, including impurities with potential carcinogenic effects, such as nitrosamines¹⁰ and petroleum oils,⁸ and very low or high levels of some minerals/trace elements with possible protective or carcinogenic effects, respectively.^{8,11} However, EC is usually associated with poor socioeconomic status,² and in some regions people from low socioeconomic groups may have more limited access to safe drinking water than those with higher socioeconomic status. Therefore, the observed associations may be, at least partly, confounded by other risk factors related to poor socioeconomic status and may not be related to quality of drinking water itself. On the other hand, the fairly consistent association reported in studies from high-incidence areas, including studies with adjustments for some indicators of socioeconomic status, argues for a possible association between drinking water quality and risk of ESCC. Considering the similar incidence rates of ESCC in men and women in high-risk regions, such an association seems to be plausible. The recent decline in the incidence of EC in Golestan, which coincides with overall improvements in socioeconomic status in the region, among which is better access to safe water,⁴ may also support the above argument. Further studies on this association and its biological relevance are strongly warranted, because if such an association exists, measures for reducing the exposure to relevant carcinogenic factors in drinking water can be beneficial in lowering the incidence of ESCC at the population level.

An association between selenium deficiency and EC incidence and mortality has been reported in experimental and observational studies.² More importantly, an inverse association between selenium supplementation and eventual mortality from EC has been reported in a clinical trial with a long-term follow-up in Linxian.¹⁸ Within the same study, significant inverse associations between baseline serum selenium and death from ESCC were also reported. The relative risk (95% confidence interval) for the highest quartile ($>1.06 \mu\text{mol/L}$) of serum selenium compared to the lowest quartile ($\leq 0.77 \mu\text{mol/L}$) was 0.35 (0.16 – 0.81).¹⁹ On the other hand, an earlier study in Golestan study did not find any difference in selenium levels in hair samples from esophageal cancer patients, their unaffected family members, and members of families with no history of cancer.²⁰ In another study, the median selenium levels in 100 randomly selected healthy inhabitants of Golestan was higher than the levels in 200 healthy inhabitants of three low-incidence provinces of Iran and above the level needed to saturate serum selenoproteins.²¹ These findings suggest that a major contribution of selenium deficiency to development of EC in Golestan is unlikely. Results of Keshavarzi and colleagues and earlier studies indicate that selenium in drinking water can be one of the major sources of selenium intake in Golestan and may provide sufficient amounts of selenium to the inhabitants. The different observations in Golestan and Linxian with regard to selenium indicate that some of the risk

Archive of SID

factors for EC may be dissimilar in those two high-risk regions, although the epidemiologic features and known risk factors in both regions have shown many similarities. Nevertheless, the role of selenium in development of EC in Golestan needs to be examined in prospective studies.

In summary, results of Keshavarzi and colleagues' study provide further evidence for excluding selenium deficiency as a major risk factor for ESCC in Golestan and indicate the need for further studies on the association between drinking water quality and risk of ESCC in the region.

Conflicts of interest: None

Farhad Islami MD PhD^{1,2}

¹Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, North Kargar Avenue, 14117 Tehran, Iran, ²Tisch Cancer Institute, Mount Sinai School of Medicine, 96 East Street, New York 10029, NY, United States. E-Mail: farhad.islami@mssm.edu

References

- Keshavarzi B, Moore F, Najmeddin A, Rahmani F, Malekzadeh A. Quality of drinking water and high incidence rate of esophageal cancer in Golestan province of Iran: a probable link. *Environ Geochem Health*. 2011 Mar 19.
- Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterol Clin North Am*. 2009; **38**: 27–57. vii.
- Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer*. 2008; **98**: 1857–1863.
- Islami F, Kamangar F, Nasrollahzadeh D, Møller H, Boffetta P, Malekzadeh R. Oesophageal cancer in Golestan Province, a high-incidence area in northern Iran - a review. *Eur J Cancer*. 2009; **45**: 3156–3165.
- Malekshah AF, Kimiagar M, Pourshams A, Yazdani J, Kaiedi Majd S, Gogiani G, et al. Vitamin deficiency in Golestan Province, northern Iran: a high-risk area for esophageal cancer. *Arch Iran Med*. 2010; **13**: 391–394.
- Marjani HA, Biramijamal F, Hossein-Nezhad A, Islami F, Pourshams A, Semnani S. Prevalence of esophageal cancer risk factors among Turkmen and non-Turkmen ethnic groups in a high incidence area in Iran. *Arch Iran Med*. 2010; **13**: 111–115.
- Semnani S, Sadjadi A, Fahimi S, Nouraei M, Naeimi M, Kabir J, et al. Declining incidence of esophageal cancer in the Turkmen Plain, eastern part of the Caspian Littoral of Iran: a retrospective cancer surveillance. *Cancer Detect Prev*. 2006; **30**: 14–19.
- Amer MH, El Yazigi A, Hannan MA, Mohamed ME. Water contamination and esophageal cancer at Gassim Region, Saudi Arabia. *Gastroenterology*. 1990; **98**: 1141–1147.
- Yang CY, Chiu HF, Cheng MF, Tsai SS, Hung CF, Lin MC. Esophageal cancer mortality and total hardness levels in Taiwan's drinking water. *Environ Res*. 1999; **81**: 302–308.
- Yokokawa Y, Ohta S, Hou J, Zhang XL, Li SS, Ping YM, et al. Ecological study on the risks of esophageal cancer in Ci-Xian, China: the importance of nutritional status and the use of well water. *Int J Cancer*. 1999; **83**: 620–624.
- Yang CY, Chiu HF, Tsai SS, Wu TN, Chang CC. Magnesium and calcium in drinking water and the risk of death from esophageal cancer. *Magn Res*. 2002; **15**: 215–222.
- Tao X, Zhu H, Matanoski GM. Mutagenic drinking water and risk of male esophageal cancer: a population-based case-control study. *Am J Epidemiol*. 1999; **150**: 443–452.
- Xibib S, Meilan H, Moller H, Evans HS, Dixon D, Wenjie D, et al. Risk factors for oesophageal cancer in Linzhou, China: a case-control study. *Asian Pac J Cancer Prev*. 2003; **4**: 119–124.
- Yang CX, Wang HY, Wang ZM, Du HZ, Tao DM, Mu XY, et al. Risk factors for esophageal cancer: a case-control study in South-western China. *Asian Pac J Cancer Prev*. 2005; **6**: 48–53.
- Yu Y, Taylor PR, Li JY, Dawsey SM, Wang GQ, Guo WD, et al. Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China. *Cancer Causes Control*. 1993; **4**: 195–202.
- Lu JB, Yang WX, Dong WZ, Sang JY. A prospective study of esophageal cytological atypia in Linxian county. *Int J Cancer*. 1988; **41**: 805–808.
- Tran GD, Sun XD, Abnet CC, Fan JH, Dawsey SM, Dong ZW, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer*. 2005; **113**: 456–463.
- Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. *J Natl Cancer Inst*. 2009; **101**: 507–518.
- Wei WQ, Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Sun XD, et al. Prospective study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death. *Am J Clin Nutr*. 2004; **79**: 80–85.
- Azin F, Raie RM, Mahmoudi MM. Correlation between the levels of certain carcinogenic and anticarcinogenic trace elements and esophageal cancer in northern Iran. *Ecotoxicol Environ Saf*. 1998; **39**: 179–184.
- Nouarie M, Pourshams A, Kamangar F, Sotoudeh M, Derakhshan MH, Akbari MR, et al. Ecologic study of serum selenium and upper gastrointestinal cancers in Iran. *World J Gastroenterol*. 2004; **10**: 2544–2546.