Cancer Detection and Prevention 29 (2005) 464–469

Cancer Detection and Prevention

www.elsevier.com/locate/cdp

# Riboflavin deficiency and esophageal cancer: A case control-household study in the Caspian Littoral of Iran

Fereydoun Siassi PhD[a,b], Parviz Ghadirian PhD[b,*]

[a] Department of Nutrition and Biochemistry, School of Public Health and Institute of Public Health Research, Tehran University of Medical Sciences and Health Services, P.O. Box 14155-6446, Tehran, Iran

[b] Epidemiology Research Unit, Research Center, CHUM, Hotel-Dieu, Department of Nutrition, University of Montreal, 3850 Urbain St., Que., Canada H2W 1T7

Accepted 22 June 2005

## Abstract

*Background:* In a case-household–control-household study in two very high and low esophageal cancer (EC) risk regions of the Caspian Littoral of Iran, a total of 21 cases (12 subjects from the high risk and 9 subjects from the low-risk region) with a total of 91 household members (57 subjects from the high risk and 34 subjects from the low-risk region) were investigated. Cases were matched for sex and age (±5 years) with non-blood relative controls. *Methods:* A standard 24-h dietary recall questionnaire was used to estimate riboflavin intake. The erythrocyte glutathione reductase activity coefficient (EGR-AC) was measured to assess riboflavin status. The Student *t*-test was used to test differences, and $\chi^2$ analysis was applied to test associations. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were also calculated. *Results:* Results indicated that in both regions, the mean daily intake of riboflavin for cases was less than that of the controls ($0.66 \pm 0.43$ mg/day versus $0.82 \pm 0.37$ mg/day) whereas for their households, it was virtually the same. Both cases and control households showed riboflavin deficiency in two regions, with higher deficiency in the high risk area. Statistical analysis revealed significant differences between the two regions for EGR-AC ($P < 0.001$). Odd ratios indicated that the risk of developing EC for persons living in riboflavin-deficient households was more than twice of non-deficient households. *Conclusion:* Therefore, this study suggests that riboflavin deficiency may play an important role in the etiology of esophageal cancer in the Caspian Littoral of Iran.



*Keywords:* Nutrition; Riboflavin intake; Glutathione reductase; Esophageal cancer; Carcinogenesis; Iran; High-risk; Case-household control; Tumor progression

## 1. Introduction

The possible role of riboflavin in the etiology of esophageal cancer (EC) is complex. Despite more than half a century of research in this field, its precise role in the development of this tumor at different stages of initiation, promotion and progression still remains to be defined [1–11]. Riboflavin deficiency may decrease the rate of spontaneous tumors growth in experimental animals [3]; may participate in the reduction of gastric acid secretion, relaxation of the pylorus and reduction in lower esophageal sphincter pressure leading to reflux of duodenal and gastric juices with low in acidity, into the esophagus and hence predisposing to local squamous carcinogenesis [4]; may also cause ulceration, epithelial hyperplasia and hyperkeratosis at the lower third of the esophagus or at the cardioesophageal junction in baboons [5]; injured oral and esophageal epithelium [12] and may increase the carcinogenicity of specific drugs, such as azo dyes [6]. The earliest change in progressive riboflavin deficiency in mice is atrophy of the epithelium of the esophagus and stomach, followed by epithelial hyperplasia and hyperkeratosis [7,8]. High intake of riboflavin has been associated with increased gastric cancer risk [9]. It may reduce frequency of micronucleated cells and carcinogen DNA adducts [10]; and associated with reduced risk of esophageal adenocarcinoma [11]. A study to

* Corresponding author. Tel.: +1 514 890 8000x14448; fax: +1 514 412 7204.

*E-mail address:* parviz.ghadirian@umontreal.ca (P. Ghadirian).

0361-090X/$30.00 
doi:10.1016/j.cdp.2005.08.001

assess the effect of riboflavin deficiency and riboflavin supplementation on carcinogen-DNA binding showed that riboflavin deficiency may increase the risk of carcinogenesis by way of an increase in carcinogen binding [13].

In a case–control study in China [14] it was revealed that increased dietary riboflavin was associated with reduced esophageal cancer.

In a vitamin intervention trial of the esophageal cancer, it was found that large increases in retinol, riboflavin and zinc blood level were more likely to have histologically normal esophagus at the end of trial [15].

