Abstract

This study aimed review studies conducted on Mexican patients diagnosed with gastric cancer and/or diseases associated with its development, in which at least one Mexican institute has participated, and to assess their contributions to the primary and secondary prevention of this disease. A search of the Medline database was conducted using the following keywords: gastric/stomach cancer, Mexico. Studies of the Mexican population were selected in which at least one Mexican Institute had participated and where the findings could support public policy proposals directed towards the primary or secondary prevention of gastric cancer. Of the 148 studies found in the Medline database, 100 were discarded and 48 were reviewed. According to the analysis presented, these studies were classified as: epidemiology of gastric cancer (5/48); risk factors and protectors relating to gastric cancer (9/48); relationship between Helicobacter pylori and pathologies associated with gastric cancer and the development of the disease (16/48); relationship between the Epstein-Barr virus and pathologies associated with gastric cancer and the development of the disease (3/48); molecular markers for the development of diseases associated with gastric cancer and gastric cancer (15/48). Mexico requires a program for the prevention and control of gastric cancer based on national health indicators. This should be produced by a multidisciplinary committee of experts who can propose actions that are relevant in the current national context. The few studies of gastric cancer conducted on the Mexican population in national institutes highlight the poor connection that currently exists between the scientific community and the health sector in terms of resolving this health issue. Public policies for health research should support projects with findings that can be translated into benefits for the population. This review serves to identify national research groups studying gastric cancer in the Mexican population.

Key words: Gastric cancer; Mexico; Research; Prevention; Public health

Core tip: The few studies of gastric cancer in the Mexican population included in this review highlight the poor connection between the scientific community and the health sector in terms of resolving this health issue. Public policies for health research should support projects for the creation of gastric cancer research networks that include experts from different disciplines. These networks could generate, among other products, an official Mexican standard (Norma Oficial Mexicana) for gastric cancer as well as strategies for its prevention, control and treatment.

Sampieri CL, Mora M. Gastric cancer research in Mexico: A public health priority. World J Gastroenterol 2014; 20(16): 4491-4502 Available from: URL: http://www.wjgnet.com
INTRODUCTION

Mexico: A country of inequality

Mexico, according to the most recent data from the World Bank, had a gross domestic product of 1178 billion United States dollars in 2012; in 2011, 6.2% of its spending was invested in health, while 5.3% was spent on education in 2010 and 0.4% was allocated to science and technology in 2009[5]. It is considered a country of medium-high income, with a life expectancy at birth of 77 years[6]. In 2012, the population of Mexico was 120.8 million and it was estimated that 83% of the rural population had access to a water supply[6]. At the beginning of the 1970s, the number of births per year per 1000 individuals was greater than 7, but in 2009 it was 2.4[7]. In 2010, 6.5 million people were reported as vulnerable in terms of income and 46% of the population was considered to be in a situation of multidimensional poverty[6].

Cancer in Mexico

Cancer has been one of the most important diseases in Mexico since the end of the twentieth century, representing a public health problem, not only in terms of its grave clinical manifestations and high mortality, but also in the variety of individual and environmental risk factors with which it is associated[8]. In 2011, in populations of age 20 and over, the malignant tumors that caused the highest number of deaths in women were: breast (13.8%); cervical-uterine (10.4%); stomach (7.0%); liver-intrahepatic bile duct (6.4%); bronchopulmonary (5.5%); colon (4.5%); prostate (3.6%); and cervical-uterine (5.5%); stomach (4.3%), while in men these were: prostate (16.9%); bronchopulmonary (12.8%); stomach (8.6%); liver-intrahepatic bile duct (5.3%); and colon (5.3%)[2].

