

History of Cotemporary Medicine in Iran

History of Cancer in Iran

Mohammad Hossein Azizi MD¹, Moslem Bahadori MD¹, Farzaneh Azizi DVM²

Abstract

The history of human and animal cancers date back to antiquity. The earliest written document on cancer appeared on Egyptian papyrus. For centuries, the theory of “four humors” was the primary hypothesis that explained the cause for cancer. Finally, in the 19th century a new era began with the detection of the cellular origin of cancer; in due course, the nature of this lethal disease was better recognized and led to further achievements in cancer treatment. During the 20th century researchers investigated several risk factors for cancer such as tobacco smoking and environmental chemicals, in addition to the carcinogenic role of certain viruses, occupational association of cancer, its relationship with certain hormones and dietary habits, and the genetic basis of cancer. These investigations resulted in more efficient cancer management. After the advent of radiotherapy and chemotherapy as two complementary therapeutic modalities to surgery, the campaign against cancer has improved. However, cancer remains a major health challenge that accounts for substantial morbidity and mortality worldwide. The present paper briefly reviews the history of cancer in Iran, particularly during the last decades of the 20th century.

Keywords: Cancer, history of medicine, Iran

Cite the article as: Azizi MH, Bahadori M, Azizi F. History of Cancer in Iran. *Arch Iran Med.* 2013; **16(10)**: 613 – 622.

Introduction

The word ‘cancer’ is often used synonymously with carcinoma which is derived from Latin and is defined as ‘crab’.¹

For centuries, physicians have believed that cancer is an abnormal growth resembling a crab that invades and destroys the involved tissues.² Evidence of various diseases, including cancer, has been shown in the ancient world; paleo-oncologic investigations hinted at cancer in animal fossils, ancient human remains and their ancestors.^{3,4} The oldest written document on cancer, the Edwin-Smith papyrus has been traced back to ancient Egypt in 1600 B.C.⁵ Hippocrates (460–375 B.C.) believed in the theory of “four humors” (black bile, yellow bile, phlegm, blood). He presumed that cancer resulted from a humoral imbalance and excessive black bile.⁶ In addition, Hippocrates appeared to have clinically described the first case of breast cancer.⁷ Subsequently, Galen in the 2nd century C.E. explained the development of cancer according to the humoral theory.⁸ Galen’s medical idea of cancer governed medicine for over 15 centuries.⁹

From ancient times, various cancer treatment modalities that included cauterization and administration of herbal drugs and specific preparations have been used, however they were of little benefit.

Global background of cancer management in recent centuries

The first occupational malignant tumor described was scrotal cancer in the 18th century when Percivall Pott (1714–1788), an English surgeon, explained the high risk of scrotal cancer among chimney sweepers in London. These young workers who cleaned

chimneys were continuously exposed to ash and soot.¹⁰ Later several epidemiological studies demonstrated that certain occupational exposures might lead to cancer development in specific body organs. For instance, in 1968, Acheson et al. from England reported that prolonged wood dust exposure increased the risk of nasal carcinoma in woodworkers in the furniture industry.¹¹

In 1863, a German physician named Rudolph Carl Virchow (1821–1902) was the first to describe the cellular origin of cancer. In 1899, Stephen Paget (1855–1926), an English surgeon, proposed the ‘seed and soil theory’ to illustrate the metastatic nature of breast cancer. Subsequently, in 1911 the American pathologist, Dr. Peyton Rous (1879–1970) discovered the role of viruses in avian cancer. In 1914, Theodor Heinrich Boveri (1862–1915), a German biologist described the role of chromosomal mutations in cancer.¹²

Other discoveries indirectly had a positive impact on cancer management and included the following¹³:

- Marie (1867–1934) and Pierre Curie (1859–1906) discovered radium in 1895, which became the basis for application of radiotherapy in cancer patients.
- In 1896, George Beatson (1848–1933), a British physician showed that growth of breast cancer in women could be stopped by a bilateral oophorectomy. His discovery confirmed that cancer cells could be influenced by certain hormonal factors, which led to the idea of endocrine ablation of cancer.
- In 1898, William Bradley Coley (1862–1936), the American pioneer of cancer immunotherapy suggested a treatment modality based on provoking an immune response to a sterilized bacterial extract in cases of lymphoma and sarcoma.
- In the 1940s, for the first time, nitrogen mustard and antifolate were used as chemotherapy agents in the treatment of cancer. However, true success in cancer chemotherapy occurred after World War II,¹⁴ both in humans and in the field of veterinary medicine.¹⁵
- An important cytokine, tumor necrosis factor, was detected in the 1960s and improved the concept of cancer-related inflammation. Then in 1984, for the first time, Aggarwal and co-

Authors’ affiliations: ¹Academy of Medical Sciences of the I.R. of Iran, Tehran, Iran. ²Tehran, Iran.

Corresponding author and reprints: Mohammad-Hossein Azizi MD, Academy of Medical Sciences of the I.R. of Iran, Tehran, Iran. Tel: +98-212-293-98-69, E-mail: azizi@ams.ac.ir

Accepted for publication: 22 May 2013

workers isolated two cytotoxic factors.^{16,17}

However, despite these efforts and according to a report by the World Health Organization (WHO), cancer remains a major cause of death worldwide. In 2008 there were 7.6 million deaths (approximately 13% of all deaths). In addition, approximately 70% of all cancer deaths in 2008 occurred in countries of low and middle-income status. WHO has estimated that cancer mortality continues to increase globally; in 2030, cancer mortality will reach approximately 13.1 million.¹⁸

On occasion of 200th Anniversary of the foundation of the New England Journal of Medicine in 2012, DeVita and Rosenberg wrote a comprehensive paper entitled “Two Hundred Years of Cancer Research” and the authors concluded that “the overview of 200 years of the cancer field provides support for the principle of the value of patience and investment in research”.¹²

History of cancer in Iran

To the best of the authors' knowledge, there is no informative data regarding the occurrence of cancer in ancient Iran. However, according to Hajdu, cancer treatment dates back to 2000 B.C. In ancient times in Sumer (a historical region in southern Mesopotamia), China, India, Egypt, and Persia, cancer was treated by several herbal and mineral perpetrations that included iron, arsenic and mercury.¹⁹

