Published in final edited form as:
Arch Iran Med. 2013 January ; 16(1): 46–53.

The gastro-esophageal malignancies in Northern Iran research project: impact on the health research and health care systems in Iran

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Abstract

Since 2000, considerable progress has been made in health research in Iran. An example of this progress has been the Gastro- Esophageal Malignancies in Northern Iran (GEMINI). The original aim of this project was to identify etiologic factors and prevention measures for upper gastrointestinal cancers in Northern provinces of Iran, but its achievements have gone much beyond the initial goal. This project is one of the largest studies in the Middle East and North African region, has helped build and strengthen research capacity at both individual and institutional levels in Iran, and has provided international credibility to research institutes and the wider research system in Iran. The success of GEMINI reveals the feasibility of large-scale studies in developing countries and serves as a successful model not only for health research institutes within Iran, but also for research systems in other developing countries. The outcomes of the project are numerous, including establishment of research networks, development of efficient methods for planning and implementation of research projects, and introduction of methodologies for project management, data management and usage of health technology. Finally and perhaps most importantly, GEMINI is among the few projects that has had a significant impact on the attitudes and concerns of decision makers in the health sector in Iran. It signifies the importance of investment in human resources and has proved that health policies should be health-based rather

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than patient-based. Here we review the impact of GEMINI on the health research system and the broader health care system of Iran and put these into a more global perspective.

Keywords

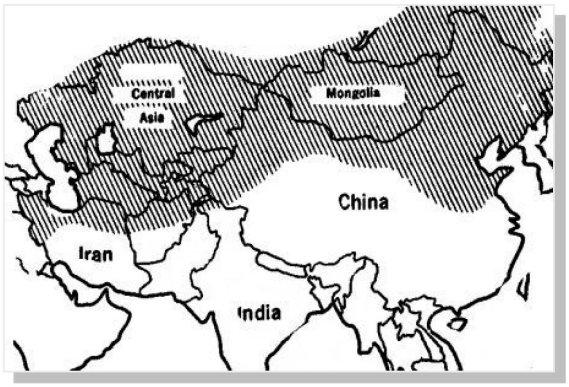
research design; prospective studies; pilot projects; feasibility studies; planning techniques; methods; cancer epidemiology; gastroenterology

Introduction

The current report is prepared in reply to the call for papers in WHO/PLOS collection on strengthening functions and components of national research systems. In this regard, the flourish of the health research system in Iran is noticeable. Significant monetary and human inputs into the research system have led to noteworthy proximal and distal outcomes. Nationally and internationally recognized research projects are numerous in Iran, some of them unique in the region, and among them is the population-based project of Gastro-Esophageal Malignancies in Northern Iran (GEMINI). This study is one of the largest in the North African and Middle East region and it is one of the credible prospective studies in the world with significant outputs, outcomes, and impacts. In this paper, we aim to describe the development of GEMINI in Iran and its impacts at the national, regional, and international levels.

Background of GEMINI

The Caspian Littoral of Iran is situated within a belt of high cancer incidence that extends from China and Mongolia to Central Asia [1-3]. In 1969, a population-based cancer registry was established in Iran as a result of the joint effort between Tehran University and the International Agency for Research on Cancer (IARC) [4]. The registry demonstrated that the incidence of upper gastrointestinal cancers in the North of Iran was the highest in the world [5, 6].



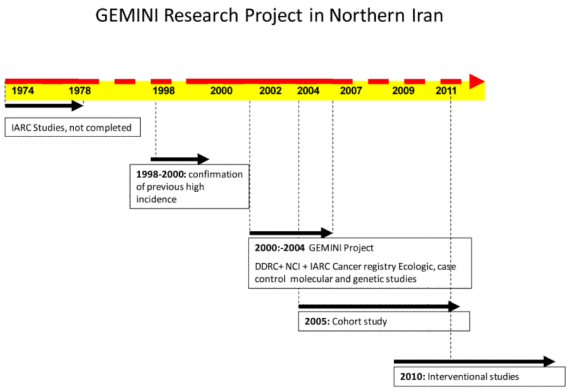
Ecological and nutritional studies were conducted by IARC and Tehran University to establish the epidemiologic features and to investigate the etiology of esophageal cancer throughout the Caspian Littoral [4]. Results demonstrated the role of some risk factors, especially poverty and very low consumption of fresh fruit and vegetables [1], but these factors have been shown to be associated with increased risk of esophageal cancer in almost all countries [7]. No clear evidence was found for other potential risk factors such as hot tea or nass consumption. However, further investigations were discontinued in 1979 due to the

sociopolitical changes in Iran, and the complete patterns of incidence and the full complement of risk factor results remained to be established.

