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Declining incidence of esophageal cancer in the Turkmen Plain, eastern part of the Caspian Littoral of Iran: A retrospective cancer surveillance

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Abstract

Background: Previous studies have shown that upper gastrointestinal cancers are the most common cancers in Caspian Littoral, and rate of esophageal cancer (EC) in Iranian Turkmens residing in the Eastern part of littoral are among the highest in the world. Our aim was to reassess the rate 30 years later and following socioeconomic changes in the region. *Methods:* A comprehensive retrospective search was undertaken to find all new cancer cases during the 1996–2000 period. Diagnosis of cancer was based on histopathological reports in 68.2%, clinical and/or radiological evidence in 29.7% and death certificate only (DCO) in 2.1% of the cases. *Results:* A total of 5143 new cancer cases were registered of whom 3063 (59.6%) were males. The median (IQR) age was 60 (44–69) years. Age-standardized rates (ASR) for all cancers in males and females were 134.7 and 104.5 per 100,000, respectively. Based on ASR, the top five common cancers in males (excluding skin cancer) were cancers of esophagus (43.4), stomach (27.8), colorectal (10.7), bladder (7.8) and oral cavity (6.3), while in females cancer of esophagus (36.3) was followed by cancers of breast (15.7), stomach (8.3) colorectal (6.6) and cervix (3.6). *Conclusion:* We conclude that EC incidence rate has decreased to less than half the rate reported 30 years ago, while the incidence rates of colorectal and breast cancers have increased significantly.

Keywords: Esophageal Cancer; Iran; Caspian Littoral; Golestan; Turkmen; Retrospective; Cancer surveillance

1. Introduction

Results of a large-scale cancer survey carried out in the Caspian Littoral in northern Iran during 1968–1971 which was based on a cancer registry centre set up jointly by the Institute of Public Health Research of Tehran University (IPHR) and the International Agency for Research on Cancer (IARC) have shown that North-eastern Iran is a very high incidence area for oesophageal cancer [1–4].

Exceptionally high age-adjusted incidence rates of EC were found in the eastern part of the survey area (Present day, Golestan Province), including rates in most eastern parts of up to 165.5/100,000 in men and 195.3/100,000 in women [2]. These same studies revealed a more than 10 folds variation in EC rates between the eastern and western parts of the littoral in areas less than 500 km apart. Until the past few years there were no comprehensive report about the current incidence rates of cancer in Iran in general and the Caspian Littoral in particular. In 2003, the results of first population-based cancer survey from Ardabil Province in the western part of the Caspian Littoral were published [5],

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and showed significant changes in cancer incidence rates in this province compared to the reports of 30 years ago.

In this paper we report the result of an active surveillance for all cancer cases and compare the results with the rates reported 30 years ago from the Golestan province.

2. Material and methods

2.1. Geographic and demographic description

Golestan was previously part of Mazandaran province but became a separate province in 1997. It is located in north-eastern part of Iran, south-east to the Caspian Sea, with an area of 20,893 km^2, constituting about 1.3% of the total area of the country. Golestan Province has considerable ecologic and ethnic diversity. It consists of deserts, mountainous and forestalls areas. The climate is moderate, damp and Mediterranean. The majority of the male populations are farmers while more than 87% of the women are housewives, who occasionally work on the farms as well. According to the last National Iranian Census (1995) its population was 1,426,288 of whom 54% live in rural areas. The major ethnicities within the province are Persians (40%), Turkmen (32%), Sistanis (also called Zabolis) (15%) and Azeri Turks (5%). Sixty-seven percent of the population are younger than 30 (median age = 21 years in the urban areas versus 20 years in the rural areas). Life expectancy at the time of birth is 69.3 years for the males and 70.2 years for the females.

According to the 1999 health statistics, there existed one physician for every 1722 people and there were 18 hospitals with 1184 beds, 14 outpatient clinics, 11 pathology laboratories and 28 diagnostic radiology clinics. There was no radiotherapy facility in the province but an oncologist, a gastroenterologist, seven urologists, 32 gynecologists, 24 surgeons, and 26 internists had the facilities and abilities for making the diagnosis and providing the appropriate therapy for the cancer patients in the province or referring them for further therapy (radiotherapy and other special cares) to Mashhad (Khorasan), Sari and Babol (Mazandaran) or Tehran.