The Persian physicians were familiar with cancer. Ali ibn Sahl-e Rabban Tabari (838–870 C.E.) in his book, “Firdous al-Hekmah” (Paradise of Wisdom) mentioned cancer, as did Ali ibn Abbas Majusi Ahvazi (10th century C.E.) or Haly Abbas in the West, in his book entitled “Tebb Maleki” (Royal Medicine). The latter discussed cancer as “a hard and solid swelling which is rarely treatable by medications and should be removed by surgical knife.” Ahvazi has mentioned that cancer is more commonly observed in a woman's uterus and breasts. He has also suggested complete resection of breast cancer and pointed out that incomplete resection may led to abscess formation, ulceration and bleeding. Ahvazi also recommended antimony as treatment for cancer.²⁰ Razi (865–925 C.E.) or Rhazes wrote about cancer and its treatment in his book, “al-Hawi”.²¹ Ibn-Sina or Avicenna (980–1037 C.E.) in his “Canon of Medicine” mentioned various types of cancers that included cancers of the nose, eyes, tongue, uterus and liver. He believed that cancer was more common in the autumn and resulted from excessive humors.²² It has been said that Avicenna was the first physician who referred to esophageal cancer.²³ Ismail Jorjani (1040–1136 C.E.), in “Zakhireh-ye Kharazmshahi” (Treasure of Kharazm Shah), discussed cancer²⁴ and also described the symptoms of esophageal cancer.²³

Historically, various cancer treatments were popular in Iran. The four Persian medical books, “al-Havi”, “Qanun fi-Tibb”, “Makhzan-o-al-advieh” and “Ekhtiyarat-e Badi'i” (written in 1368 C.E.) mentioned 201 herbal medicines, 47 drugs of animal origin, and 28 mineral medications to treat cancer and cancerous-like lesions.²⁵

Academic publications on cancer in Iran during the 19th and 20th centuries

After the establishment of the first modern higher educational center, the Dar al-Fonun School in 1851, modern medical concepts were gradually propagated. In addition several books were

translated from European resources and published in Iran.²⁶ Dr. Louis John Schlimmer (1819–1881); a medical teacher of the Dar al-Fonun School wrote several medical books that included concepts of pathology in addition to a Persian-French medical dictionary, “Terminologie Medico-Pharmaceutique et Anthropologique Francaise-Persane”. The latter was published in Tehran in 1874.²⁷ He described the word cancer in his dictionary (Figure 1).

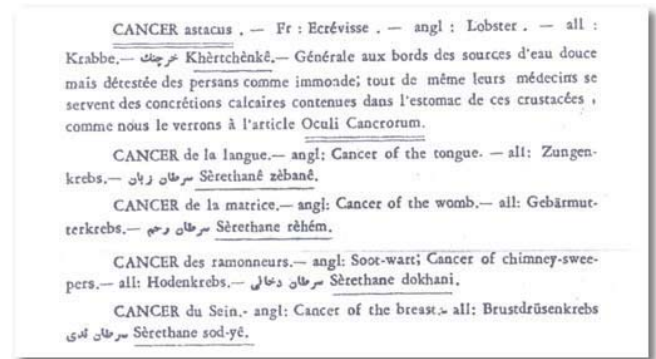


Figure 1. The word “cancer” in Schlimmer's medical dictionary, 1874.

After the establishment of Tehran University School of Medicine in 1934 academic investigations on various medical fields and cancer began. Dr. Mostafa Habibi-Golpayegani (1904–1948) was a pioneer Professor of modern Pathology in Iran who published a paper on the diagnosis of breast cancer by the transillumination technique in 1943 (Figure 2). In subsequent years, he studied other malignancies such as Hodgkin's disease, leukemia, rhabdomyoma and sweat gland carcinoma.²⁸

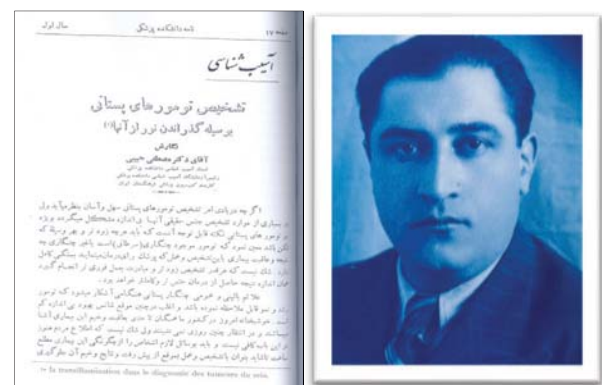


Figure 2. (Left) The first page of Dr. Habibi-Golpayegani's paper on the diagnosis of breast cancer by the transillumination technique, published in 1943 in “Nameh-ye Mahaneh-ye Daneshkadeh-ye Pezeshki” (the Monthly Letter of the School of Medicine). (Right) Dr. Habibi-Golpayegani.

Professor Charles Oberling (1895–1960), the renowned French pathologist who was appointed as Dean of Tehran University School of Medicine in 1939 published a book entitled “The Riddle of Cancer” in 1942, which was translated into English in 1952. In his book he described the possible role of viruses in the development of certain human cancers, which was initially proposed by Amédée Borrel in France (1867–1936) in 1903.^{29–31}

Later, Dr. Kamal Armin (1914–1995), Professor of Pathology at the Tehran University School of Medicine published several pa-

pers on cancer. In 1949 he published a paper on gastric sarcoma. In addition he wrote a two volume book entitled “Sartan Shenasi” (Recognition of Cancer) which was published by Tehran University in 1955 and 1958 (Figure 3).



Figure 3. Right) Dr. Kamal Armin. Middle. Dr. Armin wrote several papers on cancer, which included a case report of gastric sarcoma published in 1949 in “Nameh-ye Mahaneh-ye Daneshkadeh-ye Pezeshki” (The Monthly Letter of the School of Medicine). **Left)** Image of the book, “Sartan Shenasi” (Recognition of Cancer) that was authored by Dr. Armin. This book was published in two volumes by Tehran University in 1955 and 1958.

Dr. Hossein Rahmatin (b. 1912), Professor of Pathology at Tehran University School of Medicine translated the “Riddle of Cancer” that was authored by Professor Charles Oberling into Persian. It was published in 1948 under the name, “Moamay-e Saratan”.³² Dr. Rahmatin also published a paper on leukemia in 1949 (Figure 4).



Figure 4. A paper written on childhood leukemia by Dr. H. Rahmatin published in “Nameh-ye Mahaneh-ye Daneshkadeh-ye Pezeshki” (The Monthly Letter of the School of Medicine), 1949.

During that time, other physicians wrote their observations of cancer in Iran. For example, Dr. Jahanshah Saleh (1904–1996), a graduate of obstetrics and gynecology from Columbia University and member of the faculty of Tehran University School of Medicine published a book in Persian entitled “My Observations on Cancer in Iran and its Treatment by Radium”.³³ In addition, Dr. Mohammad Gharib (1909–1975), Professor of Pediatrics wrote a Persian paper on childhood leukemia in 1949.



Figure 5. A paper published on childhood leukemia by Dr. Mohammad Gharib in 1949, published in “Nameh-ye Mahaneh-ye Daneshkadeh-ye Pezeshki” (The Monthly Letter of the School of Medicine).

