Review Article

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

Background: The Gastro-Esophageal Malignancies in Northern Iran (GEMINI) research project is an example of recent progress in health research in Iran. 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 this initial goal.

Methods: GEMINI consists of several projects including cancer registries, pilot studies, case-control studies, and the Golestan Cohort Study. GEMINI has been conducted through extensive collaborations between the Digestive Disease Research Center of Tehran University of Medical Sciences with other domestic and international health organizations. The achievements of GEMINI include producing new knowledge, introducing new research methods, developing and expanding health research and health care infrastructures, investing in human resources, and increasing the awareness and knowledge of policy makers and officials at all levels about the importance of chronic diseases in Iran's health priorities.

Conclusions: The success of GEMINI reveals the feasibility of large-scale health research studies in developing countries and serves as a successful model not only for health research in Iran, but also for similar research studies in other developing nations.

Keywords: Chronic disease, esophageal cancer, gastric cancer, gastroenterology, Iran, research design

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Introduction

The current report presents examples of how medical research can contribute to the improvement of health care systems, especially in developing countries. We describe the Gastro-Esophageal Malignancies in Northern Iran (GEMINI) project, a group of related research studies originally designed to identify etiologic factors and prevention measures for upper gastrointestinal cancers in the Northern provinces of Iran. The success of the GEMINI project shows the feasibility of large-scale scientific studies in developing countries and the positive effects that such studies can have on both health research and the larger health care system of the country in which they have been performed.

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The Caspian littoral of Iran is situated at the western end of the Central Asian Esophageal Cancer Belt, an area that extends from the Caspian Sea through Central Asia and Mongolia to northern China (Figure 1).[1,2] In 1969, the population-based Caspian Cancer Registry was established in the northern provinces of Iran as a result of the joint efforts of Tehran University and the International Agency for Research on Cancer (IARC).[3] This registry recorded esophageal cancer incidence rates up to 165/100,000 population/year in men and 195/100,000 population/year in women, some of the highest incidence rates of esophageal cancer ever reported in the world.[1–4]

In addition to the Caspian Cancer Registry, preliminary ecological and nutritional studies were conducted by IARC and Tehran University to establish the epidemiologic features and investigate the etiology of esophageal cancer throughout the Caspian littoral.[5,6] The results of these studies documented the role of some risk factors, especially poverty and very low consumption of fresh fruit and vegetables,[6] factors that have been shown to be associated with increased risk of esophageal cancer in almost all countries.[2] The role of other potential risk factors such as hot tea or nass consumption could not be fully assessed.[5,6] 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 trends of upper gastrointestinal cancers in northern Iran, as such data are essential for proper prioritization and budgeting of limited health care resources. Hence GEMINI

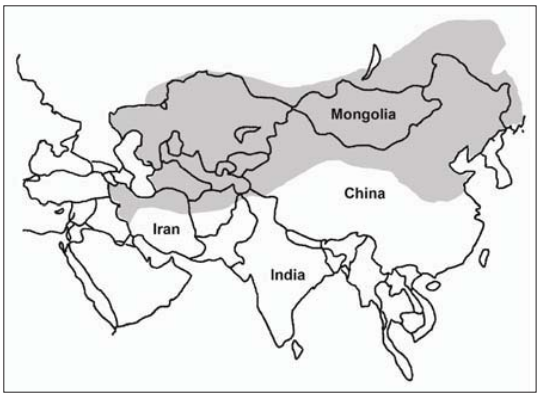

Figure 1. The Central Asian Esophageal Cancer Belt (adopted from Kmet et al. 1972)[1]

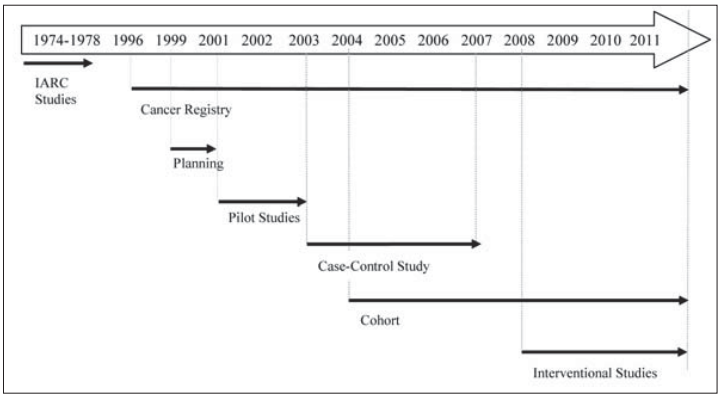

Figure 2. Development of the GEMINI Research Project. 20(50): 7368 – 7374.

was launched in northern Iran to address these needs and also to find an answer for questions that had remained unresolved for so many years. The following sections describe the development and achievements of this project.

