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Dietary Factors and Esophageal Cancer in the Caspian Littoral of Iran[1]

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Summary

A study was undertaken to attempt to relate the distribution of exogenous factors to the varying incidences of esophageal cancer in the Caspian Littoral of Iran. For the study, 38 villages were chosen by random sampling in 14 regions defined by their esophageal cancer incidence and environmental characteristics. Information was obtained on the dietary, social, and cultural features of each village. In addition, an extensive 5-day study of 6 randomly selected households in each of the 38 villages was conducted. The study consisted of measured dietary intake, a historical food consumption questionnaire, and clinical examinations of adult occupants.

Preliminary results show no single factor responsible for the etiology of esophageal cancer. However, there were some major dietary differences between the regions of different esophageal cancer risk. Bread was the chief staple food in high-incidence areas; rice, in low-incidence areas. In high-incidence areas, there was a low intake of vitamins A and C, riboflavin, animal protein, and fresh vegetables and fruit, but a greater consumption of sheep's and goat's milk. Analyses of food samples for aflatoxins, polycyclic aromatic hydrocarbons, and nitrosamines showed low levels of these carcinogens in areas of high and low incidences. The use of tobacco and alcohol was not found to be of significance.

Introduction

Striking variations in the incidence of esophageal cancer have been found within the relatively small area of the CLI[3] (Chart 1). The data collected by the Caspian Cancer Registry show that the incidence of esophageal cancer varies by as much as 30-fold in women and 6-fold in men within a 300-mile area. The rates recorded in the Gonbad region of the north-eastern section of the CLI are among the highest reported for this tumor anywhere in the world, being 262 $\times$ 10^5/year in women and 206 $\times$ 10^5/year in men (3) (truncated age-standardized rates).

The CLI is densely populated and ecologically diverse. There are 4 million inhabitants and an average of 164 persons per square mile. The length of this narrow strip of land, from the northeast corner of Mazandran Province to the northwest corner of Gilan Province, is about 800 miles, and its width varies from 155 miles in the areas of Gorgan and Gonbad to 40 miles in Shahsavar and Chalus in the meridian of Teheran (Chart 1). The residents of part of the eastern region of the area are Turkomans, a formerly nomadic central Asian people speaking a Turkic-related language. Most of the other residents of the area speak some Persian dialect.

In previous communications (1-3), salient information was given about the ecological features of the Caspian Littoral as they relate to the incidence of esophageal cancer, together with the results of the 1st 3 years of cancer registration in the CLI. The medical facilities (*i.e.*, the number of hospitals, beds, physicians, and reporting doctors) and the level of accuracy and methods of diagnosis were considered in the paper describing the cancer registry (3).

Because of the high levels and great variations in incidence rates of the disease, an intensive search was initiated to determine its etiology. The 1st step in this approach was to study the way of life of the population at differing risk in an attempt to identify factors closely associated with the geographical variation in incidence. Accordingly, a multidisciplinary etiological investigation was initiated, which was jointly organized by the IPHR of Teheran, the FNI, and the IARC. Additional support came from the United States National Cancer Institute and the Medical Research Council of the United Kingdom. This paper surveys the methodology used, describes the work of some of the field teams, and outlines a portion of the preliminary results. It is not meant to give a comprehensive account of methods or of the results, nor does it discuss the nutritional consequences of the dietary study.

Materials and Methods

The aim of the study was to investigate the populations at different risks for esophageal cancer with respect to all

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[3] The abbreviations used are: CLI, Caspian Littoral of Iran; IPHR, Institute of Public Health Research; FNI, Food and Nutrition Institute; IARC, International Agency for Research on Cancer.

Chart 1. Incidences of esophageal cancer in the CLI.

environmental factors possibly relevant to the etiology of the disease. For this purpose, the area was stratified by cancer incidence into 8 regions, and these 8 regions were further stratified into a total of 15 regions on the basis of economic, demographic, and agricultural factors. The information for this latter division was collated from many different sources, among them the Iranian Central Statistical Office, the Iranian Soil Institute, the Meteorological Bureau of Iran, the IPHR, and the FNI. Of particular value was the village gazeteer, based on the 1966 census, in which economic, agricultural, and demographic information is given on each village in the region.