2.2. Survey method

In order to conduct the study, the Golestan Cancer Registry office was established in Gonbad, the second major city in the province, where the Atrak Clinic, Golestan's main referral center for upper gastrointestinal (GI) cancers, is also located. This registry which is still functional has two permanent staff members and is run by the Golestan University of Medical Sciences under the supervision of the Cancer Registry Unit of the Digestive Diseases Research Center (DDRC), Tehran University of Medical Sciences (TUMS). The Cancer Registry Unit of DDRC consists of a gastroenterologist, two epidemiologists, and two pathologists. The Medical Ethics Committee of DDRC had approved the survey methods. The survey team consisted of three general practitioners and 12 medical students who were trained to go to the hospitals, pathology laboratories, diagnostic radiology services, outpatient public and private clinics to check their records to find cancer cases and whenever possible to make copies of the documents according to which the diagnosis of cancer had been made. These documents were then sent to the registry office in Gonbad and subsequently to the Cancer Registry Unit in DDRC in Tehran. Data about name, sex, age at the time of diagnosis, pathologic diagnosis, and place of residence, diagnostic methods were collected.

During the 8 months period of (February–September 2001), the survey team collected and compiled data for a period of 5 years (1996–2000) from 17/18 hospitals, 12/14 of the outpatient clinics, 11/11 of the pathology laboratories and 7/28 of the radiology clinics. The private radiology centers recorded the identifying data of subjects and only occasionally kept the radiological or sonographic reports, while the public centers, usually located within the hospitals, had kept the radiology reports for a majority of the patients. Physicians in all seven districts issued death certificates in duplicate, one for themselves and one to be kept by graveyard authorities. The physicians sent their copies to the Deputy for medical care to receive new death certificates in Gorgan city and these certificates to be compiled later. Death certificates of urban areas (for all the seven cities) were obtained from the office of the provincial medical care deputy.

The provincial deputy for health (mainly concerned with rural Health), covering the rural area of the whole province, conducted annual health censuses each year. This is performed by behvarzes (auxiliary health care workers in health houses who are responsible for public health care and health census of each village) at the beginning of each year through direct, home to home data collection which included data about the number of new births and deaths and enquiries regarding the cause of death. The results of these censuses, including information about the causes of death in rural areas, were compiled in the Deputy of Health, where the final annual death statistics were issued. Data about rural cancer cases, which seems to be more comprehensive than urban areas were obtained from the Census Office in Deputy of Health. A number of Golestan Province residents seek medical care outside the province, mainly in Mashhad, Tehran and occasionally in Sari or Babol in Mazandaran. A through search was done in medical centers of these cities which provide care for cancer patients to find any cancer cases from Golestan inhabitants. The hospital-based cancer registry of the Cancer Institute, Tehran University of Medical Sciences, currently provides the most reliable and comprehensive data in this large city. All the incident cancer cases from Golestan, recorded in the Cancer Institute were also included for the same time period (1996–2000).

The collected data were summarized in data sheets and were coded using the ICD-O 3 (International Classification of Disease for Oncology), 3rd edition [6]. All data were alphabetically sorted and duplicate cases with the same name, sex, age and place were eliminated by manual and computerized linkage. Each alphabetical group was reassessed manually by two individuals, on two different occasions. The data were computerized using SPSS (Statistical Package for Social Sciences) software version 10.0 and M.S. Excel Software with Persian fonts. We calculated the population at risk based on the annual health census and then calculated person-years of the population at risk by using each year method. Age- and sex-specific rates, crude rates, and age-standardized rates (ASRs) per 100,000 cases were calculated for each site (ICD-O, 3rd) using the direct method of standardization to the world population [7].

3. Results

During the 5-year period (1996–2000), 5143 new cancer cases were registered from the Golestan Province of whom 3063 were men (59.6%). The median (IQR) age was 60 (44–69) years. Tables 1 and 2 show the principal cancer sites, age-specific incidence rates, total number of cancer cases, relative frequencies as well as the crude rates and ASR for both males and females. Diagnosis of cancer was based on histopathology in 68.2%; (percentage of microscopic verification (MV) for some cancer sites is shown in Table 3), clinical or radiology in 29.7% and death certificate only (DCO) in 2.1% of the cases. As determined by the calculated ASR, the top five cancers in males (excluding skin cancer) were esophagus (43.4), stomach (27.8), colorectal (10.7), bladder (7.8) and oral cavity (6.3), while in the females they were cancers of esophagus (36.3), breast (15.7), stomach (8.3), colorectal (6.6) and cervix (3.6). In Table 4 we have compared ASR and truncated age standardized rate (TASR) for esophageal and gastric cancer from this study with the previous survey done by Mahboubi et al. about 30 years ago [2].

