Original Article

# Vitamin Deficiency in Golestan Province, Northern Iran: A High-risk Area for Esophageal Cancer

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**Abstract**

**Objectives:** Dietary factors seem to play a major role in esophageal carcinogenesis in Golestan Province, a high-incidence area for esophageal cancer in northern Iran. The current study was conducted to evaluate previous reports on severe deficiency of vitamin intake in Golestan.

**Methods:** Using a food frequency questionnaire, food intake data were collected from 30,463 healthy participants in the Golestan Cohort Study. Intake of selected nutrients was compared with recommended daily allowance and lowest threshold intake values.

**Results:** Vitamin A intake in the majority of participants was lower than recommended values. The proportion of participants with intakes lower than lowest threshold intake was as follows: urban men, 20%; urban women, 31%; rural men, 48%; and rural women, 64%. The pattern of vitamin C deficiency was similar to that of vitamin A, however, vitamin C deficiency was less common. Daily intake of vitamin C lower than the LTI was as follows: urban men, 6%; urban women, 9%; rural men, 13%; and rural women, 19%. On the other hand, protein intake in the majority of the general population in Golestan was higher than recommended values.

**Conclusion:** Severe deficiency in vitamin intake among women and rural dwellers may partly explain the high incidence of EC among inhabitants in rural areas and the male:female ratio that is approximately 1 in Golestan; while EC is much more common in men in many low-incidence areas.

**Keywords**: Caspian Littoral, esophageal cancer, Golestan, Iran, Turkmen, vitamins

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## Introduction

Cancer of the esophagus is the eighth most common malignancy worldwide.[1] There is a remarkable variation in the incidence of esophageal cancer (EC) in different parts of the world. While the incidence in North America and Western Europe is about 5 to 10 per 100,000; it is more than 100 per 100,000 in some parts of China and Iran. Golestan Province in northern Iran has one of the highest incidence rates of EC worldwide.[2,3]

Dietary factors seem to play a major role in esophageal carcinogenesis in Golestan.[3,4] Earlier studies have suggested low fruit and vegetable intake as etiological factors for EC in the region.[5] Nevertheless, information on food and nutrient intake in Golestan is limited. To investigate risk factors of EC in a prospective setting, a large-scale cohort study (Golestan Cohort Study) has been established in

Golestan Province. For this cohort, a semi-quantitative food frequency questionnaire (SFFQ) has been developed and validated against multiple 24-hour recall questionnaires.[6,7] Using 24-hour recall data, we previously compared the intake of selected nutrients among 131 participants in a pilot phase of the cohort study with recommended daily allowance (RDA) and lowest threshold intake (LTI) values.[8,9] To re-evaluate and corroborate our earlier findings, we performed and reported the same comparison using SFFQ data collected from 30463 participants in the Golestan Cohort Study.

## Materials and Methods

For the current study, data from the first 30,463 participants enrolled in the Golestan Cohort Study were used. Details of the cohort study are available elsewhere.[10] Briefly, approximately 50,000 inhabitants (40 to 75 years) in Golestan Province were enrolled in the cohort study. Urban inhabitants were selected randomly from five areas of Gonbad City by systematic clustering based on the household number. In rural areas, all residents of all villages in the study catchment area (n=326) who were eligible for the study were invited to participate. A total of 10,032 participants with participation rates of 70% for women and 50% for men were enrolled from urban areas. The number of participants from rural areas was 40,013 participants, with participation rates of 84% for women and 70% for men.

After obtaining written informed consent from participants; demographic, lifestyle, and past medical history data were collected in face to face interviews and anthropometric indices were measured by trained interviewers.[10] To collect SFFQ data, each participant was interviewed by a trained nutritionist, either in the local language (Turkmen) or in the national formal language (Persian), depending on the participant's preference. Another nutritionist reviewed and controlled the SFFQs to ensure completeness of the questionnaire and lack of unusual outlier values; in this case the participants were contacted again. The study was not conducted during the month of Ramadan (in each year) when the Muslims refrain from food and drink from dawn to dusk.[6]

Recorded food intake portion sizes were converted to grams according to raw-cooked coefficients. For most items, the USDA Food Consumption Table (USDA, Release 11, 1994), which was adapted for Iranian foods, was used to calculate nutrient values (for both uncooked and cooked foods), daily nutrient intake and daily energy intake. For some items such as bread, vetch, green peppers, wild plums, mint, sweet canned cherries, and sour cherries, an Iranian food composition table was consulted.[11]

### Statistical methods

We presented frequency distribution of categorical demographic variables as well as the mean and standard deviation for continuous variables. Mean daily intake of nutrients was calculated for each subject using SFFQ data. Similar to our previous report,[8] we compared the mean daily nutrient intakes in Golestan with recommended daily allowances (RDAs) and lowest threshold intakes (LTIs) for Ireland[9] by performing one sample *t*-tests. As the distribution of dietary intake variables was severely skewed in Q-Q plots, we used geometric means of daily nutrient intakes for our analyses. The comparable nutrients between our data and the Irish RDAs and LTIs were protein, and vitamins A and C. We utilized the Irish system because no recommended intake values have been validated for Iran and most of the Irish values were identical to their equivalents in the United Kingdom or the Commission of the European Communities systems. Additionally, the Irish system was recently updated for a few items, including vitamin C.