There also remained a need to obtain ongoing and accurate data on the burden and time trend of upper gastrointestinal cancers in North of Iran as such data are essential for proper prioritization and budgeting of limited health care resources. To overcome budget limitations, the possibility of attracting available international resources such as IARC, was evaluated. As proved later on, these resources can help organize and implement studies and infrastructures (such as cancer registries) that can be beyond the financial capacity of developing countries.

New studies were launched in late 1990s in continuation of initial investigations. The first study was a survey on esophageal cancer which was carried out from 1995 to 1997 in Turkmen plain (now known as Golestan province) at the southeastern corner of the Caspian Sea. In this study, the estimated prevalence of esophageal squamous cell carcinoma (ESCC) ranged from 47.7 to 71.5 per 100,000 [8]. While lower than the prevalence in the 1970, it is still among the highest rate in the world [9]. These results were further supported by another survey in Ardabil in Western side of the Caspian Littoral [10]. With internal and international support, a new cancer registry was established in Iran in 1996. This new cancer registry also generated valuable data on the prevalence of all types of cancer in Northern Iran [11-15].

Thereafter in 1999, the idea of a comprehensive prospective study on gastric and esophageal cancer in North of Iran was put forward by Digestive Disease Research Center (DDRC), which was affiliated to Tehran University of Medical Sciences (TUMS). DDRC took the lead in the establishment of the Gastro-Esophageal Malignancies in Northern Iran (GEMINI) project. The initial aims of GEMINI were restricted to investigate the etiology of upper gastrointestinal cancers in Iran. GEMINI consisted of several localized projects including cancer registries in Golestan and Ardabil provinces in North of Iran and case-control studies on esophageal cancer in Golestan and Ardabil. Initial results from these research projects, including some ecologic, molecular and genetic studies generated new hypotheses and provided the impetus to initiate a more comprehensive prospective cohort study on upper gastrointestinal cancers in Golestan.



The aims of the prospective cohort project were: 1) to identify risk factors for upper gastrointestinal cancers; 2) to provide sampling frame for nested case-control studies on upper gastrointestinal cancers; and 3) to provide a model for population-based studies in a country in economic and social transition. The ultimate goal of the project was to study the dietary, life-style, anthropometric, biochemical, and genetic determinants of upper gastro-

intestinal cancers and to find an explanation for the high incidence of these types of cancer in Northern Iran.

At first, agreement of governmental officials and religious leaders was obtained. Iranian faculty members from TUMS in relevant fields of research were asked to participate in the project. Later on, an international network was created. The principal investigators of the 1960s cancer registry were invited to take part in planning the project. Moreover, well-known international experts were included in the project from several organizations, including scientists from the US National Cancer Institute (NCI), IARC, the University of Cambridge Cancer Genetics Group, the Karolinska Institute (Sweden), University of Glasgow and University of Leeds (UK), Johns-Hopkins University,and University of Toronto (Canada). The network prepared the ground to obtain internal and external funds for the preliminary phase of the project. A meeting of participants held in IARC in 2000 was crucial in strengthening and integrating the network.

The planning phase took two years (1999 to 2001) at the end of which, two specialized clinics were established in 2001: Atrak clinic in Golestan and Aras clinic in Ardabil. The two clinics were established with the dual purpose of improving the gastro-intestinal health care services for the surrounding population and establishing a permanent local base for research studies. A federal-wide assurance (FWA00001331) was obtained for DDRC followed by the establishment of an institutional review board or institutional ethics committee (IRB/IEC) which was also registered (IRB00001641 DDRC) with the Office for Human Research Protections and the U.S. Department of Health and Human Services.

Along with the planning, additional studies were conducted to address the main questions that investigators of GEMINI faced, including studies on: the epidemiologic features of upper gastrointestinal cancers in North of Iran [16], reliability and validity of opiate use self-report [17], serum selenium and upper gastrointestinal cancers [18], genetic determinants of esophageal cancer [19-21], the role of exposure to polycyclic aromatic hydrocarbons in risk of esophageal cancer [22], and familial risk of esophageal cancer in Golestan [23].