Despite the high mortality of cancer in Mexico, few studies have provided indicators, such as magnitude, transcendence and vulnerability, of utility to the planning of this public health problem. Of the studies that do exist, the foremost are: (1) Tovar-Guzmán et al[9] (1999), who report that during the period 1980 to 1995, the crude mortality rate of prostate cancer increased from 3.16 to 6.75 cases per 100000 men of age 40 years and over. The age-adjusted rate for the same period was 2.71 to 7.01 cases per 100000 men of age 40 years and over. The standardized mortality ratio (SMR) for the different states of Mexico showed a loose relationship among different regions, with high SMR values in the states of Baja California Sur at 183.28 (95%CI: 158.36-208.18), Jalisco at 161.81 (95%CI: 156.18-167.44) and Aguascalientes at 152.21 (95%CI: 136.115-168.27), while the lower SMR values corresponded to Quintana Roo at 47.87 (95%CI: 35.86-59.98), Guerrero at 57.69 (95%CI: 52.89-62.49) and Estado de Mexico at 59.91 (95%CI: 57.46-62.36)[5]; (2) Tovar-Guzmán et al[10] (2001), who report a general increase in the rate of gastric cancer mortality during the years 1980 to 1997, from 4.43 cases per 100000 habitants (95%CI: 4.27-4.59) in 1980, to 6.46 (95%CI: 6.28-6.64) cases in 1997[11]. Interestingly, these authors found a differential trend in mortality per gender, which probably reflected the regional socioeconomic conditions of the country[12]. Male:female ratio was 1.2:1.0. The SMR per state showed that the states with the highest rates were Yucatan at 149.96 (95%CI: 142.64-157.29), Sonora at 144.67 (95%CI: 138.55-150.80), Zacatecas at 135.95 (95%CI: 128.79-143.10) and Michoacan at 135.57 (95%CI: 131.03-139.71), while the states with the lowest SMR values were Quintana Roo at 36.02 (95%CI: 47.95-64.09); Estado de Mexico at 57.57 (95%CI: 56.05-59.10) and Guerrero at 73.64 (95%CI: 70.00-77.28). For females, the highest index of potential years of life lost (IPYLL) was found in Chiapas at 192.52 (95%CI: 189.3-195.7), Oaxaca at 155.48 (95%CI: 152.8-158.2) and Yucatan at 130.01 (95%CI: 126.6-133.4), while the lowest IPYLL was found in the states of Durango at 64.06 (95%CI: 61.6-66.5), Sinaloa at 69.11 (95%CI: 67.1-71.1) and Nuevo Leon at 71.00 (95%CI: 69.3-72.6)[5]. For males, the highest IPYLL was in Chiapas at 169.51 (95%CI: 166.8-172.2), Sonora at 159.02 (95%CI: 156.1-162.0) and Chihuahua at 125.74 (95%CI: 123.4-128.1), while the lowest IPYLL were in the states of Quintana Roo at 73.19 (95%CI: 68.7-71.7), Estado de Mexico at 77.05 (95%CI: 76.2-77.9) and Guerrero at 82.48 (95%CI: 80.6-84.4)[5]; and (3) Tovar-Guzmán et al[12] (2008), who state that over the period 1980 to 2004 cervical-uterine cancer had a crude mortality rate of 20.2 in 1980, 24.2 in 1989 and 14.4 in 2004 per 100000 women of age 25 years and over. The age-adjusted mortality rate was 12.8 in 1980, 15.6 in 1988 and 8.8 in 2004 per 100000 women of age 25 years and over. The highest SMR values were found in the states of Colima at 164.6 (95%CI: 153.3-175.8), Nayarit at 151.2 (95%CI: 143.4-159.0) and Yucatan at 150.6 (95%CI: 144.7-156.5), while the lowest values were detected in Estado de Mexico at 59.8 (95%CI: 58.6-61.0), Distrito Federal at 68.3 (95%CI: 66.9-69.7) and Nuevo Leon at 71.9 (95%CI: 69.2-74.6)[5]. The IPYLL due to cervical-uterine cancer during this period ranged from 168.8 (95%CI: 156.0-181.5) in Colima, 154.4 (95%CI: 146.9-161.9) in Tabasco and 149.9 (95%CI: 141.3-158.4) in Nayarit, to 61.6 (95%CI: 60.2-63.0) in Distrito Federal, 64.9 (95%CI: 63.5-66.3) in Estado de Mexico and 68.4 (95%CI: 65.5-66.3) in Nuevo Leon[5].

Gastric cancer in Mexico

In Mexico, despite the fact that gastric cancer represents the third highest cause of death by cancer in people of age 20 years or more[13], and is a disease that is subject to epidemiological surveillance[14], no specific program exists for its prevention, nor is there an official Mexican standard (Norma Oficial Mexicana) for its prevention, detection, treatment and control. An official clinical practice guide was only published in 2009 for the diagnosis and treatment of gastric adenocarcinoma in adult patients[15].

It is important to highlight that, in terms of biologi-
cal behavior and epidemiology, gastric cancers constitute a highly heterogeneous group of tumors, a fact that is likely to cause difficulty for the prediction of patient outcome using classifications. Perhaps the best-known classification for gastric cancer is the system of Lauren, which distinguishes two groups of tumors: intestinal and diffuse. The intestinal type typically presents cohesive neoplastic cells that form gland-like tubular structures, and a defined pattern of histological changes in healthy gastric mucosa[6]. In the diffuse type, there is no neoplastic cell cohesion, so cells infiltrate and thicken the stomach wall without the formation of a discrete mass[6]. The intestinal type is normally diagnosed in older people and its development depends on environmental factors[3]. In contrast, the diffuse type usually occurs in young people, and is associated with individual factors[7].

