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• BRIEF REPORTS •

Ecologic study of serum selenium and upper gastrointestinal cancers in Iran

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Abstract

AIM: Both observational and experimental studies have shown that higher selenium status reduces the risk of upper gastrointestinal cancers in selenium deficient populations. Recent cancer registry data have shown very different rates of esophageal cancer (EC) and gastric cancer (GC) in four Provinces of Iran, namely Ardabil, Mazandaran, Golestan, and Kerman. The aim of this study was to have a preliminary assessment of the hypothesis that high rates of EC in Golestan and high rates of GC in Ardabil may be partly attributable to selenium deficiency.

METHODS: We measured serum selenium in 300 healthy adults from Ardabil (n = 100), Mazandaran (n = 50), Golestan (n = 100), and Kerman (n = 50), using inductively coupled plasma, with dynamic reaction cell, mass spectrometry (ICP-DRC-MS) at the US Centers for Disease Control (Atlanta, Georgia).

RESULTS: The median serum selenium concentrations were very different in the four Provinces. The medians (IQR) for selenium in Ardabil, Mazandarn, Golestan, and Kerman were 82 (75-94), 123 (111-132), 155 (141-173), and 119 (110-128) μg/L, respectively (P<0.001). The results of linear regression showed that the Province variable, by itself, explained 76% of the variance in log selenium (r^2 = 0.76). The proportion of the populations with a serum selenium more than 90 μg/L (the concentration at which serum selenoproteins are saturated) was 100% in Golestan, Kerman, and Mazandaran but only 29% in Ardabil.

CONCLUSION: Our findings suggest that selenium deficiency is not a major contributor to the high incidence of EC seen in northeastern Iran, but it may play a role in the high incidence of GC in Ardabil Province.

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INTRODUCTION

Esophageal cancer (EC) and gastric cancer (GC), collectively known as upper gastrointestinal (UGI) cancers, constitute 16% of all cancer deaths worldwide and are responsible for approximately one million deaths each year[1].

Both observational and experimental studies have shown that higher selenium status reduces the risk of UGI cancers in selenium deficient populations[2-5]. In a large-scale, prospective cohort study conducted in Finland, a low selenium region prior to a current supplementation program, Knekt and colleagues found a lower risk of stomach cancer in individuals with higher baseline serum selenium concentrations[3]. In another large cohort study, Mark and colleagues also found a reduced risk of esophageal cancer and gastric cardia cancer among individuals with higher initial serum selenium concentrations in a selenium deficient population in Linxian, China[4]. A double-blind, randomized clinical trial in this same Chinese population showed a reduced risk of both cardia and non-cardia gastric cancers in individuals supplemented with a combination of selenium, beta-carotene, and alpha-tocopherol[2].

Iran also has high rates of both EC and GC[6-8], and these cancers are the two most common causes of cancer death in Iran[9]. However, recent cancer registry data showed highly varying rates of EC and GC in four Provinces of Iran, namely Ardabil[7], Mazandaran, Golestan, and Kerman (unpublished data). The annual age-standardized incidence rates (ASRs) for EC were 15, 19, 40, and 3 per 10^5, and ASRs for GC were 38, 22, 18, and 8 per 10^5 in these four Provinces, respectively.

We hypothesized that differences in serum selenium may partly explain the highly varying rates of EC and GC in Iran. Here, we present the results of an ecologic study that compared serum selenium concentrations in randomly selected healthy subjects from Ardabil, Mazandaran, Golestan, and Kerman Provinces.

MATERIALS AND METHODS

Serum samples from 300 healthy adults were selected for this study. These subjects had all been recruited for previous studies. Ardabil serum samples (100 samples) were selected from participants in an endoscopic survey of gastric precancerous lesions conducted among rural and urban subjects >/=40 years old[10]. These subjects were selected using simple random sampling, and all resided in Meshkinshahr, a major city in Ardabil, or its surrounding villages. Mazandaran and Kerman serum samples (50 samples each) were selected from participants in a survey of the prevalence of celiac disease among urban inhabitants >/=18 years old in these two Provinces. These subjects were selected randomly from the entire urban population of Sari and Kerman, the two major cities of these Provinces. In Golestan, 100 serum samples were selected from urban and rural individuals >/=40 years of age who were recruited during the pilot phase of a cohort study of UGI cancers. In all of these studies, the only inclusion criteria were residence, age, and lack of life-threatening conditions. All samples were collected in the years 2002 and 2003. From these subjects, we selected our study samples such that they represented male and female participants equally (Table 1). Samples from Ardabil and Golestan included both urban and rural populations, but samples from Kerman and Mazandaran represented only urban subjects.