The basic sampling unit was the village (occasionally, this was a group of adjacent villages with an overall minimum population of 250). Ultimately, 45 study units (villages) were selected (*i.e.*, 3 villages per region) with the goal that 15 in each of the 3 seasons, winter, spring, and summer, were to be investigated. Towns (any population center of more than 5000) were excluded from the study since the modes of living of their inhabitants were more likely to have changed in recent times. Later, 1 region (a mountainous and inaccessible area) was eliminated, and in the 3rd season, 4 villages were omitted due to lack of time. Thus, 38 villages in all were visited (14 villages in winter, 14 in spring-summer seasons, and 10 during the summer-autumn seasons). To minimize the bias that could arise as a result of seasonal changes in the ways of life, the investigators moved through the study areas (the 14 regions) twice in each of the 3 seasons.

Chart 2 shows the CLI and the 15 study regions, with the villages investigated in each.

In each village, a detailed 5-day food consumption survey was conducted in 6 households. Each house was visited 3 times a day, and the total food to be consumed at each meal was weighed. Special attention was given to food eaten between meals and food given away or left over. Biological samples (hair, urine, feces, and blood) from the adult members of these 6 households were also taken for a limited range of clinical, chemical, and hematological estimations and genetic markers. In addition, retrospective information was obtained on past food habits in the households (household questionnaire), and, from an additional 50 adult males and 50 adult females in each village, questions were asked on socio-economic status, use of tobacco and alcohol, tea consumption, and a range of other cultural and social characteristics (individual questionnaire).

Food and water samples were collected to determine the level of selected chemical carcinogens in food items and of nitrate and nitrite in water.

Work of the Field Teams. The preparation of the village and villagers for the arrival of interviewers was accomplished by a geographer and technician who conducted a census of the village. The households to which the individual questionnaires were applied and the households for the dietary survey were chosen by systematic sampling from the village census. The teams conducting the household surveys consisted of nutritionists and interviewers who worked on a staggered timetable basis in measuring food intake in 6