4. Discussion

According to the last nation-wide annual mortality report (2000), excluding accidents, cancer is the second cause of death in Iran after cardiovascular disease. Fifty percent of all cancer deaths are attributed to GI cancers, and gastric cancer alone accounts for more than 20% of all deaths due to cancer [8]. The striking high incidence rates of EC 30 years ago and an absence of any comprehensive study since then were the major motivations behind this survey. Our results demonstrate that GI cancers account for 57% of all cancers in the

Table 1
Cancer in Golestan Province, Iran, 1996–2000: crude, age-specific, and age-standardized incidence rates in males

Sites for males	%	All ages	0–14	15–24	25–34	35–44	45–54	55–64	≥65	Crude rate	ASR
Oral cavity	4.5	137	0.2	1.1	1.6	4.7	6.5	22.5	38.9	4.1	6.3
Oropharynx	0.5	16	0.0	0.0	0.0	0.5	0.5	2.3	7.0	0.5	0.8
Nasopharynx	0.1	3	0.0	0.0	0.0	0.0	0.0	0.8	1.4	0.1	0.2
Hypopharynx	0.2	5	0.0	0.0	0.0	0.0	1.4	0.8	0.7	0.1	0.3
Esophagus	27.5	843	0.0	0.4	2.5	12.9	72.4	178.8	274.6	25.2	43.4
Stomach	17.7	541	0.1	0.6	1.4	7.1	24.8	118.9	205.8	16.2	27.8
Colon/rectum	8.1	247	0.1	1.1	3.7	12.6	15.4	45.9	43.8	7.4	10.7
Liver	1.1	33	0.0	0.0	0.6	1.1	1.9	8.6	7.6	1.0	1.6
Gallbladder, etc.	0.6	17	0.0	0.0	0.2	0.5	1.4	1.6	5.6	0.5	0.8
Pancreas	0.4	12	0.0	0.0	0.2	0.3	0.9	1.6	2.8	0.4	0.5
Larynx	0.7	20	0.0	0.0	0.0	0.3	2.3	2.3	7.0	0.6	1.0
Bronchus and lung	1.5	46	0.0	0.0	0.2	1.4	2.3	9.3	13.9	1.4	2.2
Bone	1.2	36	0.4	1.0	1.2	0.5	0.5	4.7	2.8	1.1	1.1
Connective tissue	0.3	10	0.0	0.0	0.2	0.5	0.0	3.1	1.4	0.3	0.4
Skin melanoma	0.8	26	0.0	0.4	0.4	0.5	2.8	4.7	4.2	0.8	1.2
Other skin	9.6	295	0.3	0.6	2.5	10.1	26.6	50.5	79.9	8.8	14.3
Prostate	3.5	106	0.0	0.2	0.2	0.0	2.3	10.1	57.7	3.2	5.2
Testis	0.6	18	0.1	0.1	1.6	1.1	0.9	1.6	0.0	0.5	0.6
Other male genital	0.1	4	0.0	0.0	0.0	0.0	0.0	1.6	1.4	0.1	0.2
Bladder	6.2	189	0.3	2.3	2.9	4.7	11.2	24.1	41	5.7	7.8
Kidney, etc.	1.3	40	0.2	0.0	0.2	0.5	3.7	8.6	9.7	1.2	1.9
Nervous system	2.0	60	1.0	0.7	2.3	1.9	2.3	5.4	4.2	1.8	2.0
Thyroid	1.8	56	0.2	0.5	1.2	5.7	4.2	2.3	6.3	1.7	2.1
Hodgkin's disease	0.8	26	0.0	0.0	0.6	1.1	1.9	8.6	7.6	1.0	1.6
Non-Hodgkin's lymphoma	1.3	41	0.4	0.7	0.8	1.1	3.3	3.9	7.0	1.3	1.7
Myeloid leukemia	0.7	21	0.0	0.1	0.4	0.3	0.5	0.8	0.7	0.2	0.3
Other leukemia	0.5	16	0.6	0.6	0.2	0.0	0.5	0.0	1.4	0.5	0.5
Lymphoid leukemia	0.3	10	0.1	0.1	0.2	0.6	0.9	0.8	0.7	0.3	0.4
Others	6.2	189	1.3	2.3	2.9	4.7	11.2	24.1	41.0	5.7	7.8
All sites	100.0	3063	8.8	13.5	28.5	69.5	178.4	502.2	821.7	87.5	134.7