A single blood sample was collected from each person. Serum was separated and frozen in -20 °C freezers in plastic vials, and the samples were transported to the U.S. Centers for Disease Control (Atlanta, Georgia) on dry ice, where serum selenium was measured using inductively coupled plasma, with dynamic reaction cell, mass spectrometry (ICP-DRC-MS). The analytical limit of detection for assessment was 5.2 μg/L with a reference range of 80-300 μg/L[11]. We pooled samples to make an internal quality control serum, and 20 quality control samples were randomly inserted among the other serum samples. The coefficient of variation in these samples was 0.04.

The distribution of serum selenium in the four Provinces was not normal. Therefore we used medians and interquartile ranges (IQRs) to present the descriptive results and the Kruskal-Wallis test to test the differences in serum selenium ranks among provinces, between males and females, and between urban and rural participants. The distribution of the natural logarithm of selenium (log selenium) in each province did not deviate from normal. Therefore we used linear regression to test the effect of age on log selenium values. We also used linear regression to find the proportion of variance of log selenium that was explained by the province. All statistical analyses were done using STATA® Software, version 8 (Stata Corporation, Tx).

RESULTS

The median age of all the study subjects was 45 years. Half of the subjects from each area (a total of 150) were males (Table 1). Half of the subjects from Ardabil and Golestan (n = 100) and all of the subjects from Mazandaran and Kerman (n = 100) were from urban areas.

The median serum selenium concentrations were very different in the four Provinces. The medians (IQR) for selenium in Ardabil, Mazandarn, Golestan, and Kerman were 82 (75-94), 123 (111-132), 155 (141-173), and 119 (110-128) μg/L, respectively (P<0.001). The results of linear regression showed that the province variable, by itself, explained 76% of the variance in log selenium (r^2 = 0.76). The proportion of these populations with serum selenium concentrations more than 90 μg/L (the concentration at which serum selenoproteins are saturated[12]) was 100% in Golestan, Kerman, and Mazandaran, but only 29% in Ardabil.

The median (IQR) serum selenium concentrations in males and females were 124 (95-145) and 116 (92-143) μg/L, respectively (P = 0.49).

Simple linear regression did not show a significant effect of age on log selenium in any of the four Provinces. The correlation coefficient between selenium and age in all samples combined was very low (r = 0.006).

Median (IQR) serum selenium concentrations in the urban and rural samples of Ardabil were 81 (76-86) and 83 (74-96) μg/L, respectively (P = 0.57). Median (IQR) serum selenium concentrations in urban and rural samples from Golestan were 150 (135-165) and 161 (144-183) μg/L (P = 0.003).

DISCUSSION

Shamberger and Frost first suggested a role for selenium in the prevention of cancer in 1969, when they observed an inverse association between the geographic distribution of selenium in forage crops and cancer mortality rates in the United States[13]. A growing body of evidence, from both laboratory and epidemiologic studies, has since shown that selenium may have anticarcinogenic effects, especially against cancers of the lung, prostate, skin, and gastrointestinal system[14,15].

In this study, we measured serum selenium in 300 Iranian adults from four provinces with varying risks of EC and GC to have a preliminary assessment of the hypothesis that the high rates of EC in Golestan and GC in Ardabil may be partly attributable to selenium deficiency. The proportion of the populations with a serum selenium more than 90 μg/L (the concentration at which the serum selenoproteins are saturated) was 100% in Golestan, Kerman, and Mazandaran, and these three provinces had medium to high concentrations of serum selenium compared with the other areas of the world. Therefore, it is unlikely that high incidence of EC in Golestan and Mazandaran is due to selenium deficiency. This is consistent with a case-control study in Mazandaran that did not find any difference in hair selenium between EC cases and controls[16]. In Ardabil, however, only 29% of the population had a serum selenium concentration above 90 μg/L. This suggests that the high incidence of GC and pre-neoplastic gastric lesions in Ardabil[10] could be partly due to selenium deficiency.

This is the first study that has examined serum selenium concentrations in different Iranian populations. Median serum selenium ranged widely, from 82 μg/L in Ardabil to 155 μg/L in Golestan. The median serum selenium concentration in these four provinces combined, weighted for the population of each province, was 123 μg/L. For comparison, median serum selenium in other areas of the world varies from very low concentrations (<50 μg/L) in some parts of China and Serbia to very high concentrations (>200 μg/L) in parts of the USA and some other regions of China. However, the majority of median serum selenium concentrations in the world range from 80-120 μg/L[17].