What has been done?

In the late 1990s, new studies were launched to continue the evaluations of the earlier investigations. The first study was a 1-year active surveillance of esophageal cancer which was carried out from 1996 to 1997 in the Turkmen plain (now known as Golestan Province) at the southeastern corner of the Caspian Sea. In this study, the age-standardized incidence rates (ASR) of esophageal cancer were 144/100,000 in men and 49/100,000 in women.[7] A second retrospective survey of all cancers in Golestan Province in 1996-2000 reported esophageal cancer ASRs of 43/100,000 in men and 36/100,000 in women.[8] While lower than the incidence figures in the 1970s, these rates were still among the highest reported in the world.[2,8] With internal and international support, a new cancer registry was established in Iran in 1996, and this new cancer registry generated valuable data on the prevalence of all types of cancer in northern Iran.[9–14]

Thereafter, in 1999, the idea of comprehensive studies of gastric and esophageal cancer in northern Iran was put forward by the Digestive Disease Research Center (DDRC), which is affiliated with Tehran University of Medical Sciences (TUMS), and DDRC took the lead in the establishment of the GEMINI project. The aim of GEMINI was to investigate the etiology and genetics of upper gastrointestinal cancers in high-risk areas of Iran and to decrease the mortality and morbidity of these diseases by appropriate, targeted preventive strategies.

At first, GEMINI consisted of several related projects, including cancer registries in Golestan and Ardabil Provinces, initial descriptive studies of epidemiologic features in the two provinces, and a case-control study of esophageal cancer in Golestan. Ardabil Province is located at the southwestern corner of the Caspian Sea, where the incidence of gastric cancer is one of the highest in the world and the incidence of esophageal cancer is moderate.[13] Results from these studies generated new hypotheses and provided the impetus to initiate a more comprehensive large prospective cohort study on upper gastrointestinal cancers in Golestan (Figure 2).

Before beginning GEMINI, agreement of governmental officials and religious leaders was obtained, and Iranian faculty members from TUMS in relevant fields of research were asked to participate in the project. Then an international network was created. The principal investigators of the 1970s cancer registry were invited to take part in planning the project. Moreover, well-known international experts from the US National Cancer Institute (NCI) and IARC joined and supported the project from the beginning. This 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. Later on, scientists from several other institutions, including the University of Cambridge Cancer Genetics Group (UK), the Karolinska Institute (Sweden), the University of Glasgow (UK), the University of Leeds (UK), the Johns Hopkins University (US), Mount Sinai School of Medicine (US), and the University of Toronto (Canada) were involved in various aspects of the GEMINI project.

The planning phase for GEMINI took two years (1999 to 2001), at the end of which two gastroenterology specialty clinics were established in 2001: Atrak clinic in the city of Gonbad, in Golestan Province, and Aras clinic in the city of Ardabil, in Ardabil Province. These two clinics were established with the dual purpose of improving the gastrointestinal health care services for the surrounding populations and establishing permanent local bases for research studies. A U.S. federal-wide assurance (FWA00001331) was obtained for DDRC, followed by the establishment of an institutional review board (IRB) which was also registered (IRB00001641 DDRC) with the Office for Human Research Protections in the U.S. Department of Health and Human Services.

Also in 2001, scientists at DDRC, NCI and IARC developed guidelines for the functioning of GEMINI. In general, each group was responsible for the phases of the project that were conducted in their own country, and all groups cooperated at every step in the design, conduct, and analysis of the project and in all resulting publications. DDRC was involved in data gathering through interviews and medical and endoscopic examinations, and also in the collection, storage, and transfer of hard data, electronic data, and biological samples. NCI and IARC were responsible for providing specialized laboratory assays in their countries and also for training DDRC researchers at their institutions. All parties were involved in providing methodological expertise. A Scientific Committee composed of selected scientists from DDRC, NCI, IARC and other experts in this field was responsible for oversight of the project.