Flavin coenzymes are widely distributed in the body and are involved in carbohydrate, fat, amino acid and vitamin metabolism [3]. Furthermore, since riboflavin influences epithelial integrity, tissue flavin concentrations, the rates of prostaglandin biosynthesis and glutathione metabolism [6–17], the possible effects of its deficiency on development of esophageal tumor and its growth are intricate. Nevertheless, it is plausible to hypothesize that riboflavin deficiency enhances the risk of EC tumors development at initiation and promotion stages while reducing tumors growth at progression stage.

The highest incidence of EC in the world has been observed among Turkoman inhabiting the northern areas of Gonbad district in the Caspian Littoral of Iran [18], with a male–female sex ratio of 0.7:1 which drops 34-fold for males and 47-fold for women within a short distance of 300 miles to the west in the province of Gillan [19,20]. Therefore, two distinct high and low risk areas for this cancer are defined in the Caspian Littoral of Iran.

An extensive nutritional and food-consumption survey in these areas revealed low intake of Vitamins A and C and of riboflavin in the high-risk region [21]. Furthermore, clinical signs of some nutrient deficiencies, particularly of riboflavin, were also seen in these regions [22]. Therefore, to investigate the possible implications of riboflavin in the etiology of EC, a case–control study was conducted in these areas. We assumed that riboflavin intake and status of case households reflect riboflavin status of cases during childhood and early adulthood. This is a valid assumption because of extremely slow changes in the food habits in these areas. Hence, the purpose of the present study was to compare riboflavin intake and its status among EC cases, controls and their households in both the high- and low-risk regions of EC in the Caspian Littoral of Iran.

## 2. Materials and methods

### 2.1. Study groups

In this population-based, case–control study, a total of 21 cases (12 subjects from the high risk and 9 subjects from the low-risk region) and 91 household members (57 subjects from the high risk and 34 subjects from the low-risk region) were compared with a total of 21 non-blood relative control subjects (12 from the high risk and 9 from the low risk area) matched for sex and age (±5 years) as well as 97 household members (49 subjects from the high risk and 48 subjects from the low-risk region) (Table 1).

All cases and controls were from rural areas, and cases had either pathological or radiological confirmation of EC. The study subjects and all household members older than 6 years of age were interviewed and examined within 2 months of the date of diagnosis of EC, with biological samples also being collected.

Table 1
Composition of case and control subjects and their households in high and low esophageal cancer risk regions of the Caspian Littoral of Iran

| Variable | Case | Control | Case household | Control household |
|---|---|---|---|---|
| Number | | | | |
| High risk | 12 | 12 | 57 | 49 |
| Low risk | 9 | 9 | 34 | 48 |
| All | 21 | 21 | 91 | 97 |
| Male to female ratio | | | | |
| High risk | 1.4 | 1.4 | 0.8 | 0.8 |
| Low risk | 2.6 | 2.6 | 0.7 | 0.9 |
| All | 1.6 | 1.6 | 0.8 | 0.8 |
| Mean age ± S.D. (y) | | | | |
| High risk | 46.3 ± 10.1** | 46.0 ± 9.5* | 22.1 ± 15.1 | 22.8 ± 15.2 |
| Low risk | 56.9 ± 8.5 | 55.8 ± 8.7 | 28.6 ± 15.2 | 24.2 ± 15.8 |
| All | 50.9 ± 10.7 | 55.8 ± 10.2 | 24.5 ± 15.4 | 23.5 ± 15.5 |
| Mean number of persons/household ± S.D. | | | | |
| High risk | 6.7 ± 2.1 | 5.8 ± 2.6 | 7.2 ± 2.3* | 7.2 ± 2.3 |
| Low risk | 5.3 ± 1.5 | 8.0 ± 2.8 | 6.3 ± 1.5 | 8.2 ± 2.9 |
| All | 6.1 ± 1.9 | 6.7 ± 2.8 | 6.8 ± 2.1 | 7.7 ± 2.6 |

S.D.: standard deviation; y: year.
* Significant differences (Student's *t*-test) between high- and low-risk regions: $P < 0.05$.
** Significant differences (Student's *t*-test) between high- and low-risk regions: $P < 0.02$.