During the 1960s and 70s, numerous scientific papers on cancer, mostly in French and English, were reported by Iranian investigators. Dr. Rahmatin wrote a paper on programs and implications of the campaign against cancer in Iran that was published in 1965.³⁴ Dr. Abdulla Habibi, a pathologist at Tehran University School of Medicine and pioneer in cancer data reporting in Iran, published several papers on cancer, including: ‘Cancer in Iran: Statistical Data for the Most Frequent Forms’ (1962); ‘Cancer in Iran: A Survey of the Most Common Cases’ (1965); ‘Survey on the Most Common Cancers in Iran’ (1970); ‘Cancer in Iran, Statistical Review on 28000 Cases’ (1970).^{35–39}

In addition, specific cancers were slowly evaluated for which the results have been reported. In 1958, a case of childhood thyroid cancer was published by K. Armin, M. Sadgadi, and M. Bahadori; in 1960, a paper entitled ‘A Study of Carcinoma of the Esophagus in Iran’ was published by S. A. Sarkissian, in 1964 M. Jahromi, D. Azizi, and M. Bahadori published an article on testicular malignancy in Iran, and in 1965 another study entitled ‘Thyroid Cancer in Iran’ was published by R. Boulvin and M. Chahinfar.^{40,41}

Investigators from other Iranian medical schools, in addition to the Tehran University School of Medicine, researched various aspects of cancers. In Isfahan Dr. Parviz Dabiri (1921–2012), Professor of Pathology, examined malignant diseases such as lymphoma, bladder, breast and esophageal carcinomas. Dr. Dabiri wrote, “Pathology of Tumors” (in 40 volumes), of which six volumes that included pathology of tumors of the lungs, prostate, bladder, thyroid, kidneys, bones and joints have been published.⁴²

During the 1970s several papers on cancer were published by physicians at the Shiraz University School of Medical Sciences. These papers included ‘Primary Lymphoma of the Upper Small Intestine’ (K. Nasr, P. Haghighi, K. Bakhshandeh, M. Haghsheenas, 1970); ‘Gastrointestinal Cancer in Iran’ (P. Haghighi, K. Nasr, 1971); ‘Cancer in Southern Iran’ (P. Haghighi, et al., 1971); ‘Intestinal Lymphoma and Sprue’ (W. Dutz, S. Asvadi, S. Sadri, E. Kohout, 1971); ‘Cancer Survey in Southern Iran with Special Reference to Gastrointestinal Neoplasms’ (A. A. Barekat, F. Saidi, W. Dutz, 1971); ‘Clubbing and Osteoarthropathy Associated with Primary Upper Small Intestinal Lymphoma’; (K. Bakhshandeh, K. Nasr, P. Haghighi, M. Haghsheenas, 1971); ‘Leukemia in Southern

Iran' (E. A. Mahallatee, 1972); 'Primary Upper Small Intestinal Lymphoma' (P. Haghighi, K. Nasr, 1973); 'Childhood Cancer in Southern Iran' (P. Haghighi, et al., 1974); 'Primary Upper Small-intestinal Lymphoma, a Report of 40 Cases from Iran' (K. Nasr, et al., 1976); 'Colorectal Polyps and Carcinoma in Southern Iran' (P. Haghighi, et al., 1977); 'Childhood Lymphoma in Southern Iran' (P. Haghighi, 1979); and 'Roentgenologic Observations in Small Bowel Lymphoma' (K. Vessal, W. Dutz, E. Kohout, 1980).⁴³⁻⁵⁵

Cancer Institute of Iran

The late Dr. Mostafa Habibi-Golpayegani was the first physician who suggested the foundation of a cancer institute in Iran in 1946. Then, three years later in 1949, a contract was signed between the authorities of the former Red Lion and Sun Society (currently the Red Crescent Society) and Tehran University to establish a hospital for cancer patients (Figure 6).⁵⁶



Figure 6. News of the contract to establish a hospital for cancer patients in "Nameh-ye Mahaneh-ye Daneshkadeh-ye Pezeshki" (The Monthly Letter of the School of Medicine), 1949.

Accordingly, the hospital for cancer patients was inaugurated in 1955. It was constructed in the eastern part of the Hezar Takht-e Khabī Hospital and the first cobalt unit in Iran was used to treat patients. The hospital was supervised by the former Red Lion and Sun Society (currently the Red Crescent Society). In 1957, the hospital's departments that included the Surgery, Radiology, Laboratory, and Pathology departments as well as the Outpatient Clinic were established. Then, in 1958, a project to establish a 'Cancer Research Institute' was approved by the officials. In 1966, the Red Lion and Sun Society transferred the supervision of the hospital to the Tehran University School of Medicine; in 1970, the Cancer Research Institute and hospital were integrated, which resulted in the establishment of the Cancer Institute of Iran (Figure 7).⁵⁷ Since that time, this institute has served as an influential research and educational center in Iran.



Figure 7. Cancer Institute of Iran. **Source:** <http://crc.tums.ac.ir> (Accessed 20.2.2013).

Three physicians had a prominent role in the establishment and development of the Cancer Institute of Iran, Dr. Abbas Maleki (Professor of Radiotherapy, Figure 8), Dr. Hossein Rahmatin (Professor of Pathology, Figure 8- A) and Dr. Hassan Hashemian (Professor of Surgery, Figure 8-B). The first Director of the Cancer Institute was Dr. Rahmatin, but in 1970 Dr. Abdulla Habibi (Professor of Pathology, Figure 9-C) became its Director. Following Dr. Habibi, Dr. Yahya Diba became the Cancer Institute's director.



Figure 8. Dr. Abbas Maleki.

Dr. Hassan Hashemian (born in Kashan) was a trained surgeon from England who returned to Iran in 1956. He was a pioneer surgeon who worked at the hospital for cancer patients at the Cancer Institute. He trained several surgeons who were experts in cancer surgery.⁵⁸ Dr. Hashemian and his co-workers published a paper on



Figure 9. A) Dr. Hossein Rahmatin. **B)** Dr. Hassan Hashemian. **C)** Dr. Abdulla Habibi.

esophageal cancer in Iran in 1965.⁵⁹

In 1961, when the Pathology Laboratory of the Cancer Institute was incorporated into the Department of Pathology of Tehran University School of Medicine, Dr. Armin was appointed as Chair. Dr. Seyed Abdul Mahmood Zia Shamsa (1922–1999) (Figure 10), Professor of Pathology at Tehran Medical School worked at the Pathology Department of the Cancer Institute for four decades. He was a founding member of the ‘Iranian Society for Helping Cancer Victims’.⁶⁰