The next part of the plan consisted of pilot studies that were conducted by DDRC in collaboration with IARC and NCI. The aims of the studies were: to assess the response rate of the study population, to develop valid and reliable methods for data collection [17, 24], to develop follow-up methods [25], to crudely estimate the sample size and operating costs, and to evaluate the necessary logistics and human resources. The pilot studies were conducted from 2002 to 2003. Results of the studies confirmed the feasibility of launching a prospective cohort study in Northern Iran [26].

Before launching the final cohort, a case-control study was conducted in Golestan in 2003. In this study, 300 cases of esophageal cancer and 571 controls were enrolled. Cases were recruited from patients who were referred to Atrak clinic. Age- and sex-matched controls were recruited from neighbors of cases. Data were gathered using the detailed life-style and food frequency questionnaires that were validated by pilot studies. Blood samples were taken from cases and controls by trained staff who visited health houses and district health centers. All biological samples were later transferred to Tehran.

Some results from this study have been disseminated in papers examining several plausible risk factors for esophageal cancer, including opium, tobacco, and alcohol use [27], poor oral hygiene [28], tea drinking habits [29], socio-economic determinants [30], and exposure to polycyclic aromatic hydrocarbons [31]. This study continues to serve as a resource for other hypotheses.

Dissemination and publication of these results in peer-reviewed journals was helpful in obtaining further financial support from internal and external resources. The Iranian Ministry of Health agreed to grant funds equivalent to those offered by external sources.

From 2003 to 2004, upon collaboration of the DDRC with Golestan University of Medical Sciences, the necessary infrastructure for the cohort study was built on the existing Primary Health Care (PHC) system in Golestan. The PHC system had originally been established to provide basic health care services and to improve reproductive health in remote rural areas in Iran [32], but it also has inherent capabilities for improving the health services and health research. In GEMINI, the PHC has evolved into a research-oriented network. Adjuvant specialized referral centers were also established in the districts under study.

In 2004, the Golestan Cohort Study (GCS) was launched [33]. The sample size was based on disease incidence data derived from previous studies and over 50,000 subjects were recruited. Enrollment was closed in 2007. Subjects were selected using systematic cluster sampling from 3 main districts of Golestan. In rural areas, all residents of all villages in the study catchment area who were willing to participate in the study, were apparently healthy, and had 40 to 75 years of age were invited. Temporary recruitment centers were established in the health houses of 198 selected villages, and the Behvarz (Auxiliary health worker) accompanied the GCS research team to contact the selected subjects at their homes. In urban areas, subjects were contacted at home by specially trained health workers and invited to visit the Golestan Cohort Study Center. Data collection was accomplished as expected. Biobanks with -- −80 °C freezers and CO2 back up were established with extra electricity back up in Gonbad and Tehran. In order to be cautious of natural disasters such as earthquakes that are frequent in Iran, all samples were aliquotted in two sets and one set of the samples was shipped to be stored in special nitrogen tank in IARC biobank at Lyon, France.

All participants have been followed up actively every 12 months. Each cohort member has received a special membership card that facilitates their visit in Atrak clinic to explore upper gastrointestinal symptoms. Members were also instructed at the time of enrollment to contact the GCS team in case any unusual condition occurred. These contacts are registered and subsequently followed up. The databases of Atrak Clinic and of the Golestan Cancer Registry have also been reviewed monthly to look for cancer cases among the study subjects. The follow-up is expected to continue for a minimum of 10 years. As a result of recent developments in telecommunication and transportation, access of the majority of people to telephone and cell phones, and active monitoring and adequate instruction of study subjects, loss to follow-up has been minimal (about 0.2%) [33]. Mortality has been monitored through available medical and hospital documents and for those who die at home via accurate verbal autopsy [25]. Up to now, 2150 deaths have been recorded in GCS and first series of papers on total and cause-specific mortality and their risk factors are in preparation.

GEMINI has provided a unique opportunity for studying non-communicable chronic diseases (NCDs) which based on WHO reports are raising more and more concerns in low- and middle-income countries [34, 35]. More importantly, GEMINI set the grounds for studies on cost-efficiency of life-style interventions for primary, secondary, and tertiary prevention of NCDs. Studying the effectiveness of Polypill in preventing cardiovascular diseases is another plan [36, 37].