Along with the development of collaborative networks and project planning, initial studies were conducted to address some of the main questions that GEMINI investigators would face, including studies on the epidemiologic features of upper gastrointestinal cancers in northern Iran,[15–18] the reliability and validity of opiate use self-report,[19] the association of serum selenium levels and upper gastrointestinal cancers,[20] genetic determinants of esophageal cancer, [21–23] exposure to polycyclic aromatic hydrocarbons in the study population,[24] and familial risk of esophageal cancer in Golestan.[25]

In 2001 to 2003 pilot studies were also conducted by DDRC, NCI and IARC to assess the feasibility and optimize methods for a case-control study of esophageal cancer in Golestan. The main aims of these studies were to optimize strategies for (a) data management and questionnaire design, (b) recruitment of all incident cases, (c) biological specimen collection/preservation, (d) clinic and population-based control selection, and (e) validation of laboratory methods.

Following these pilot studies, the Golestan Case-Control Study was conducted between 2003 and 2007 to compare demographic features and environmental exposures in esophageal cancer cases and controls in Golestan Province. In this study, designed jointly by DDRC, NCI and IARC, 300 cases of esophageal squamous cell carcinoma (ESCC), 300 clinic controls and 571 neighborhood controls were enrolled. Cases and age- and sex-matched clinic controls were recruited from patients who were referred to Atrak clinic for upper gastrointestinal symptoms. Cases had histology-proven ESCC and controls had no esophageal dysplasia or cancer identifiable by endoscopic examination. Another group of controls, population-based neighborhood controls, were matched to cases for age, sex, and village or urban area of residence. Cases and clinic controls were interviewed and endoscoped at Atrak clinic, and biological specimens were collected including mucosal biopsies, blood, hair and nails. The neighborhood controls underwent the same interview and blood, hair, and nails collection in their local health house or district health center. All samples were later transferred to Tehran. Environmental risk factors were assessed through detailed life-style and food frequency questionnaires that had been validated by pilot studies and through objective measurements in biological specimens from both cases and controls. The role of genetic polymorphisms was studied using genomic DNA from cases and controls, and these variants were matched with associated carcinogen data collected from questionnaires and carcinogen assays.

Results from the Golestan Case-Control Study have been disseminated in papers examining several plausible risk factors for esophageal cancer, including opium, tobacco, and alcohol use,[26] poor oral hygiene,[27] tea drinking habits,[28] socio-economic determinants,[29] and exposure to polycyclic aromatic hydrocarbons.[30] This study continues to serve as a resource for testing other hypotheses.

At the same time that the case-control study began enrolling subjects, planning began for a large prospective cohort study in Golestan. The aims of this prospective cohort were: 1) to identify risk factors for upper gastrointestinal cancers; 2) to provide a 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, ethnic, 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.

In 2003 and 2004, DDRC and Golestan University of Medical Sciences collaborated to establish the necessary infrastructure for the cohort study, 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,[31] but it also has inherent capabilities for improving other 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.

Pilot studies for the cohort study were also performed, 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,[19,32] to develop follow-up methods,[33] to estimate the sample size and operating costs, and to evaluate the necessary logistics and human resources. Results of these studies confirmed the feasibility of launching a prospective cohort study in Golestan.[34]

In 2004, the Golestan Cohort Study (GCS) was launched.[35] The sample size was based on disease incidence data derived from previous studies and over 50,000 subjects were recruited. 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 40 to 75 years old, were apparently healthy, and were willing to participate in the study were invited. Temporary recruitment centers were established in the health houses of 198 selected villages, and the Behvarz (auxiliary health workers) 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 in Gonbad. Data collection was accomplished as expected. Biobanks with -80°C freezers and extra electricity and CO2 back-ups were established in Gonbad and Tehran. Because of the probability of natural disasters such as earthquakes, which are frequent in Iran, all samples were divided into two sets, and one set was shipped to be stored in special conditions, including liquid nitrogen tanks, in the IARC biobank in Lyon, France.