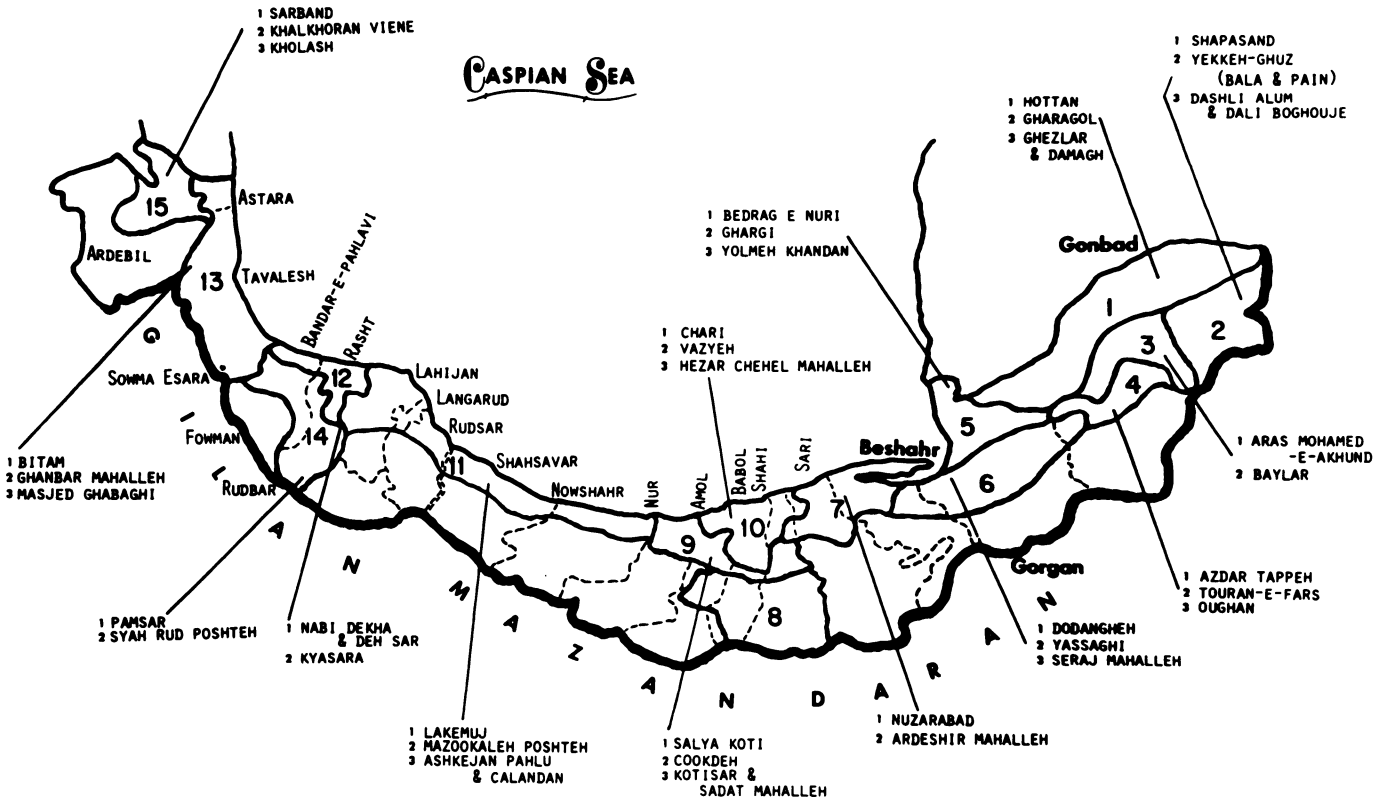

Chart 2. Fifteen regions and 38 study villages in the CLI.

households for a 5-day period. They also completed special household and individual intake measurements for 2 meals during 2 given days at the end of the dietary survey. The problem of possible bias created by the presence of observers had been discussed with the subjects before the interviews and the measurement of food intake.

After the dietary survey team completed its work, the clinical team, composed of a clinician, nurses, and laboratory technicians, arrived at the village. They performed examinations on each adult in the households selected for the dietary intake survey. These consisted of anthropometric measurements, a clinical examination to assess the extent of vitamin deficiency present, as well as electrocardiogram and blood pressure estimation. Samples of urine, feces, saliva, blood, hair, and nails were also collected for biochemical tests.

Results

The results of this multidisciplinary epidemiological investigation will be published later. The purpose of this paper is to discuss preliminary results of the nutritional and food consumption surveys in the areas of high and low incidences of esophageal cancer in the CLI.

Consumption of Staple Foods. The food consumption survey (Tables 1 and 2) revealed a very much higher intake of bread as the staple food in the high-incidence areas of Gorgan and Gonbad, which are located in the northeastern part of the region (Charts 1 and 2). In the western part of the study area, which is of lower incidence, rice was the chief staple.

Calorie and Protein Content. Calorie intake was found to be generally adequate within the study area (Tables 1 and 2). Total protein intake was substantially the same throughout the CLI, but the source of protein varied. For example, 90% or more of the protein in some households in the high-incidence area, Regions 1, 2, and 3, came from vegetable sources. Households in the low-incidence areas of Regions 12, 13, and 14 obtained a considerably greater proportion of their protein from pulses and meat products. There were wide differences in animal fat intake between regions, but these showed no relationship to esophageal cancer incidence.

Vitamin Intake. A low intake of vitamins A and C and of riboflavin was observed in the regions of highest incidence. Fresh fruits and vegetables were infrequently eaten in these areas. There were large interhousehold variations for vitamin A and C intake, with the intake for many families considerably less than the mean. No overt clinical signs of malnutrition and hypovitaminosis were reported by the clinical team, apart from a few individuals with clinical evidence of riboflavin deficiency.