Achievements of GEMINI

Impacts of GEMINI can be classified into the following categories:

Producing new knowledge

GEMINI has been successful in investigating existing as well as new hypotheses for the etiology of upper gastrointestinal cancers, some of which have been revealed for the first time. GEMINI has also advanced our knowledge on NCDs including: burden and trend of cancers [16, 38, 39] and other NCDs in Northern Iran, prevalence of exposure to risk factors of NCDs [40-44], the entire causal web for cancers and NCDs, and effective screening and preventive methods for NCDs. Specific in this regard is a study on epidemiologic features and risk factors of end-stage kidney disease that has been done in collaboration with the nephrology research center in TUMS [45].

Results of GEMINI show that the incidence and prevalence of upper gastrointestinal cancers have declined in recent years [9]. This decline may be in part due to improvement in socio-economic status and decreased exposure to risk factors [30]. On the other hand, results clearly show that cardiovascular diseases are the major cause of death in Northern Iran, and the decline in prevalence of cancers may be somehow due to the fact that subjects may die of cardiovascular diseases before they are victims of cancer. Further studies on NCDs that are nested in GEMINI can advance our knowledge on the interplay between various causes of death in Northern Iran.

Since the beginning of pilot studies in 2002 up to now, over 40 papers have been published on the results of this project in medical journals indexed in ISI database including: 5 papers on methodology of GEMINI, 24 papers on upper gastrointestinal cancers [23, 30, 46-50], and 3 papers on non-cancerous digestive diseases [51-53]. Over 11 projects have been completed on subjects not directly relevant to gastroenterology. These papers were the result of collaboration of DDRC with other departments in TUMS, including the endocrinology and the nephrology research centers. Papers published in local journals were even much more numerous than those mentioned above. The majority of publications were original articles.

GEMINI has clearly demonstrated that it is false to assume that the pathogenesis of diseases is similar in industrialized, developing, and underdeveloped countries. Most studies on chronic disease epidemiology are localized in Western countries. Due to existing difference in dietary, life-style, environmental and genetic determinants of NCDs between developed and developing countries, the results of these studies can not be generalized to countries all over the world. Studies on inductive and protective determinants of NCDs in developing countries will not only satisfy the needs of people in these countries, but also will advance our knowledge on the causal web of these diseases [54].

Introducing new research methods

In the course of GEMINI, tools for data collection have been tailored to religious, ethical, social, and cultural background of inhabitants in Golestan and Ardabil. Several new research methods have been devised in GEMINI projects, including innovative methods to measure tea temperature [29], applying complex methods for developing a composite score to scale the socio-economic status [30], adopting a new method for verbal autopsy [25], innovative follow-up methods [33], and new methods for evaluation of target organ toxic exposures [31].

The methods of data collection have also been designed in a way that makes the most of existing health system. The process of devising and evaluating the accuracy of these tools during pilot studies can be an excellent model for later research projects to ensure the reliability and validity of the data they gather [17, 24].

Another outcome of GEMINI is the introduction of the latest health technologies to the health system in Iran. Some of the laboratory equipment have been imported and used in research for the first time in Iran. A bio-bank has been established for genetic and molecular studies in DDRC. Furthermore, DDRC has been successful in taking advantage of laboratory facilities in IARC and NCI. The tissue samples collected in GEMINI have the potential value for future '-omics' applications: Genomic, Proteomic, Metabolomic, and Transcriptomic studies.

Providing opportunities for new research projects

As mentioned earlier, GEMINI has set the grounds for comprehensive studies on NCDs. Based on the results of GEMINI thus far, cardiovascular diseases, cancers, cerebrovascular diseases, injuries, pulmonary and renal diseases are the leading causes of mortality in Golestan and Ardabil. Prevalent life-style habits that increase the risk of NCDs can be the main targets of preventive measures at large scale.

Additionally, in the context of GEMINI, launching cohort multiple Randomized Controlled Trials (cmRCT) will become possible. The cmRCTS have several advantages over simple RCTs: they are less costly, more powerful, more efficient and more generalizable to the whole population. GEMINI can be among the first and most extensive studies within which, pragmatic clinical trials can be effectively launched. In fact, the largest clinical trial in Iran on polypill intervention that recruits over 7000 subjects is already designed and launched in Golestan. This study will be one of the largest studies in the world on efficacy and safety of polypill for prevention of cardiovascular death (55).

Developing and expanding health research and health care infrastructure

The local infrastructure has been built in Golestan and Ardabil, mainly on the existing Primary Health Care (PHC) in these two provinces. Establishment of cancer registry is another part of the entire infrastructure. Addition of new specialized health care centers, namely Atrak and Aras clinics, has expanded the local health network.