Figure 10. Dr. Seyed Abdul Mahmood Zia Shamsa

Other pioneer radiotherapists and oncologists

Dr. Seyed Hossein Mortazavi, Professor of Clinical Oncology at the former National University (now Shahid Beheshti University) and Director of the Radiotherapy Department between 1972 and 2002 established a Department of Radiotherapy at Jorjani Hospital, Tehran in 1972.⁶¹ At that time, Dr. Rooshan and Dr. Shah Mohammadi, both at the Ministry of Health, were involved in the campaign against cancer. Dr. Kamal ad-Din Dehshiri (b.1928), a Professor of Radiotherapy at Tehran University School of Medicine established the radiotherapy specialty at this university.⁶²

After the establishment of a Radiotherapy Department at Tehran University School of Medicine and the former National University, a Radiotherapy Department was also established at Shiraz University School of Medical Sciences. In Southern Iran, the first cobalt-60 unit began treating patients in 1961 at Nemazi Hospital in Shiraz. It was initially supervised by two radiologists, Dr. Manouchehr Zarrabi and Dr. Khajavi where a few cancer patients were treated each day. Then, between 1971 and 1974, Dr. S. H. Mortazavi treated the cancer patients with the cobalt-60. Afterwards, in 1974, Dr. Heshmatulla Toosi, a graduate of radiotherapy from Switzerland was employed as full-time faculty where he treated approximately 20 cancer patients each day.⁶³

Other activities

The ‘National Association against Cancer’ was founded in 1967. Dr. Rahmatin was appointed its president. In 1976, to promote public awareness on cancer, a stamp was issued on the occasion of Cancer Week.⁶⁴ Its motto was ‘on time diagnosis and proper treatment, save lives’, a fact that is still true after more than three decades (Figure 11).⁶⁵



Figure 11. A stamp issued on the occasion of cancer week, 1976.⁶⁴

Cancer registry

The history of a formal cancer registry, worldwide, dates to 1927 when it was initiated in Hamburg and subsequently continued in New York (1940), Connecticut (1941), and Denmark (1942).⁶⁶

As previously mentioned, cancer data reporting in Iran began in 1960 by Dr. Abdulla Habibi, a pathologist employed at the Cancer Institute of Iran. In due course, the cancer data of the Caspian Littoral (1969) and Fars Province (1976) were reported.⁶⁷ An abnormally high prevalence of esophageal cancer was noticed in the Caspian Littoral of Iran.⁶⁸

In 1985 cancer registration at the national level was approved by the Parliament. However, it practically began from 2000 when the authorities of the Ministry of Health invited several pathologists from the medical universities of Tehran, Shahid Beheshti, Shiraz, Isfahan, Mashhad and Tabriz. Afterwards, the national cancer rates were recorded and the National Cancer Registration Report was published annually by the Cancer Control Office of the Ministry of Health and Medical Education (Figure 12).

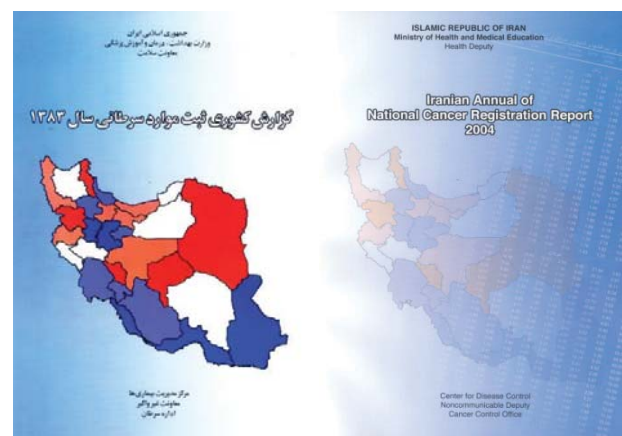


Figure 12. Annual Iranian National Cancer Registration Report, 2004.

The Society to Support Children Suffering from Cancer (MAHAK)

It was founded in Tehran as non-governmental charity medical organization in 1991 to support children suffering from cancer and in the past two decades has been successful in fighting

against childhood cancers and managed around 18,000 patients.⁶⁹ Dr. Parvaneh Vossough (born in Tafresh in 1936, passed away in Tehran in 2013), who continued her medical training in USA after graduating from Tehran School of Medicine and became the Professor of Pediatric Hematology and Oncology (Figure 13) at Iran University of Medical Sciences and was the Head of the Board of Trustees of the Society to Support Children Suffering from Cancer (MAHAK). She was a pioneer physician who saved the lives of numerous children and devoted over 50 years of her life to management of children with cancer. She passed away in Tehran at the age 78.⁷⁰ Dr. Vossough was a great researcher and published more than 100 informative papers on childhood cancers in Iran.



P. Vossough, MD

Figure 13. Professor Parvaneh Vossough and her signature.⁷⁰

Academic cancer research centers

In recent year several academic cancer research centers are founded in Iran. These centers are as following:

- Cancer Research Center affiliated with Tehran University of Medical Sciences; a sub division of the Cancer Institute of Iran has been conducted more than 200 research project on cancer and reported over 260 papers so far. It also publishes a quarterly journal entitled "Basic and Clinical Cancer Research."⁷¹
- Cancer Research Center affiliated with Shahid Beheshti University of Medical Sciences, founded in 2006.⁷²
- Shiraz Institute for Cancer Research established in June 1998, affiliated with Shiraz Medical School and consisted of six research groups and two out-patient clinics on breast and prostate cancers.⁷³
- Cancer Research Center, Ahvaz, Jundishapur University of Medical Sciences.⁷⁴
- Cancer Research Center, Mashhad University of Medical Sciences.⁷⁵

The Iranian Cancer Research Network affiliated with the Ministry of Health and Medical Education conducts researches on cancer and its main mission is controlling cancer in Iran.⁷⁶

Foundation of new cancer hospitals

In recent years, new cancer hospitals are established including Omid Hospital in Mashhad, Amir Oncology Hospital in Shiraz and Milad Hospital in Isfahan.

Omid Hospital in Mashhad, established prior to the Islamic Revolution of 1979 by pious charities, then in 1979 its supervision was transferred to the Ministry of Health and it is currently

affiliated with the Mashhad University of Medical Sciences. It has chemotherapy, radiotherapy and surgery departments and offers monthly proper out-patient health care to around 8000 adult cancer patients (Figure 15).⁷⁷



Figure 15. Omid Hospital in Mashhad, Khorasan Province.⁷⁶

Amir Oncology Hospital in Shiraz (Figure 16) is founded by an endowment of 150 billion Rials by a generous lady, Mrs. Zahra Saadat (Figure 17).⁷⁸⁻⁸⁰ The hospital is supervised by Shiraz University of Medical Sciences.⁸¹



Figure 16. Amir Oncology Hospital, Shiraz.⁸⁰



Figure 17. Mrs. Zahra Saadat, the founder of Amir Oncology Hospital, Shiraz.⁷⁹

History of cancer research; the example of scientific investigations on esophageal cancer epidemiology in Northeastern Iran