Special Foods. A special pregnancy diet, a mixture known as majouvah, composed of a preparation of raisins, ground pomegranate seeds, and black pepper, was sometimes ingested by Turkoman women. This food, eaten especially during the 1st trimester of pregnancy, was used to resolve digestive discomfort and as a snack.

Tea Intake. There are 2 sources of information on the

Table 1

Daily food consumption in the CLI

The consumption of selected foods according to study region in the area during each of 3 seasons is given in g.

	Region													
	1	2	3	4	5	6	7	9	10	11	12	13	14	15
Bread	474.3[a]	589.0	595.5	383.3	551.5	311.3	331.0	254.0	124.8	96.9	225.3	94.2	65.8	434.9
	570.7	738.4	460.1	403.0	421.7	365.2	348.0	259.8	57.0	198.5	75.1	426.2	238.3	561.6
	453.6	769.9	[b]	685.1	606.9	477.8		250.3	314.3	363.8		463.6		590.7
Rice	167.7	86.7	140.7	97.4	57.0	417.9	342.4	521.3	660.2	536.0	413.6	612.1	584.4	170.8
	112.4	54.7	69.2	202.8	113.7	435.9	457.1	859.8	550.7	428.6	532.0	469.2	273.4	128.1
	102.3	101.8		76.6	127.0	294.1		406.5	360.5	499.2		361.0		127.3
Pulses, seeds, and nuts	0	2.7	11.4	16.7	2.0	6.0	6.7	14.8	7.5	64.0	35.1	7.2	20.2	5.8
	0	0.5	5.5	4.0	3.4	0.3	12.2	10.0	18.5	2.7	101.6	1.0	73.5	10.2
	0	4.3		14.4	0	2.9		4.6	38.5	2.6		11.9		22.1
Green vegetables	0	0	1.5	24.2	2.0	72.7	13.3	8.2	12.3	3.2	14.0	2.9	9.8	2.7
	0	0	6.4	102.0	47.7	11.2	16.1	3.3	6.5	17.8	9.7	29.4	2.5	47.1
	0	0		7.6	0	50.4		6.5	14.5	1.2		0.5		6.3
Fresh fruit	0.5	59.6	2.7	5.8	39.7	11.3	28.3	6.0	246.7	5.9	11.0	0	9.2	24.1
	0	3.9	7.5	3.9	0.2	18.3	1.0	34.6	40.9	6.8	6.9	6.8	15.3	6.8
	204.0	3.9		27.7	106.8	45.2		148.3	56.4	67.4		55.8		55.6
Meat and poultry	33.0	44.3	24.5	60.7	13.0	66.0	74.9	70.6	73.5	41.4	25.1	11.2	50.8	35.4
	5.8	12.5	24.1	31.5	33.9	32.9	11.1	76.8	62.1	17.7	12.8	12.7	13.2	71.4
	30.8	12.5		26.8	41.0	13.3		50.8	87.3	3.4		24.8		38.9
Fish	0	0	0	0	0	0	0	4.0	22.4	8.5	13.5	7.2	37.6	2.4
	0	0	0	0	0.3	3.8	0	0	0	0	5.6	13.7	0	0
	0	0	0	0	0	0	0	0	0	0		0.7		5.4
Milk and Yogurt	73.1	38.6	77.6	42.3	69.1	70.9	59.4	98.5	53.3	45.9	34.2	26.9	47.0	170.8
	226.9	83.7	64.7	106.2	194.3	55.6	83.7	190.8	86.8	341.1	16.7	119.8	85.7	172.3
	246.6	34.6		45.8	73.7	100.3		149.0	60.7	142.9		22.1		64.9
Cheese	0	0	0	3.1	0	0.9	3.6	1.0	0	6.5	3.1	0.4	9.4	28.8
	0	3.1	0	3.6	0	0	8.0	0	0	7.7	4.1	6.6	0	17.3
	0	0		1.1	0	3.5		0	0	4.2		20.4		10.7
Tea	5.2	4.4	6.2	3.7	3.2	3.2	17.9	4.3	6.0	6.2	4.0	3.0	4.9	3.7
	7.8	6.3	5.3	16.6	4.4	9.8	14.2	5.1	5.6	7.0	4.7	5.1	2.3	5.3
	4.7	5.9		5.0	3.2	4.7		7.1	4.4	3.4		3.9		4.0