GEMINI has also led to formation of research networks within TUMS and a larger national research network between TUMS, medical universities in Golestan and Ardabil, and other health institutes such as Iran Blood Transfusion Organization Research Center, Pasteur Institute, and National Research Center for Genetic Engineering in Iran. Finally, GEMINI has facilitated the establishment of an international research network. Members of this network are among the most credible health institutes around the world.

During the past 7 years, DDRC has served as a model for the establishment of at least seven new gastroenterology research centers in medical universities all over the country [56, 57]. Furthermore, the success of GEMINI has encouraged other research centers in Iran to launch cohort studies. As examples, two cohort studies on different types of cancers have been conducted in Shiraz in South of Iran, and in Tabriz in North West of Iran. Another cohort on ophthalmologic diseases has been launched in Shahrood in central Iran.

Investing on human resources

During the course of GEMINI, existing healthcare personnel were trained for accurate data collection. Additional staff were also recruited and trained. All of the internists and gastroenterologists in districts under study were involved and re-trained through specially designed Continuous Medical Education (CME) to further their talents in medical and endoscopic examinations. A large number of health assistants (Behvarz) in health houses,

technicians, nurses, nutritionists, and general physicians were trained in the course of GEMINI.

Several medical graduates were trained on areas related to research in gastroenterology, epidemiology, and biostatistics. Training was offered in both internal and external academic institutes. Overall 9 gastroenterology fellows finished their post-doctoral training. GEMINI also offered opportunities to 10 medical graduates to attain their MPH degree and helped 14 PhD candidates complete their studies. As a result of GEMINI achievements, DDRC was qualified to launch a PhD trajectory to enroll medical graduates who are interested in medical/epidemiologic research.

Faculty members in medical universities in Golestan and Ardabil as well as those in Shariati Hospital and other departments of TUMS, and some other well-known research centers in Iran were involved in GEMINI and have contributed to joint publications.

Increasing awareness and enhancing the knowledge of officials at all levels

GEMINI clearly demonstrated that CVD and other chronic diseases including cancers should be the focus of health care system in the country, consequently results of GEMINI have attracted the attention of headquarters in the Ministry of Health towards the outbreak of chronic diseases in Iran. Results of GEMINI have challenged the present dogma of health care delivery system from treating patient (tertiary and secondary prevention) toward maintaining the health of normal subjects (primary prevention).

GEMINI has somehow changed the attitudes of policy makers and faculty members that the existing health care infrastructure in the rural area can be used efficiently in health system research .Policy-makers in the Ministry of Health have been encouraged to devise procedures to expand research infrastructure and to accurately evaluate Iran's health research system.

Improving DDRC credit and structure

One of the main achievements of GEMINI at the regional and international levels is that DDRC has been chosen as the World Health Organization (WHO) collaborating center on cancer research across Middle East and North Africa from 2006 to 2010. This position has recently been extended for the coming 4 years (2011 to 2014).

During the past 7 years, DDRC has virtually obtained all types of national scientific prizes in Iran (Avicenna, Razi, Hadavi, TUMS …), and prizes directly given by the President, the Governor of Tehran provinces, and the Minister of Health. DDRC has also gained the prize of Islamic Countries Scientific Organization in 2011.

Since the beginning of the project, DDRC has expanded and will in near future evolve into an independent research institute. The DDRC budget, staff, logistics, and laboratory equipments have been developed. DDRC lab research capabilities including bio-bank, DNA extraction, PCR, and serologic and microbiologic assays have been upgraded. The overall quantity as well as quantity of DDRC publications has improved, and so has the international credit of DDRC.

International endowments

The ultimate outcomes of GEMINI have been and will be introduced to academic medical institutions not only inside of Iran but also across the world. In fact, the principal investigators of this study have made several speeches in medical universities and research

institutes across the country on strategies and methods taken on by DDRC in planning, launching, managing and follow-up of GEMINI. The development of GEMINI and its achievements have been presented to medical universities in Middle Eastern and North African countries such as Syria, Lebanon Morocco and Tunisia, in Asian countries such as China, and even in Western countries including USA (NCI, University of Pennsylvania), Germany, Italy, Canada, Cambridge and Birmingham (UK), and IARC in France.

Overall, well-designed research projects that set the grounds for scientific collaboration of both developed and developing countries will achieve much more than their initial scientific goals. Such collaborations can lead to exchange of social and cultural capital between nations. Despite the instability of political relationships between governments, these cultural links can serve as an unbreakable backup for nations and can bring stability, peace, tolerance, understanding, and hope for generations to come.

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