Enrollment in the Golestan Cohort Study was completed in 2008. Since enrollment, 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 medical condition occurred, and these contacts are registered and subsequently followed up. The databases of Atrak Clinic and of the Golestan Cancer Registry are also 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 telephones and cell phones, adequate instruction of study subjects and active monitoring, loss to follow-up has been minimal (about 0.2%).[35] Mortality has been monitored and cause of death ascertained through available medical and hospital documents and, for those who die at home, verbal autopsy.[33] Up to now, 2145 deaths have been recorded in the GCS, and the first series of papers on total and cause-specific mortality and their risk factors has been pub-

lished.[36]

Throughout its development, GEMINI has been supported financially by a combination of internal and external sources. The majority of the support has come from the Iranian government, both in direct grants and through the use of government-run facilities (such as the Public Health Care system), but external grants, such as those available through IARC and Cancer Research UK, have also been obtained. These latter sources can also provide expertise to help organize and implement studies and infrastructures (such as cancer registries) that may be beyond the capacity of some developing countries. Dissemination and publication of results in international peer-reviewed journals has also been helpful in obtaining further financial support from both internal and external resources.

What has been achieved?

Since the beginning of pilot studies in 2002, over 60 papers have been published on the results of the GEMINI project in medical journals indexed in the Institute for Scientific Information (ISI) database. GEMINI studies have been successful in documenting cancer trends and investigating existing as well as new hypotheses for the etiology of upper gastrointestinal cancers. GEMINI studies have reported a 50% decline in esophageal cancer but no significant change in gastric cancer incidence in Golestan since the 1970s.[8] GEMINI studies in Ardabil have investigated the epidemiology, anatomic distribution and histologic subtypes of gastric cancer,[37,38] and studies in both Ardabil and Golestan have shown that about half of all gastric cancers in this region occur in the gastric cardia.[15] Ultimately, the results of the ongoing cancer registry have shown that between 2004 and 2008, the rate of esophageal cancer has declined while the rates of stomach, colorectal, and breast cancers are still increasing.[39,40]

GEMINI studies in Golestan have shown that self-report is a reliable and valid measure of opium use in this province,[19] and that both opium and tobacco use are modest risk factors for ESCC in this population (odds ratios (OR) of 2.0 and 1.5, respectively).[26] However, these results may be different in case-control designs due to difference in the method of selecting controls[41] Another study has shown that opium use increases the risk of both cardia and non-cardia gastric adenocarcinoma.[42] They have also suggested that dietary patterns may affect the risk of esophageal cancer[43] and gastric cancer,[44] and that prevalence of risk factors of esophageal cancer are not significantly different among various ethnicities in Golestan.[45] They have demonstrated that drinking very hot tea (OR 8.2) is strongly associated with ESCC,[28] that poor oral health increases risk of ESCC,[27,46] and that several measures of low socioeconomic status are associated with this disease.[29] Finally, they have shown that the Golestan population is highly exposed to polycyclic aromatic hydrocarbons (PAH),[24,47,48] and that PAH content in non-tumoral esophageal epithelial tissue (the target tissue for ESCC carcinogenesis) is dramatically higher in ESCC cases than in clinic controls (OR 26.6 for the 5th vs. 1st quintile of PAH content).[30] Meanwhile, more recent studies have demonstrated genetic differences in PAH-related DNA adduct levels between female smokers and non-smokers in GCS.[49]

GEMINI study also shows that among environmental risk factors, infections (including helicobacter pylori causing gastritis[50] and human papilloma virus[51]) may play an important roles in increasing risk of upper gastro-esophageal cancers. Results of another study suggest a synergistic effect between oral health and infection-induced atrophic gastritis in causing esophageal and gastric cancer, especially in the cardiac region.[46] Studies in GCS are on the way to investigate the validity of this finding and among them, one study has been designed to examine the role of animal contact in tranmission of bovine viruses.