[a] The upper figure in each entry refers to the winter season, the central figure refers to spring-summer, and the lowest refers to summer-autumn.
[b] Blank space, no measurement was taken.

consumption of tea; 1st, questions in the individual questionnaire on quantity drunk daily; 2nd, a measurement of the weight of leaf used daily. Both types of information indicate a 50% higher consumption among the very highest incidence population than among the lowest incidence population, but the highest consumption was in the region of intermediate incidence.

Milk Products. There was no overall relationship between milk or milk product consumption and the incidence of esophageal cancer. However, when asked the source of the milk products in the household questionnaire, the responses clearly indicated a greater consumption of milk (and yogurt) from both sheep and goats in the highest incidence area.

Use of Local Plants as Herbs or Medicines. In the highest incidence areas, there was no indication of a wide use of wild plants, either as herbs or medicines. This lack is a clear reflection of the ecological conditions as, for most of the year, such plants are not available. However, for a period of a few weeks in the spring, a plant known as wild spinach is occasionally consumed.

Alcohol, Tobacco, and Opium. The information from individual questionnaires confirmed earlier reports of the negligible intake of opium, tobacco, and alcohol. Women did not use alcohol at all, nor did they consume nass (a mixture of tobacco, lime, and ash) favored by some male inhabitants.

Discussion

The main dietary factors that were found to be associated with the incidence of esophageal cancer were the consumption of bread, the consumption of sheep and goat's milk or yogurt, and the lack of fruits and vegetables, with a

Table 2

Daily intake of selected nutrients in the CLI

The measurement of nutrients in either g, mg, or μg (as indicated) in the 15 study areas during each of the 3 seasons.