No specific histological type of gastric cancer predominates in Mexico, according to the Lauren classification[10], and gastric cancer exhibits different behavior in patients under 30 years of age. Nevertheless, delays in diagnosis and behavior of the tumor are the most important factors in prognosis[11].

Gastric cancer is one of the main causes of hospital morbidity in Mexican males; the highest rate is found in the population of 75-79 years of age (47 per 100000 males in this age group), followed by the population of 65 to 74 years of age (38 per 100000)[2]. The most recent data, produced by the now defunct Histopathological Register of Malignant Neoplasms (RHNMs, by its Spanish acronym), reported that gastric cancer constituted 3% of cancer cases diagnosed in Mexico during the year 2000, with three cases recorded per 100000 habitants[13]. The high mortality[13], low survival and the considerable deterioration in life quality of the people suffering this disease, mean that gastric cancer represents a public health problem in Mexico that requires research aimed at proposing health interventions. In theory, prevention strategies could be effective, given the following factors: (1) prolonged latency period during which intervention should be possible[14]; (2) infection with Helicobacter pylori (H. pylori), which commonly begins in infancy or early childhood and persists as a chronic gastritis, is a principal cause of gastric cancer[15]; while chronic infection with H. pylori is a major force behind the precancerous process, H. pylori eradication only produces a modest retardation of the precancerous process[16]; and (3) antioxidant micronutrients may play an etiological role[17]. While there have been no studies on the incidence of environmental and inherited gene defects in gastric cancer in Mexico, it is clear that potentially modifiable factors associated with the development of the disease can play an important role in its prevention. According to Anand et al[18], only 5%-10% of all cancers are caused by an inherited gene defect; although all cancers are a result of multiple mutations, these mutations are the result of interaction with the environment. In terms of population attributable risk in gastric cancer, a study conducted in Italy indicated that approximately 8% of stomach cancers could be related to this familial component[19]. Most cancers are not hereditary in origin and potentially modifiable factors, such the consumption of alcohol and tobacco, diet and infections, can have an important effect on their development[20].

Given the relevance of gastric cancer to public health in Mexico, this study aimed to review those studies that have been conducted on Mexican patients with a diagnosis of gastric cancer, and/or associated diseases, in which at least one Mexican institute has participated, and that have generated knowledge of utility to the primary and secondary prevention of the disease. In this context, it is important to highlight that the scientific, technological and commercial sectors in Mexico have been tasked with researching “Malignant neoplasms in Children and Adults” with the support of the Sectoral Fund for Research in Health and Social Security (Fondo Sectorial de Investigación en Salud y Seguridad Social, SSA/IMSS/ISSSTTE). This was done with the aim of reducing the morbidity, mortality and most prevalent complications among the susceptible population, as well as to improve the life quality of cancer patients and reduce the costs of their care[21]. The products expected from this priority line of research include effective strategies of prevention, procedures for early diagnosis, new schemes of treatment; strategies to reduce complications and mortality or improve life quality and proposals for molecular markers[18]. These research funds are administered by the National Council of Science and Technology (Consejo Nacional de Ciencia y Tecnología, CONACyT)[22]. The National Health Institutes, a group of twelve institutions belonging to the Ministry of Health (Secretaría de Salud) that conduct scientific research in the field of health, and specifically the National Cancerology Institute (Instituto Nacional de Cancerología, INCan), has the task of developing excellent medical care, teaching and oncological research in Mexico[23].

RESEARCH METHODS

Search strategy
The Medline database was searched on the 21st of August 2013, using the following combinations of key words: (1) gastric cancer, Mexico; and (2) stomach cancer, Mexico. English and Spanish language was selected as a limit. A total of 148 articles were obtained: 111 in English and 37 in Spanish.