One of the most important aspects of cancer in Iran is the reported very high incidence of esophageal cancer in its Northeastern

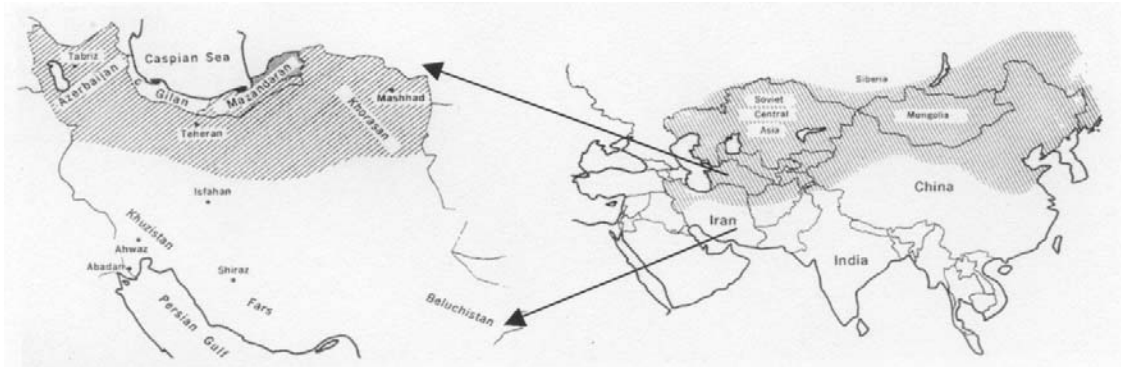


Figure 18. Position of Iran in the Central Asian Esophageal Cancer Belt.

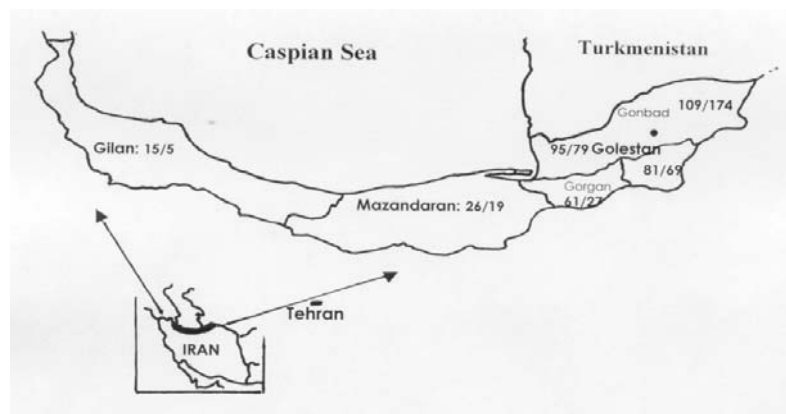


Figure 19. Age-standardized incidence rates /100,000 of esophageal cancer in men/women according to the data of the Caspian Littoral Cancer Registry, 1970.

regions. In Gonbad district, the reported rate of esophageal cancer was shown to be one of the highest rate of any cancer reported anywhere in the world. Following is the history of this important epidemiologic finding and what have been done up to now.

Early epidemiological studies

The esophageal cancer geographic distribution in Iran has wide variations within relatively small areas. Despite limited accurate data based on cancer registry information, very high rates of esophageal cancer (over 50/100,000) have been reported for both genders from Northern Iran, the provinces of North-Central China⁸² in certain areas of Kazakhstan and among native Siberians.⁸³ The aforementioned populations are part of a "Central Asian Esophageal Cancer Belt" (Figure 18). It is unclear whether these extremely high rates are due to a common risk factor, nevertheless, one possibility is that very high rates of esophageal cancer are associated with several factors including: a diet severely deficient in fruits and vegetables, a mucosal injury due to consumption of very hot beverages, and intense carcinogen exposure from lifestyle factors such as opium consumption. This hypothesis is however untested.

The earliest reports on high incidence of esophageal cancer in the northern Iran date back to the mid-1960s and early 1970s.^{47,35,38,44} These reports revealed the frequency of the disease in many young patients, a high proportion of squamous cell carcinomas and a slight female predominance. In due course, in order to investigate this finding in more detail, a population-based cancer registry was established in 1969, as a joint effort between

Tehran University and the International Agency for Research on Cancer (IARC), in the city of Babol in Mazandaran province, on the eastern side of the Caspian Littoral. This was subsequently extended to the western province of Gilan and the neighboring city of Ardabil in the southwest of the Caspian Sea in 1970 (Figure 19). Initial results from this cancer registry emphasized the very high incidence of esophageal cancer in the eastern portion of Mazandaran province, close to Turkmenistan (Gonbad and Gorgan districts, now Golestan province), particularly in the semi-desert plain settled mainly by people of Turkmen ethnicity, with incidence rates of 109/100,000 among men and 174/100,000 among women.⁶⁸ Sharp changes in the incidence of esophageal cancer were evident between regions only a few hundred kilometers apart. The incidence dropped to 15/100,000 for men and 5.5/100,000 for women in Gilan, 300 miles to the west.

Detailed dietary, social and lifestyle habits of 3,800 people in 38 randomly selected villages were studied.^{84,85} This was supplemented by an extensive 5-day study of 6 randomly selected households in each of the 38 villages. Food and water samples were also collected to determine the level of selected carcinogens in food items and of nitrate and nitrite in the water. The factors which appeared to be prevalent in villages in the high-risk region included:

- Very low intake of fresh fruits and vegetables
- High frequency of opium usage, in particular in the form of 'sukhteh'
- Hot tea consumption
- Chewing of 'nass' (confined to males)
- Preservation of meat by salting and sun-drying

- Consumption of bread as the staple food
- Consumption of sheep's milk and yogurt
- Use of sesame oil for cooking
- Manufacture of carpets (confined to women)

'Sukhteh' is prepared by boiling and filtering opium and it is usually ingested rather than smoked, resulting in significant exposure to carcinogenic pyrolysis products including polycyclic aromatic hydrocarbons (PAHs) of the digestive tract. Opium is normally smoked in Iran, although preparing and ingesting sukhteh is a more efficient method of opium consumption than smoking it, and given the relative poverty of the Turkmen people explains why it is traditionally prevalent in this region. 'Nass' is a tobacco product which is traditionally mixed with lime and ash, and is chewed.

These potential risk factors were subsequently tested in a case-control study involving 344 cases of esophageal cancer, recruited between 1975 and 1976, and 688 randomly selected controls matched on age, sex and place of residence.⁸⁶ No association was identified between consumption of sheep's milk or yogurt, use of sesame oil, chewing of nass, making of carpets, and preservation by salting and sun-drying. Strong associations were however found between esophageal cancer and self-reported low intake of various fresh fruits and vegetables as well as self-reported consumption of hot tea.