Nutrients	Region													
	1	2	3	4	5	6	7	9	10	11	12	13	14	15
Calories	2510[a]	2511	2863	2271	2235	3235	3416	3490	3736	3084	2751	2914	3088	2892
	2408	2672	2200	2537	2116	3272	3384	4163	2932	2801	3325	3728	2768	3105
	2346	3245	[b]	3167	2712	3063		2954	3057	3354		3380		2851
Protein (g)	63.4	71.1	76.4	59.8	62.3	76.7	73.3	81.2	80.0	75.6	70.2	60.7	73.5	74.2
	63.9	74.7	58.3	62.1	62.5	73.5	77.4	93.8	62.8	66.4	88.9	100.5	77.3	86.8
	57.7	84.9		93.9	75.9	76.2		69.6	79.1	79.7		81.3		85.7
Fat (g)	43.4	31.7	40.0	50.9	23.3	60.4	83.1	43.1	59.2	42.8	32.9	21.9	49.9	68.6
	35.5	35.2	32.1	46.7	31.9	47.6	41.0	51.9	53.5	42.9	41.9	39.7	43.9	57.0
	49.1	48.5		57.0	39.9	33.7		49.5	53.6	32.5		53.5		38.7
Calcium (mg)	408.3	438.9	504.1	373.3	443.3	429.3	400.7	400.6	352.8	280.4	319.7	208.7	278.2	672.2
	494.9	522.7	385.4	468.8	526.8	380.3	438.5	483.4	289.7	635.6	278.2	640.8	444.7	655.7
	397.2	541.9		688.4	486.3	545.5		421.5	390.4	512.6		444.9		551.4
Iron (mg)	32.9	40.6	41.9	30.8	37.8	30.4	29.3	25.8	18.9	18.2	23.6	14.7	13.7	34.4
	37.4	46.2	33.5	31.1	31.0	32.1	29.9	26.4	14.7	19.1	20.0	44.9	31.2	43.5
	32.9	52.4		60.3	43.7	37.7		24.9	29.4	31.5		37.1		44.8
Vitamin A (μg of retinol)	32.9	77.9	52.8	316.9	78.2	422.1	139.4	364.5	339.0	79.6	171.5	36.9	225.2	489.7
	224.3	45.8	125.4	400.0	286.1	226.9	188.3	226.4	260.9	236.8	269.6	184.2	388.4	422.2
	166.6	184.3		242.3	124.6	341.8		679.2	295.1	183.2		281.5		185.1
Thiamine (mg)	2.01	2.06	2.46	2.04	2.41	2.02	2.07	2.25	1.73	1.62	1.71	1.53	1.46	1.95
	2.38	2.64	1.98	1.98	1.89	2.20	2.18	2.28	1.43	1.60	1.80	2.56	2.14	2.53
	2.25	3.00		2.90	2.53	2.45		1.87	2.05	2.28		2.41		2.57
Riboflavin (mg)	0.52	0.42	0.65	0.72	0.56	0.73	0.87	1.07	0.76	1.04	0.77	0.61	1.00	0.92
	0.55	0.60	0.53	0.85	0.83	0.70	1.20	1.02	1.81	1.16	2.66	0.98	0.86	0.98
	0.05	0.60		0.87	0.63	0.76		1.06	1.03	0.83		0.76		0.80
Niacin (mg)	29.8	30.1	35.5	29.8	34.9	29.5	32.3	34.5	26.8	22.6	24.4	23.3	23.5	28.3
	31.9	37.5	28.8	28.5	27.5	31.1	32.5	34.5	21.3	22.6	23.9	37.2	25.8	35.6
	28.6	43.4		41.1	37.7	34.4		28.2	31.2	32.7		35.8		36.5
Vitamin C (mg)	1.9	15.8	8.3	29.0	19.0	40.2	32.4	29.8	113.1	14.1	17.4	12.6	11.1	8.82
	1.1	23.0	41.9	49.5	12.3	72.2	21.9	25.1	77.1	21.3	44.2	22.5	98.1	18.8
	35.3	27.4		80.5	48.4	52.1		61.8	44.3	42.1		38.1		21.1

[a] The upper figure for each entry refers to the winter, the central figure refers to the spring-summer, and the lowest refers to the summer-autumn season.

[b] Blank space, no measurements taken.

correspondingly low intake of vitamin A, riboflavin, and vitamin C. The most striking feature of the diet in many households in the high-incidence area was the quantity of bread consumed to the exclusion of other foods. Some households had nothing but bread, sugar, and tea for the entire 5 days of the dietary survey. As a separate part of the study, the main elements of the diet have been examined for volatile nitrosamines, polycyclic aromatic hydrocarbons, and aflatoxins. The results will be reported in full elsewhere, but up to the present, there has been no indication that unusual levels of any of these compounds are to be found in the foodstuffs of the high-incidence region.

When considering the distribution of esophageal cancer in the CLI, one must bear in mind that the relatively low incidence found in Gilan is a moderately high incidence by the standards of North America or Western Europe. Therefore, one might speculate that there is present throughout the region a carcinogen active for the esophagus, but that, in the eastern part of the area, the restricted diet renders the population highly susceptible. The nature of the putative carcinogen is unclear, but one can be almost certain that alcohol and tobacco, the 2 main factors identified in North America and Europe, are not involved to an appreciable extent. Whether hot tea consumption is associated with the disease awaits further investigation, but the evidence from the present study shows that hot tea cannot be responsible as the main factor for the gradient in cancer incidence. The postulated increased susceptibility could well be due to nutritional factors.

Present investigations are aimed at testing the hypothesis of increased susceptibility. If proved correct, future studies will have to investigate in depth the biological mechanisms which might mediate such susceptibility.

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