Table 2
Cancer in Golestan Province, Iran, 1996–2000: crude, age-specific, and age-standardized incidence rates in females

For females sites	%	All ages	0–14	15–24	25–34	35–44	45–54	55–64	≥65	Crude rate	ASR
Oral cavity	3.4	70	0.1	0.5	1.0	3.3	4.0	14.7	17.8	2.2	3.5
Oropharynx	0.3	6	0.0	0.0	0.0	0.3	0.5	1.6	1.4	0.2	0.3
Nasopharynx	0.1	2	0.0	0.0	0.0	0.3	0.0	0.9	0.0	0.1	0.1
Hypopharynx	0.2	4	0.0	0.0	0.0	0.0	0.9	0.9	0.8	0.1	0.2
Esophagus	31.0	645	0.2	0.2	2.9	16.6	55.2	180.9	189.0	19.9	36.3
Stomach	7.6	158	0.1	0.4	1.5	3.3	4.9	35.5	60.8	4.9	8.3
Colon and rectum	6.2	129	0.1	0.6	2.5	5.8	8.0	34.6	25.1	4.0	6.6
Liver	0.4	9	0.0	0.0	0.2	0.0	0.9	1.7	3.2	0.3	0.5
Gallbladder, etc.	0.6	13	0.0	0.0	0.2	0.6	1.3	0.9	4.9	0.4	0.7
Pancreas	0.3	6	0.0	0.0	0.0	0.6	0.0	0.0	3.2	0.2	0.3
Larynx	0.1	2	0.0	0.0	0.0	0.0	0.0	0.0	1.6	0.1	0.1
Bronchus and lung	0.6	12	0.0	0.0	0.2	0.6	0.9	2.6	3.2	0.4	0.6
Bone	0.8	16	0.3	0.5	0.8	0.0	0.4	1.7	1.6	0.5	0.6
Connective tissue	0.1	2	0.0	0.0	0.0	0.0	0.0	1.7	0.0	0.1	0.1
Skin melanoma	0.6	13	0.0	0.1	0.2	0.3	2.2	1.7	2.4	0.4	0.6
Other skin	6.3	132	0.2	0.6	1.4	6.6	13.4	22.5	32.4	4.1	6.7
Breast	18.1	377	0.0	1.5	13.6	33.7	44.5	30.3	30.8	11.6	15.7
Cervix	3.9	82	0.0	0.2	3.1	5.8	9.4	11.3	7.3	2.5	3.6
Uterus	2.3	47	0.1	0.2	0.6	2.8	6.2	5.2	8.9	1.4	2.2
Ovary	2.9	60	0.3	0.5	1.5	6.1	4.9	8.7	1.6	1.8	2.5
Other female genital	0.9	18	0.0	0.1	0.2	0.0	0.9	5.2	6.5	0.6	1.0
Bladder	1.4	30	0.0	0.0	0.4	1.4	0.4	6.9	11.4	0.9	1.6
Kidney, etc.	0.7	15	0.2	0.0	0.2	0.0	3.1	1.7	2.4	0.5	0.7
Nervous system	1.1	22	0.6	0.1	0.4	0.8	1.3	3.5	1.6	0.7	0.9
Thyroid	1.9	40	0.2	0.2	1.0	4.4	2.2	2.6	5.7	1.2	1.6
Hodgkin lymphomas	0.7	15	0.1	0.5	0.6	0.6	0.9	2.6	3.2	0.5	0.8
Non-Hodgkin lymphomas	2.0	41	0.4	0.4	1.0	1.1	1.8	5.2	4.1	0.9	1.4
Myeloid leukemia	0.6	12	0.2	0.3	0.2	0.3	0.5	1.7	2.4	0.4	0.5
Lymphoid leukemia	2.1	43	0.1	0.1	0.4	0.6	0.9	2.6	1.6	0.4	0.6
Other leukemia	0.9	18	0.6	0.3	0.2	0.6	0.9	2.6	1.6	0.6	0.7
Others	2.0	41	1.7	0.7	0.6	1.4	2.2	0.0	2.4	1.3	1.3
All sites	100.0	2080	7.0	10.1	37.8	99.9	176.8	400.8	454.3	65.9	104.5