As opium is commonly used as a pain-relieving medication among the Turkmen population, and is likely to be especially common among cancer patients, it was not possible to investigate the carcinogenic effect of opium consumption in this case-control study. Furthermore, questioning on past use is of uncertain validity, as reporting of past use may be differential between cases and controls. Opium use has however been reported to correlate strongly within households,⁸⁷ and a second case-control study was designed to specifically test the hypothesis of opium use, by comparing members of households living with a case of esophageal cancer to members of control households in the same village.⁸⁸ The study initially planned to include 200 case-control households. However, after 41 household pairs had been recruited, civil disturbances related to Iran's political events in 1979 led to the study being halted. Based on this limited number of samples, recent opium use, as measured in urine samples, was more common in members of case households compared to control households, although the confidence interval was wide (odds ratio 2.1, 95% confidence interval 0.7-6.5).

Recent epidemiological studies

In order to verify the previously recorded high incidence rates of esophageal cancer rates from the 1970s, a balloon cytology screening was carried out in 1996 among 4,192 adults from three villages in the high-risk Turkmen area-Iran⁸⁹. Esophagoscopy was conducted on 183 patients with abnormal cytological findings, resulting in the finding of 3 squamous cell cancers corresponding to an estimated prevalence of between 48 and 72/100,000. During a 12-month active surveillance of all 4192 adults, 14 new cases were identified with clinically advanced esophageal squamous cell carcinoma, resulting in an estimated age-standardized incidence rate of 144/100,000 for men and 49/100,000 among women. Although based on a small sample size, this study confirmed that the very high incidence of esophageal cancer reported in the 1970s was still present. A possible role of human papillomavirus

(HPV) in explaining the higher rates of esophageal carcinoma is also apparent from a recent study conducted in the Turkmen Plain. Among 85 cases, HPV-16 was detected in 54.7% of esophageal squamous cell tumor samples, while HPV-18 was found in 4.8%, HPV-6 in 14.3%, HPV-66 in 7.1% and HPV-52 in 4.8%; 14.3% of samples were positive for more than one type of HPV.⁹⁰

In 2000, the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences continued to build on this effort by establishing Atrak Clinic, a referral clinic for upper gastrointestinal tract diseases in Gonbad, one of the major cities of Golestan Province, and began collaborations with several international cancer research groups, including the U.S. National Cancer Institute, IARC, Karolinska Institute, the University of Toronto, and Cambridge University. These collaborations are currently involved in a wide range of studies, including cancer surveillance and cancer registry program, a case-control study, a cohort study, and a number of genetic and molecular epidemiologic studies. Thus far several reports have been published based on pilot studies for these case-control, cohort, and cancer surveillance projects, and more recently few full-scale studies have been completed. In addition to DDRC, several other Iranian groups have recently conducted smaller etiologic studies.

The first important finding of DDRC during reexamined incidence rates was the marked decline in the rate of esophageal cancer in Golestan Province in Northern Iran. These studies have shown that the male to female ratio is still close to one and the majority of cancers are still of the squamous type. Rates are still high, but they seem to have declined considerably in the past 30 years, perhaps to half of what they were in the past. Lower esophageal cancer rates may partly be due to misclassification of gastric cardia cancer cases as lower esophageal cancer cases in the older studies. In the 1960s and early 1970s, the majority of the cases were diagnosed by history and physical examination and/or radiologic findings. Since both cardia cancers and esophageal cancers cause dysphagia, and the radiologic features can be similar, it is possible that some cardia cancers were misclassified as esophageal cancers. Consistent with this possibility, gastric cancer rates have slightly increased in the most recent studies. Nevertheless, there is little doubt that there has been a significant real reduction in esophageal cancer rates, which probably reflects the highly improved socioeconomic status in Gonbad City and the rest of Golestan Province. Of interest, in Cixian County, a high-risk area in China, esophageal cancer rates also decreased at a much lower pace from 1974 to 1996 which may indicate a lower rate of socioeconomic change in this area during the study period.⁹¹

Acknowledgments

The authors wish to thank Professor Reza Malekzadeh, Tehran University of Medical Sciences for reviewing the manuscript and providing valuable data regarding history of esophageal cancer research in Iran.

References

1. *Dorland's Illustrated Medical Dictionary*. 29th ed. Philadelphia, USA: W. B. Saunders Company; 2000: 273.
2. *The History of Cancer*, American Cancer Society; 2012. Available from: URL: <http://www.cancer.org/the-history-of-cancer-pdf> (Accessed 21.2.2013)
3. Vuorinen HS. Diseases in the ancient world. *Hippokrates (Helsinki)*.