Inclusion and exclusion criteria
The abstract of each article was carefully revised to verify the following criteria: (1) inclusion criteria: the study must have involved at least 10 Mexican gastric cancer patients, with associated pathologies or precursor lesions of gastric cancer, that were in Mexico at the time of the study; at least one of the authors of the study had to be an investigator in Mexico; (2) exclusion criteria: the study included only one case of gastric cancer, the study focused on a particular treatment; strategies to reduce complications and mortality or improve life quality and proposals for molecular markers; studies that have been conducted on Mexican patients with a diagnosis of gastric cancer, and/or associated diseases, in which at least one Mexican institute has participated, and that have generated knowledge of utility to the primary and secondary prevention of the disease. In this context, it is important to highlight that the scientific, technological and commercial sectors in Mexico have been tasked with researching “Malignant neoplasms in Children and Adults” with the support of the Sectoral Fund for Research in Health and Social Security (Fondo Sectorial de Investigación en Salud y Seguridad Social, SSA/IMSS/ISSSTTE). This was done with the aim of reducing the morbidity, mortality and most prevalent complications among the susceptible population, as well as to improve the life quality of cancer patients and reduce the costs of their care[21]. The products expected from this priority line of research include effective strategies of prevention, procedures for early diagnosis, new schemes of treatment; strategies to reduce complications and mortality or improve life quality and proposals for molecular markers[18]. These research funds are administered by the National Council of Science and Technology (Consejo Nacional de Ciencia y Tecnología, CONACyT)[22]. The National Health Institutes, a group of twelve institutions belonging to the Ministry of Health (Secretaría de Salud) that conduct scientific research in the field of health, and specifically the National Cancerology Institute (Instituto Nacional de Cancerología, INCan), has the task of developing excellent medical care, teaching and oncological research in Mexico[23].

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of the disease and secondary, detection of the disease at early stages, before presentation of symptoms; and (2) exclusion criteria: literature reviews; case studies; studies of tertiary prevention (considered as the reduction of incapacitation and restoration of patient functionality) of gastric cancer, diagnostic tests, treatment or detection in the environment of *H. pylori*; basic science *in vitro* or *in vivo* models in which the authors omitted recommendations for the primary or secondary prevention of gastric cancer; studies that did not specify the number of gastric cancer cases or patients with preneoplastic lesions; and studies of epidemiological description in a medical unit.

Applying these criteria, 100 studies were discarded and 48 were reviewed. A further 35 studies were incorporated into the introduction and conclusions sections of this review.

### GASTRIC CANCER RESEARCH IN MEXICO

While support exists in Mexico for research into strategies of prevention, diagnosis and control of cancer,[16] and gastric cancer is a public health problem because of its high mortality and high percentage of late-stage detection,[23,13,19], there are few studies that provide results to support the development of public policies directed to the prevention and control of this disease. The paucity of research into gastric cancer of any form is reflected in the fact that in the official clinical practice guide for diagnosis and treatment of gastric adenocarcinoma in adult patients[36], produced only five years ago by the Ministry of Health, only two of the 33 references correspond to studies conducted on Mexican patients and in Mexican institutes.

The trend of mortality in cancer, including gastric cancer, has remained relatively stable in Mexico for at least 40 years[7,13,11]. In this context, it is notable that of the total number of publications found in the Medline database with the key words stomach/gastric cancer and Mexico, 73% (108/148) were published after the year 2000. Publications from the 1970s and 1980s are practically non-existent.

Nonetheless, data generated by the National Institute of Statistics and Geography (Instituto Nacional de Estadística y Geografía, INEGI) has made a considerable contribution to understanding trends in gastric cancer mortality in Mexico. Epidemiological studies of gastric cancer are scarce in Mexico; to the best of our knowledge, only one study has presented indicators with which to prioritize public health problems since 2001[23]. Other studies analyzed hospital registers[20,21], a now defunct official database[22] or investigated the possible relationship between altitude and the risk of development of the disease[23], given that altitude has been reported as a factor associated with gastric cancer in other Latin American countries (Table 1).

The natural history of gastric cancer includes a long period of latency[14], the latency period for alcohol consumption for the development of gastric cancer has been estimated theoretically at 20 years[24], during which intervention is possible. Research into strategies for screening subjects that are or have been exposed to risk factors that increase the probability of developing gastric cancer is therefore of great importance. Among these risk factors, the potentially modifiable factors related to lifestyle (dietary habits, smoking, and alcohol consumption) present a great window of opportunity in terms of primary prevention of the disease.

The studies found in the Medline database relating to

### Table 1  Epidemiological studies of gastric cancer in Mexico

| Ref. | Year | Institute of adscription of corresponding author-city | Period of study | Main finding | Source |
|------|------|--------------------------------------------------------|----------------|-------------|--------|
| [23] | 2013 | IMSS Mexico City                                      | NA             | There is no association between altitude and the incidence and mortality of gastric cancer | Epidemiological observations |
| [20] | 2012 | UV Veracruz                                             | 2005-2009      | From a total of 1803 cases of digestive tract cancers, gastric cancer was the second most common, with 302 cases (16.76%) | Hospital registries from 5 institutions of Veracruz state |
| [22] | 2012 | INCan Mexico City                                      | 1993-2002      | From a total of 767464 cases of digestive system cancers, gastric cancer was the sixth most common with 27699 cases (4%): the third most common in males and seventh in females | Data-base of the histopathological register of malignant neoplasms in Mexico (RHNM) |
| [21] | 2003 | INCMNSZ Mexico City                                   | 1978-2001      | A total of 90% of the cases were diagnosed in people of age 41 years and more | Hospital registries from 6 institutions of Mexico City |
| [5]  | 2001 | INSP Cuernavaca, Morelos                               | 1980-1997      | Increase in adjusted mortality rate | INEGI |