The wide range of serum selenium concentrations among the four provinces and its small range within each province was an interesting finding. The major predictor of serum selenium is dietary intake[14,17], and the observed differences

Table 1 Distribution of age, sex, location, and serum selenium in study sample

Province	Number of samples	Median age (yr)	Male (%)	Urban (%)	Annual incidence of EC / 10^5	Annual incidence of GC / 10^5	Median serum selenium (IQR) in μg / L
Ardabil	100	49	49 (49)	49 (49)	15	38	82 (75-94)
Mazandaran	50	35	24 (48)	50 (100)	19	22	123 (111-132)
Golestan	100	50	51 (51)	51 (51)	40	18	155 (141-173)
Kerman	50	33	26 (52)	50 (100)	3	8	119 (110-128)
Total	300	45	150 (50)	200 (67)	-	-	123[1]

[1]A weighted median based on the total population of each province.

among the provinces are most likely due to variation in the selenium content of their diets.

We plan to conduct further observational studies to confirm or refute the association of selenium intake and the risk of GC in Ardabil.

REFERENCES

1 **Parkin DM**, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; **94**: 153-156

2 **Blot WJ**, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993; **85**: 1483-1492

3 **Knekt P**, Aromaa A, Maatela J, Alfthan G, Aaran RK, Hakama M, Hakulinen T, Peto R, Teppo L. Serum selenium and subsequent risk of cancer among finnish men and women. *J Natl Cancer Inst* 1990; **82**: 864-868

4 **Mark SD**, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni JF Jr, Blot WJ, Dong ZW, Taylor PR. Prospective study of serum selenium levels and incident esophageal and gastric cancers. *J Natl Cancer Inst* 2000; **92**: 1753-1763

5 **Wei WQ**, Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Sun XD, Fan JH, Gunter EW, Taylor PR, Mark SD. 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

6 **Mahboubi E**, Kmet J, Cook PJ, Day NE, Ghadirian P, Salmasizadeh S. Oesophageal cancer studies in the Caspian Littoral of Iran: the caspian cancer registry. *Br J Cancer* 1973; **28**: 197-214

7 **Sadjadi A**, Malekzadeh R, Derakhshan MH, Sepehr A, Nouraie M, Sotoudeh M, Yazdanbod A, Shokoohi B, Mashayekhi A, Arshi S, Majidpour A, Babaei M, Mosavi A, Mohagheghi MM, Alimohammadian M. Cancer occurrence in Ardabil: Results of a population-based cancer registry from Iran. *Int J Cancer* 2003; **107**: 113-118

8 **Saidi F**, Sepehr A, Fahimi S, Farahvash MJ, Salehian P, Esmailzadeh A, Keshoofy M, Pirmoazen N, Yazdanbod M, Roshan MK. Oesophageal cancer among the turkomans of northeast Iran. *Br J Cancer* 2000; **83**: 1249-1254

9 Iranian Disease Prevention and Control Department. Cancer Incidence in Iran. Tehran: *Ministry of Health and Medical Education* 2000: 6

10 **Malekzadeh R**, Sotoudeh M, Derakhshan MH, Mikaeli J, Yazdanbod A, Merat S, Yoonessi A, Tavangar M, Abedi BA, Sotoudehmanesh R, Pourshams A, Asgari AA, Doulatshahi S, Alizadeh BZ, Arshi S, Madjidpoor A, Mir MS, Fleischer DE. Prevalence of gastric precancerous lesions in Ardabil, a high incidence province for gastric adenocarcinoma in the northwest of Iran. *J Clin Pathol* 2004; **57**: 37-42

11 Agency for Toxic Substance and Disease Registry. Toxicological Profile for Selenium. Atlanta, GA: *U.S. Department of Health and Human Services* 2001

12 Panel of dietary antioxidants and related compounds. Selenium. In: Panel of dietary antioxidants and related compounds, eds. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington DC: *National Academy Press* 2000: 284-324

13 **Shamberger RJ**, Frost DV. Possible protective effect of selenium against human cancer. *Can Med Assoc J* 1969; **100**: 682

14 **Combs GF Jr**, Gray WP. Chemopreventive agents: selenium. *Pharmacol Ther* 1998; **79**: 179-192

15 **Combs GF Jr**, Lü JX. Selenium as a cancer preventive agent. In: Hatfield DL, ed. Selenium: Its molecular biology and role in human health. Norwell, MA: *Kluwer Adademic Publishers* 2001: 205-217

16 **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

17 **Alfthan G**, Neve J. Reference values for serum selenium *in various* areas-evaluated according to the TRACY protocol. *J Trace Elem Med Biol* 1996; **10**: 77-87

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