- 1997; 79 – 97.
4. Halperin EC. Paleo-oncology: the role of ancient remains in the study of cancer. *Perspect Biol Med.* 2004; **47**: 1 – 14.
 5. Papavramidou N, Papavramidis T, Demetriou T. Ancient Greek and Greco-Roman Methods in Modern Surgical Treatment of Cancer. *Ann Surg Oncol.* 2010; **17**: 665 – 667.
 6. Hajdu SI. Greco-Roman thought about cancer. 2004; 2048 – 2051. Available from: <http://www.interscience.wiley.com> (Accessed 12.2.2013)
 7. Retief FB, Ciller SL. Breast cancer in antiquity. *S Afr Med J.* 2011; **101**: 513 – 515.
 8. Olszewski MM. Concepts of cancer from antiquity to the nineteenth century. *UTMJ.* 2010; **87**: 181 – 186.
 9. Androtsos KM, Diamantis A. Cancer and Roman Medicine. *J Buon.* 2009; **14**: 537 – 540.
 10. Waldron AH. A brief history of scrotal cancer. *Br J Ind Med.* 1983; **40**: 390 – 401.
 11. Acheson ED, Cowdell RH, Hadfield E, Macbeth RG. Nasal cancer in woodworkers in the furniture industry. *BMJ.* 1968; **2**: 587–596.
 12. De Vita VTT, Rosenberg SA. Two Hundred Years of Cancer Research. *NEJM.* 2012; **23**: 2207 – 2214.
 13. Baguley BC. A brief history of cancer chemotherapy. In: Baguley BC, Kerr DJ. *In Anticancer Drug Development.* Amsterdam: Elsevier Inc; 2002: 1–10.
 14. Bruce A. Chabner and Thomas G. Roberts Jr. Chemotherapy and the war on cancer. *Nat Rev Cancer.* 2005; **5**: 65–72.
 15. Kardinal CG. Cancer chemotherapy, historical aspects and future considerations. *Postgrad Med.* 1985; **1**: 165 – 174.
 16. Chu WM. Tumor necrosis factor. *Cancer Lett.* 2013; **328**: 222 – 225.
 17. Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its super family: 25 years later, a golden journey. *Blood.* 2012; **119**: 651 – 665.
 18. Cancer, Fact sheet No. 297, WHO, Feb. 2012. Available from: URL: <http://www.who.int/mediacentre/factsheets/fs297/en/> (Accessed 12.2.2013)
 19. Hajdu SI. 2000 years of chemotherapy of tumors. *Cancer.* 2005; **103**: 1097 – 1102.
 20. Najmabadi M. *Tarikh Tebb dar Iran Pas Az Islam (History of Medicine in Iran after Islam)* [in Persian]. Tehran: Tehran University Press; 1979:
 21. Armin. *Saratan Shensi* [in Persian]. Vol. 1. Tehran: Tehran University Press; 1955: 22.
 22. Avicenna. *Canon of Medicine* [in Persian]. Vol. 4. Translated by A. Sharafkandi (Hajar). Tehran: Soroush Press; 1979: 464, 474, 475.
 23. Saidi F. The Historical basis for the esophageal cancer belt of south-central Asia. *Arch Iran Med.* 1999; **2**: 26 – 27.
 24. Browne EG. *Arabian Medicine Tariikh-e Tebb Eslami.* Translated into Persian by M. Rajab-Nia. 6th ed. Tehran: Entesharat-e Elmi Farhangi; 2005: 150.
 25. Motavalizadeh Ardakani A, Hashemi M, Safakish M, Alem-Bagheri A, Baradaran Shokoochi SH, Mosaddegh M. Medical treatment of cancer in traditional Iranian medicine. *J Islamic Iran Traditional Med.* 2012; **1**: 3 – 18.
 26. Adamiyat F. *Amir Kabir and Iran.* 5th ed. Tehran: Kharazmi Publication; 1978: 335, 362.
 27. Schlimmer JL. *Terminologie Medico-Pharmaceutique et Anthropologique Francaise-Persane.* Preface by Afshar I. 2nd ed. Tehran: Tehran University Press; 1970: 102.
 28. Azizi MH, Moslem M. In commemoration of Dr. Mostafa Habibi-Golpayegani (1904 – 1948): pioneer of modern pathology in Iran. *Arch Iran Med.* 2006; **9**: 438 – 441.
 29. Azizi MH. In the memory of the late Professor Charles Oberling, the first dean of faculty of medicine in Tehran. *Arch Iran Med.* 2005; **8**: 336 – 338.
 30. Haguenu F. Charles Oberling, a herald of modern oncology. *Int J Surg Pathol.* 2003; **11**: 109 – 115.
 31. de Harven E. Viral etiology of human cancer, a historical perspective. *Haematologica.* 1999; **84**: 385 – 389.
 32. Bahadori M. A historical review of the development of pathology in Iran. *Arch Iran Med.* 2004; **7**: 213.
 33. *A Guide to the Schools of Medicine, Pharmacy, Dentistry, Hospitals and Affiliated Schools of University of Tehran* [in Persian]. Tehran: Tehran University Press; 1951: 38.
 34. Rahmatian H. The anti-cancer campaign in Iran; implications and projects. *Rev Med Moyen Orient.* 1965; **22**: 40 – 46.
 35. Habibi A. Cancer in Iran. Statistical data for the most frequent forms. *Rev Med Moyen Orient.* 1962; **19**: 302 – 308.
 36. Habibi A. Cancer in Iran. A Survey of the most common cases. *J Natl Cancer Inst.* 1965; **34**: 553 – 569
 37. Habibi A. Survey on the most common cancers in Iran. *Bull Cancer.* 1970; **57**: 133 – 150.
 38. Habibi A. Cancer in Iran. Statistical review on 28,000 cases. *Pathol Microbiol (Basel).* 1970; **35**: 181 – 183.
 39. Habibi A. Cancer in Iran. Malignant tumors of the female genitalia. *Int Surg.* 1971; **56**: 13 – 17.
 40. Boulvin R, Chahinfar M. Thyroid cancer in Iran. *Rev Med Moyen Orient.* 1965; **22**: 280 – 288.
 41. Sarkissian S. A study of carcinoma of oesophagus in Iran. *Acta Med Iran.* 1960; **3**: 10 – 13.
 42. Azizi MH, Bahadori M. The life and career of Professor Parviz Dabiri (1921–2012). *Arch Iran Med.* 2012; **10**: 657 – 658.
 43. Nasr K, Haghghi P, Bakhshandeh K, Haghshenas M. Primary lymphoma of the upper small intestine. *Gut.* 1970; **11**: 673 – 678.
 44. Haghghi P, Nasr K. Gastrointestinal cancer in Iran. *J Chronic Dis.* 1971; **24**: 625 – 633.
 45. Haghghi P, Nabizadeh I, Asvadi S, Mohallatee EA. Cancer in southern Iran. *Cancer.* 1971; **27**: 965 – 977.
 46. Dutz W, Asvadi S, Sadri S, Kohout E. Intestinal lymphoma and sprue: a systematic approach. *Gut.* 1971; **12**: 804 – 810.
 47. Barekat AA, Saidi F, Dutz W. Cancer survey in south Iran with special reference to gastrointestinal neoplasms. *Int J Cancer.* 1971; **7**: 353 – 363.
 48. Bakhshandeh K, Nasr K, Haghghi P, Haghshenas M. Clubbing and osteoarthropathy associated with primary upper small intestinal lymphoma. *J Trop Med Hyg.* 1971; **74**: 117 – 119.
 49. Mohallatee EA. Leukemia in southern Iran. *Indian J Med Sci.* 1972; **26**: 313 – 314.
 50. Haghghi P, Nasr K. Primary upper small intestinal lymphoma (so-called Mediterranean lymphoma). *Pathol Annu.* 1973; **8**: 231 – 255.
 51. Haghghi P, Mohallatee EA, Nasr K, Dezhbakhsh F, Salmasi S, Daneshbod K. Childhood cancer in southern Iran. *Cancer.* 1974; **34**: 1842 – 1848.
 52. Nasr K, Haghghi P, Bakhshandeh K, Abadi P, Lahimgarzadeh A. Primary upper small-intestinal lymphoma. A report of 40 cases from Iran. *Am J Dig Dis.* 1976; **21**: 313 – 323.
 53. Haghghi P, Nasr K, Mohallatee EA, Ghassemi H, Sadri S, Nabizadeh I, et al. Colorectal polyps and carcinoma in Southern Iran. *Cancer.* 1977; **39**: 274 – 278.
 54. Haghghi P, Mostafavi N, Dezhbakhsh F, Ariazad M, Ghassemi H, Cook A, et al. Childhood lymphoma in southern Iran. *Cancer.* 1979; **44**: 254 – 257.
 55. Vessal K, Dutz W, Kohout E. Roentgenologic observations in small bowel lymphoma [in German]. *Rofo.* 1980; **132**: 243 – 248.
 56. Nameh-ye Mahaneh-ye Daneshkadeh-ye Pezeshki (the Monthly Letter of School of Medicine). Tehran; 1949.
 57. Cancer Research center, Cancer Institute of Iran. Available from: URL: <http://crc.tums.ac.ir> (Accessed 20.2.2013)
 58. Hedayati J. *The History of Contemporary Medicine in Iran* [in Persian]. Tehran: Iran University of Medical Sciences and Health Services; 2002: 85 – 86.
 59. Maleki A, Hashemian H, Afchari R. Esophageal cancer in Iran. *J Radiol Electrol Med Nucl.* 1965; **46**: 135 – 141.
 60. Bahadori M. Obituary. Available from: URL: <http://www.ams.ac.ir/AIM/0031/obituary0031.html>
 61. Available from: URL: <http://www.jccac.ir/index.php> (Accessed 20.2.2013)
 62. Interview with Dr. K. Dehshiri. Available from: URL: <http://www.alumni.tums.ac.ir> (Accessed 20.2.2013)
 63. Mossallaie A. The History of Radiotherapy Department at Shiraz School of Medicine. in: A Collection of Essays on the History of Shiraz Medical School In the Honor of Professor Framarz Ismail-Beigi, [in Persian] edited by M. H. Azizi. Tehran: Mirmah Publisher. 2012: 174 – 176.
 64. Radiotherapy-Oncology Society of Iran. Available from: URL: <http://isro.org.ir> (Accessed 28.2.2013)
 65. Afshar A. A brief Iranian medical history through commemorative postage stamps. *Arch Iran Med.* 2010; **13**: 161 – 165.
 66. Etemadi A, Sadjadi A, Semnani S, Nouraei SM, Khademi H, Bahadori M. Cancer registry in Iran: a brief overview. *Arch Iran Med.* 2008; **11**: 577 – 580.
 67. Mohagheghi MA, Jarrahi Mosavi A. Review of cancer registration and cancer data in Iran, a historical prospect. *Asian Pac J Cancer Prev.* 2010; **11**: 1155 – 1157.
 68. Kmet J, Mahboubi E. Esophageal cancer in the Caspian littoral of Iran: initial studies. *Science.* 1972; **175**: 846 – 853.