Some of the more recent studies have investigated the accuracy of diagnostic methods for screening gastro-intestinal diseases by using novel mathematical models. In the study that has been done based on the data of Golestan Case-Control Study, a new model has been devised for predicting the risk of esophageal squamous cell carcinoma and squamous dysplasia, which can be suitable for selecting high risk individuals and or increase the pretest probability for screeing methods.[52] This study has been exclusively done on environmental risk factors of cancer. More novel comprehensive studies are on the way to examine the interaction between environmental, infectious, and genetic factors on cancers.

GEMINI has also provided an excellent opportunity for studying other non-communicable chronic diseases (NCDs), which based on WHO reports are raising ever more concerns in low- and middle-income countries,[53,54] while reports still show that they are very often neglected in health care systems.[55] Evidence shows that over 50% of mortalities are caused by NCDs and mainly by cardiovascular diseases (CVDs), and the results of GCS study have supported this finding.[33] As the etiology of NCDs very much overlaps with those of cancers, it would apparently be a cost-effective design to include NCDs among other outcomes of interest in GCS. As such, the data that has been collected on NCDs in GCS can be motives for policy makers in the health system to plan preventive measures. Useful data has been gathered on cardiovascular disease (the most common cause of death in northern Iran), other cancers,[9–14,56] cerebrovascular disease, diabetes mellitus,[57] liver diseases and their risk factors,[58–63] renal disease,[64,65] and obesity that are risk factors for several NCDs.[66–68]

Finally, GEMINI should also be useful for early detection studies, cost-benefit analyses, and intervention studies for primary prevention of NCDs.[69] Numerous methods for primary prevention of NCDs are universally recognized (mostly lifestyle interventions), but their cost-effectiveness is not clearly known.[70] Recently fixed-dose combination therapy (the so-called polypill), composed of aspirin antihypertensives, and statins, has been suggested as a probable cost-effective intervention for preventing NCDs.[71] Since 2003, when the concept of Polypill was presented, few studies have been conducted to investigate the actual effect. A new meta-analysis has suggested that Polypill can prevent large numbers of deaths due to ischemic heart disease (28,500) and stroke (12,700) in Iran.[72] Even more amazing are the findings of several studies on the protective effects of low-dose aspirin in short- and long-term cancer incidence (specifically GI and hepatic cancers). [73–75] and the benefits of statins on preventing cancer-related mortality.[76] Yet, the cost-effectiveness, feasibility, and acceptability of this prevention strategy remain to be investigated.

In this regard, DDRC decided to implement an interventional study (PolyIran) as one of the very few first studies on the dual effectiveness of Polypill on NCDs and cancers, using the infrastructure that has been built in GCS. PolyIran is in fact the largest long-term cohort multiple randomized controlled trial (cmRCT) in the world, which is designed with adequate power to look for efficacy of polypill.[77] The pilot study of the safety and efficacy of one polypill formulation and enrollment of 7,000 participants in GCS older than 50 years has been finished and results will be

published within the coming 3 years.[78,79]

In the course of GEMINI, tools for data collection have been tailored to the 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,[28] a sophisticated new composite wealth score to estimate socio-economic status,[29] a new method for verbal autopsy,[33] innovative follow-up methods,[35] and new methods for evaluation of target organ toxic exposures.[30]

The methods of data collection have also been designed in a way that makes the most of the existing health system. And the process of devising these tools and evaluating their accuracy in pilot studies can be an excellent model for other research projects wishing to ensure the reliability and validity of the data they gather.[19,32]

Another outcome of GEMINI is the introduction of new technologies to the health research system in Iran. Some of the laboratory equipment has been imported and used in research for the first time in Iran, and a new biobank of GEMINI biosamples has been established at DDRC for future genetic and molecular studies. These banked biosamples have great potential value for future '-omics' applications, including genomic, transcriptomic, proteomic, and metabolomic studies. Other DDRC lab research capabilities, including DNA extraction, PCR, and serologic and microbiologic assays have also been upgraded. Furthermore, DDRC has been successful in taking advantage of advanced laboratory facilities at IARC and NCI as well.

The local research infrastructure for GEMINI was largely built on the existing Primary Health Care (PHC) networks in Golestan and Ardabil, but the introduction of GEMINI has also added valuable new resources to the local health care systems of these provinces. Establishment of cancer registries helps central evaluation and planning for local health care needs, and the addition of new specialized health care centers, namely Atrak and Aras clinics, has expanded the capabilities and services of the local health care network.