## Results

Demographic characteristics of study participants are shown in Table 1. The mean age (standard deviation) in years was 52.2 (9.1) for all participants, 53.3 (9.6) for men and 51.4 (8.7) for women. Approximately 75% of participants resided in rural areas and 76% were from the Turkmen ethnic group. The majority of participants, particularly women, had no or limited formal education,

Table 2 shows the proportion of study participants whose intake of protein, vitamin A, or vitamin C was lower than RDAs and LTIs. The proportion of participants with vitamin A intakes lower than RDA was as follows: urban men, 69%; urban women, 79%; rural men, 92%; and rural women, 96%. The proportion for intakes lower than LTI was: urban

**Table 1.** Demographic characteristics of study subjects by sex

| Variable | Men | Women | Total |
|---|---|---|---|
| All subjects | 12962 (42.5) | 17501 (57.5) | 30463 (100) |
| Mean age (SD), years | 53.3 (9.6) | 51.4 (8.7) | 52.2 (9.1) |
| Place of residence | | | |
| Urban | 3189 (24.6) | 4861 (27.8) | 8050 (26.4) |
| Rural | 9773 (75.4) | 12640 (72.2) | 22413 (73.6) |
| Ethnicity | | | |
| Turkmen | 9951 (67.8) | 13071 (72.2) | 23022 (75.6) |
| Non-Turkmen | 3009 (23.2) | 4428 (25.3) | 7437 (24.4) |
| BMI (kg/m$^2$) | 25.2 (4.6) | 27.8 (5.7) | 26.7 (5.4) |
| Education | | | |
| No schooling | 6802 (52.5) | 14887 (85.1) | 21689 (71.2) |
| < 5 year | 3039 (23.4) | 1742 (10.0) | 4781 (15.7) |
| 6–8 year | 1010 (7.8) | 328 (1.9) | 1338 (4.4) |
| High school | 1532 (11.8) | 447 (2.6) | 1979 (6.5) |
| University | 577 (4.5) | 95 (0.5) | 672 (2.2) |
| Values are numbers (%) unless stated otherwise | | | |

men, 20%; urban women, 31%; rural men, 48%; and rural women, 64%. Vitamin C intake was lower than RDA in 28% of urban men, 39% of urban women, 55% of rural men and 68% of rural women. In 6% of urban men, 9% of urban women, 13% of rural men and 19% of rural women, the daily intake of vitamin C was lower than LTI. Protein intake in the majority of participants was higher than RDAs; few participants had intakes lower than LTIs.

## Discussion

This study confirmed results of our previous report,[8] which showed a severe deficiency in vitamin intake among inhabitants in rural areas and women in Golestan, with the most severe deficiency among rural women. Similar to the previous study,[8] protein intake in the majority of the general population in Golestan was higher than recommended values.

Severe deficiency in vitamin intake among women and rural dwellers in Golestan may partly explain the high incidence of EC among rural inhabitants and the pattern of incidence among men and women. In many low-incidence areas of the world, EC is much more common among men than women, while incidence rates for both sexes in Golestan and other high-incidence areas are approximately equal.[2] Furthermore, a significant association between duration of residence in rural areas and risk of EC has been reported in Golestan.[12] Rural dwellers in Golestan on average have lower socioeconomic status compared to urban dwellers.[12] Low vitamin intake, as well as deficiency in intake of several other nutrients,[8] may contribute to a higher incidence of EC among people with low SES. Protein intake was not deficient in any of the studied groups, which was in

**Table 2.** Proportion of subjects with daily intakes lower than RDAs or LTIs

| | Urban men | Urban women | Rural men | Rural women |
|---|---|---|---|---|
| Vitamin A (RE mg) | | | | |
| < RDA | 68.9% | 78.5% | 91.5% | 96.0% |
| < LTI | 19.8% | 30.5% | 47.9% | 64.4% |
| Vitamin C (mg) | | | | |
| < RDA | 28.0% | 38.5% | 55.3% | 67.9% |
| < LTI | 5.9% | 8.9% | 13.4% | 19.2% |
| Protein (g/kg) | | | | |
| < RDA | 9.0% | 17.9% | 9.7% | 18.3% |
| < LTI | 0.6% | 1.8% | 0.8% | 2.1% |

RDA=recommended daily allowance; LTI=lowest threshold intake. RDA and LTI for protein are 0.75 and 0.45 gram per kilogram body weight, respectively; for vitamin C, RDA and LTI are 60 and 32 mg per day; for vitamin A RDA and LTI are 700 (600) and 300 (250) retinol micrograms per day, respectively

agreement with earlier studies.[8,13]

The few previous nutritional studies in Golestan utilized short-term dietary assessment methods, such as 24-hour dietary recalls. For large-scale epidemiological studies on chronic diseases, food frequency questionnaires are often the method of choice to obtain dietary exposure data. The two main reasons for this choice are the aim of measuring habitual long-term dietary intake and the fact that the method is relatively inexpensive since highly trained interviewers are not required. This is the first report using a food frequency questionnaire from the Golestan Cohort Study. The questionnaire was validated in a pilot study against 12, 24-hour dietary recalls administered over a one year period with the use of several biomarker assessments.[6] The large sample size of the current study, with participants from a wide range of socioeconomic and ethnic groups, provides robust evidence regarding vitamin deficiency in Golestan and its potential role in esophageal carcinogenesis.

In conclusion, severe deficiency in vitamin intake among women and rural dwellers may partly explain the high incidence of EC among inhabitants in rural areas and the male to female ratio that is close to 1 in Golestan; while in many low-incidence areas EC is much more common in men. Nutritional insufficiencies may have a large impact on disease development in Golestan. Finding relevant deficiencies in specific food groups or nutrients could lead to specific preventive measures, which might significantly reduce the incidence of this malignancy in such high-incidence areas.

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