69. The Society to Support Children Suffering from Cancer (MAHAK). Available from: URL: <http://www.mahak-charity.org/main-en/en/who-we-are/our-story> (Accessed 20.5.2013).
70. Tehran Times, Volume. 11711, 20 May 2013. Available from: URL: <http://www.tehrantimes.com>. (Accessed 20.5.2013).
71. Available from: URL: <http://crc.tums.ac.ir> (Accessed 24.5.2013)
72. Available from: URL: <http://www.en.sbmu.ac.ir> (Accessed 24.5.2013)
73. Available from: URL: <http://www.icr.ir>. (Accessed 24.5.2013)
74. Available from: URL: <http://www.rc.ajums.ac.ir> (Accessed 24.5.2013)
75. Available from: URL: <http://www.mums.ac.ir> (Accessed 24.5.2013)
76. Cancer Research Network. <http://cancernet.research.ac.ir/forms/introduction.aspx> (Accessed 24.5.2013)
77. Omid Hospital. Available from: URL: <http://www.mums.ac.ir/cancer/fa/history> (Accessed 24.5.2013)
78. Amir Oncology Hospital. Available from: URL: <http://www.shasa.ir/newsdetail-68234-fa.html> (Accessed 24.5.2013)
79. Available from: URL: <http://bonyadfs.ir> (Accessed 24.5.2013)
80. The report of the Ministry of Health and Medical Education in the 9th government (2005 – 2009). Available from: URL: <http://behdasht.gov.ir/index.aspx?siteid=1&pageid=10970&newsview=4263> (Accessed 25.5.2013)
81. Amir Oncology Hospital. Available from: URL: <http://amirhp.sums.ac.ir/pages/tarikhcheh.html> (Accessed 25.5.2013)
82. Li L and Rao K A statistical analysis of registered cancer morbidity and mortality in 11 counties, China (1988–1992) [in Chinese]. *Bull Chinese Cancer*. 2000; **9**: 435 – 447.
83. Zaridze DG, Basieva T, Kabulov M, Day NE, Duffy SW. Esophageal cancer in the Republic of Karakalpakstan. *Int J Epidemiol*. 1992; **21**: 643 – 648.
84. Hormozdiari H, Day NE, Aramesh B, Mahboubi E. Dietary factors and esophageal cancer in the Caspian littoral of Iran. *Cancer Res*. 1975; **35**: 3493 – 3498.
85. Joint Iran-International Agency for Research on Cancer Study Group. Esophageal cancer studies in the Caspian littoral of Iran: results of population studies--a prodrome. *J Natl Cancer Inst*. 1977; **59**: 1127 – 1138.
86. Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C, Aramesh B. Esophageal cancer studies in the Caspian littoral of Iran: results of a case-control study. *Br J Cancer*. 1979; **39**: 293 – 309.
87. Joint Iran-International Agency for Research on Cancer Study Group. Esophageal cancer studies in the Caspian littoral of Iran: results of population studies--a prodrome. *J Natl Cancer Inst*. 1977; **59**: 1127 – 1138.
88. Ghadirian P, Stein GF, Gorodetzky C, Roberfroid MB, Mahon GA, Bartsch H, et al. Esophageal cancer studies in the Caspian littoral of Iran: some residual results, including opium use as a risk factor. *Int J Cancer*. 1985; **35**: 593 – 597.
89. Saidi F, Sepehr A, Fahimi S, Farahvash MJ, Salehian P, Esmailzadeh A, et al. Oesophageal cancer among the Turkomens of North-East Iran. *Br J Cancer*. 2000; **83**: 1249 – 1254.
90. Moradi A, de Villiers E-M, Mokhtari-Azad T, Mahmoudi M, Hazrati B, Ghaemi E, Nategh R. Detection of Human Papillomavirus DNA by PCR in Esophageal Squamous Cell Carcinoma from Turkmen Sahra, North-East of Iran. *Iranian Biomedical Journal*. 2002; **6**: 19 – 23.
91. Sepanlou SG, Etemadi A, Kamangar F, Sepehr A, Pourshams A, Poustchi H, et al. The gastro-esophageal malignancies in northern Iran research project: Impact on the health research and health care systems of Iran. *Arch Iran Med*. 2013; **16**(1): 46 – 53.

Erratum

In the December issue of Archives of Iranian Medicine, Vol. 15, No. 12, 2012, in the article entitled “Correlation of Quality of Life with Gastroesophageal Reflux Disease among Qashqai Nomads in Iran”, the correct affiliation of one of the authors, Ali Montazeri PhD⁶, is “Mental Health Research Group, Health Metrics Research Center, Iranian Institute for Health Sciences Research, ACERC, Tehran, Tehran, Iran.”