GEMINI has also led to the formation of research networks within TUMS and with a larger national research network which includes TUMS, medical universities in Golestan and Ardabil, and other health institutes such as the Iran Blood Transfusion Organization Research Center, the Pasteur Institute, and the National Research Center for Genetic Engineering in Iran. Finally, GEMINI has facilitated the establishment of an international research network that includes members from some of the most well known health institutes from around the world.

During the past decade, DDRC has also served as a model for the establishment of at least seven new gastroenterology research centers in medical universities all over Iran.[80,81] Furthermore, the success of GEMINI has encouraged other research centers in Iran to launch cohort studies. For example, two cohort studies on different types of cancers have been started in Shiraz, in southern Iran, and in Tabriz, in northwestern Iran. In addition, another cohort study on ophthalmologic diseases has been launched in Shahrood, in central Iran.

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 in specially designed Continuous Medical Education (CME) courses 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 also trained in GEMINI.

Several medical graduates were also given advanced training in areas related to research in gastroenterology, epidemiology, and biostatistics. Training was offered in both domestic and international academic institutes. Overall, 12 gastroenterology fellows finished their post-doctoral training, 12 medical graduates attained MPH degrees, and 20 PhD candidates completed their doctoral studies. As a result of GEMINI's achievements, DDRC was certified to begin a PhD degree program to enroll medical graduates who are interested in medical/epidemiologic research.

Finally, 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 have been involved in GEMINI studies and have contributed to joint publications.

As noted above, governmental officials and religious leaders have been consulted and informed at every step of the development of GEMINI, and this has enhanced the awareness, interest and knowledge of these leaders in the results of GEMINI and its implications for the overall health care system of Iran. GEMINI has clearly demonstrated the increasing importance of CVD and other chronic diseases for the health care system of the country, and the results of GEMINI have attracted the attention of the highest levels of the Ministry of Health towards the outbreak of chronic diseases in Iran. The results of GEMINI have also suggested that more energy of the health care delivery system should be focused on maintaining the health of normal subjects (primary and secondary prevention of chronic disease), rather than concentrating all of the resources on disease treatment.

GEMINI has also changed the attitudes of many policy makers and academic faculty members and persuaded them that the existing health care infrastructure in the rural areas can be used efficiently in health system research. In particular, policy makers in the Ministry of Health have been encouraged to devise procedures to expand research infrastructure and more accurately evaluate Iran's health research system.

The principal investigators of GEMINI have made many speeches in medical universities and research institutes across Iran on the strategies and methods taken by DDRC in planning, launching, managing and reporting the GEMINI studies. The development of GEMINI and its achievements have also been presented at medical universities in Middle Eastern and North African countries such as Syria, Lebanon, Morocco and Tunisia, in Asian countries such as China, and in Western countries including the USA, Germany, Italy, Canada, the UK and France.

During the past 7 years, DDRC has obtained many national scientific prizes in Iran (Avicenna, Razi, Hadavi, etc.), as well as prizes given directly by the President, the Governor of Tehran Province, and the Minister of Health. DDRC has also received the Best Research Paper Award from the Organisation of Islamic Cooperation's Standing Committee on Scientific and Technological Cooperation in 2011.

One of the main achievements of GEMINI at the regional and international level is that DDRC has been chosen as a World Health Organization (WHO) collaborating center for cancer research in the Middle East and North Africa region for 2006 to 2010 and again for 2011 to 2014.

Conclusion

There are many reasons for the inadequacy of research evidence for appropriately directing health policies and health systems in developing countries.[82] Although poor infrastructure, methodological challenges, and lack of consensus on guiding principles can be named among these reasons, "negative attitude" towards the "feasibility" of health research and its potential impact on health care is certainly one of the main barriers. Successful experiences conducting research projects that have had considerable impact on health systems may be oases in a desert, but their mere existence proves their feasibility.

Finally, well-designed research projects that provide a foundation for scientific collaboration among both developed and developing countries will achieve much more than their initial scientific goals. In addition to the exchange of intellectual and scientific expertise, such collaborations can also lead to the exchange of social and cultural capital between nations, despite the instability of political relationships between governments.

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