study region and that upper GI tract malignancies contributes to 47.8% of all cancers in Golestan in which esophageal and gastric cancers constitutes 31.2 and 16.6% of all cancers. These incidence rates of EC are strikingly different from those reported 30 years ago; also, rates of colorectal and breast cancers appear to have increased over this time period.

Table 3
Percentage of microscopic verification for some cancer sites

Site	MV (%)	Total
Esophagus	47.7	1488
Stomach	49.6	699
Colon and rectum	95.9	376
Gallbladder	86.7	30
Liver	86.4	42
Bronchus and lung	45.4	58
Breast	97.3	377
Cervix	94.4	82
Uterus	95.2	47
Ovary	96.3	60
Prostate	94.4	106
Bladder	94.7	219
Kidney	85.2	55
Brain, nervous system	65.6	82
Thyroid	97.3	96
Hodgkin's disease	95.1	41
Non-Hodgkin's lymphoma	97.2	82
Leukaemia	87.3	120

Almost all economic indices show that over the past 30 years and following the 1979 revolution, living standards have improved significantly along the entire length of the Caspian Littoral of Iran. A recent study in the rural and urban areas of Gonbad District in a region that about 70% were Turkmen revealed that about 60% of inhabitants were overweight with a body mass index (BMI) greater than 25 and 25% of them were obese (BMI > 30). In 1970, less than 5% of the people in the rural areas had refrigerators; now it has increased to more than 90%, which has resulted in better food storage systems, and decreased consumption of salted and smoked food [9]. Overall improvements in socio-economic status including higher incomes, availability of electricity, access to safe drinking water and natural gas for heating and cooking, telephone communication and transport coverage of 98% in the urban areas and 92% in the rural areas in today's Golestan could be regarded as one of the main reasons of this sharp decrease in the esophageal squamous cell carcinoma (ESCC) incidence rates.

Another major reason that could justify this decline is the fact that in the early 1970s, endoscopy was not available

Table 4
Comparison of esophageal and stomach cancer ASR and TASR (age-group 35–64) between previous and present study in Golestan

	Esophagous				Stomach			
	Male		Female		Male		Female	
	ASR	TASR	ASR	TASR	ASR	TASR	ASR	TASR
Mahboubi[a] 1970	80	165	80	180	NA	31	NA	17
Golestan Surveillance 1996–2000	43	76.8	36	72.7	27.8	42.2	8.3	12.2

NA: not available.
[a] Estimated rate for Gorgan and Gonbad regions in Mahboubi study (present day Golestan province).

and nearly all GI tumors were diagnosed and classified by clinical symptoms or radiological findings. ESCC, esophageal adenocarcinoma (EAC) and gastric cardia adenocarcinoma (GCA) all usually present with dysphagia as the dominant symptom, while patients with gastric noncardia adenocarcinoma (GNCA) usually do not complain of dysphagia. Thus, in the 1970s the first three tumors were probably all grouped and diagnosed as ''EC'', while only GNCA had been diagnosed as ''GC''. According to our recent endoscopic data [10] if we combine the current figures for ESCC, EAC and GCA as ''EC'', the ''EC'',''GC'' ratio is still 5:1, similar to the 1970 figures. Therefore, the difference from cancer registry data obtained 30 years ago is in part due to the differences between survey techniques and the fact that in that registry system, the diagnosis of EC was confirmed histologically in only about 10% of the cases [2], while in our study diagnosis was based on pathologic confirmation in 47.7% of cases (Table 3).

It is likely, therefore, that in the 70s, due to the misclassification of some of the GCs as ECs, the EC had been over-diagnosed resulting in an under-estimation of the true incidence of GC. So, the increased incidence of GC in our survey can be interpreted as an artifact. ESCC was equally distributed between the two sexes, similar to Linxian in China, but completely different from the pattern seen in low-incidence Western Countries, where the incidence of ESCC is several-fold higher in men [11].

The studies that were conducted in the 1970s in the southern border of the Caspian Sea showed that areas mainly inhabited by Turkmen had a much higher incidence rates of EC compared to the areas resided mainly by Persians [1,2]. However, it was not known whether within the high-risk areas the rates were also higher among Turkmen or not. A recent study [10] suggested that the risk of ESCC in Turkmen cannot be several-fold higher than the risk in non-Turkmen and it argues against the existence of strong Turkmen specific genetic components in the etiology of ESCC in eastern Golestan. Only 1% of the ESCC cases were younger than 30 and 4% aged less than 40, another finding that argues against genetic background as a predominant etiological factor. Also a recent genetic polymorphism study failed to show significant variations in the frequencies of genetic polymorphisms of 10 genes known to be associated with increased risk of EC among Turkmen of Iran [12].

There is only one recent study [13] from Golestan published by Saidi et al. in 2000 which reported crude rates for both male and female and ASR for females higher than our study but they inadvertently have miscalculated ASR in males in their report, and this is probably due to underestimation of over 65 age-group population; it is also important to know that they have based their calculation on a total number of 14 EC cases.

Lung cancer ranks seventh in Golestan, which seems to be very low compared to the rates in other parts of the country. Smoking rate in the general population of this area is 19% in men and 0.4% in women [14]. We rechecked our data and discussed this issue with the local oncologist and other physicians. They also had the same impression that lung cancer is relatively uncommon in the province. This strikingly low rate of lung cancer, especially in a population with high rates of ESCC, two cancers which are thought to share some risk factors, need further investigations. One possible component for this low rate could be the fact that during the study period there was no pulmonologist available in the province which may have hampered the diagnosis of lung cancer. During last 3 years that a pulmonologist has started to work in the Golestan's capital city of Gorgan, the number of diagnosed cases of lung cancer has increased about 20% but it still ranks sixth among all cancers according to the data from our ongoing cancer registry in the province. Further studies should be performed looking specifically for the reasons of this low rate of lung cancer in the area.

The increasing ASR for colorectal cancer from 3 to 10 during the same period may also be at least partially due to improving socioeconomic status and subsequent lifestyle changes. Prostate cancer which is a common cancer among males in western countries [15] ranked sixth in Golestan; this may be partly due to the fact that in the rural areas people older than 65 years do not receive a full diagnostic workup when they are sick and a significant number of deaths in older people are recorded as ''due to old age'' in the rural health census.

Golestan, a relatively small newly established province, has a low rate of migration in and out. It has the advantage of having astute health authorities who provide the best cooperation in the ongoing studies. These, together with having comprehensive rural health infrastructures, make it a suitable choice for conducting of population-based studies.

During our survey, the well-trained members of the team had access to all the patient records and were very closely monitored by expert pathologists and epidemiologists of the DDRC's Registry Unit in Tehran. The survey team obtained copies of pathologic, imaging and endoscopic documents in the majority of the cases; and the epidemiologists and pathologists were able to recheck the information, especially to exclude benign or suspicious cases and to reclassify the cancers if necessary. Finding of a linear increase in overall incidence rates by age; and similar to most other parts of the world, higher rates of colorectal and lung cancer in men than in women are also two lines of evidence that strengthen the validity of our results.

One of the shortcomings of our study was its retrospective nature in the setting of suboptimal quality medical records kept in private and, to some extent, in public hospitals and other medical centers. But the data from the first year of a new prospective cancer registry, which has begun since 2002 in East Golestan, shows rates similar to those in the current study (Malih, unpublished data). Also, not using the ICD coding system in some of the medical centers at the time of diagnosis made it impossible to classify all cancer cases from the exact topographic point of view. The alphabetical organization of data we used to eliminate cases with similar names may have resulted in 5–10% of doubles. Therefore, it is likely that we have underestimated some tumors and our results should be regarded as the minimum cancer incidence rates in Golestan. Despite these shortcomings, we did our best to find all new cancer cases, and we think that these data are the most complete and accurate estimate of cancer occurrence that have been reported up to now from this area.

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