*H. pylori: Helicobacter pylori; NA: Non applicable; IMSS: Mexican Institute of Social Security/Instituto Mexicano del Seguro Social; UV: University of Veracruz/Universidad Veracruzana; INCan: National Institute of Cancerology/Instituto Nacional de Cancerología; RHNM: Histopathological Register of Malignant Neoplasms/Registro Histopatológico de Neoplasias Malignas; INCMNSZ: National Institute of Medical Science and Nutrition Salvador Zubirán/Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; INSP: National Institute of Public Health/Instituto Nacional de Salud Pública; INEGI: National Institute of Statistics and Geography/Instituto Nacional de Estadística y Geografía.*
factors associated with the development of gastric cancer in the Mexican population have practically all been conducted in just two national institutions: the University of Veracruz (Universidad Veracruzana, UV)\(^\text{25}\) and the National Institute of Public Health (Instituto Nacional de Salud Pública, INSP). This latter institute has, on certain occasions, benefited from international collaboration\(^\text{26-33}\).

Among the factors associated with the development of gastric cancer in Mexico, those which stand out as presenting the highest risk are omission of breakfast\(^\text{25}\) and the high consumption of capsaicin\(^\text{25,26}\), saturated fat\(^\text{37}\), cholesterol\(^\text{38}\), and fresh\(^\text{39}\) and processed meat\(^\text{25,26}\). Factors that protect against the development of the disease are: high consumption of fruit\(^\text{25,26}\) and vegetables\(^\text{39}\) (Table 2).

Table 2

| Ref. | Year | Institute of adscription of corresponding author-city | Main finding | Quantity and type of groups studied |
|------|------|---------------------------------------------------------------|--------------|-------------------------------------|
| [25] | 2012 | UV Xalapa, Veracruz | Protective effect against gastric cancer: use of mouthwash, refrigeration of food and regular consumption of fruit and vegetables | 49 gastric cancer, 162 controls |
| [27] | 2012 | INSP Cuernavaca, Morelos | Risk of gastric cancer: omission of breakfast and failure to refrigerate food | 158 gastric cancer, 317 controls |
| [28] | 2009 | INSP Cuernavaca, Morelos | Protective effect against gastric cancer: higher intake of cinnamon acids, secoisolariciresinol and coumestrol | 257 gastric cancer, 478 controls |
| [29] | 2003 | INSP Cuernavaca, Morelos | Risk of gastric cancer: high consumption of capsaicin (90-250 mg of capsaicin per day, 9-25 jalapeno peppers per day), compared to low-level consumption (0-29.9 mg of capsaicin per day, 0-3 jalapeno peppers per day); this effect is independent of \(H. pylori\) status | 234 gastric cancer, 468 controls |
| [30] | 1999 | INSP Cuernavaca, Morelos | Protective effect against gastric cancer: intake of polyunsaturated fat, fiber and vitamin E, independent of the histological type of the tumor (intestinal or diffuse) | 220 gastric cancer, 752 controls |
| [26] | 1999 | NCI\(^\text{1}\) Bethesda, MD, United States | Risk of gastric cancer: consumption of saturated fat and cholesterol | 220 gastric cancer, 752 controls |
| [31] | 1998 | INSP Cuernavaca, Morelos | No association with risk of gastric cancer: consumption of foods prepared with corn, wheat or rice | 220 gastric cancer, 752 controls |
| [32] | 1998 | INSP Cuernavaca, Morelos | Risk of gastric cancer: wine consumption at least 10 glasses per month. No association with risk for gastric cancer: consumption of beer and distilled alcoholic beverages including brandy, rum and tequila | 220 gastric cancer, 752 controls |
| [33] | 1994 | INSP Cuernavaca, Morelos | Potential risk of gastric cancer: chili pepper consumption | 220 gastric cancer, 752 controls |

\(^\text{1}\)In collaboration with the INSP. \(H. pylori\): *Helicobacter pylori*; UV: University of Veracruz/Universidad Veracruzana; INSP: National Institute of Public Health/Instituto Nacional de Salud Pública; NCI: National Cancer Institute.

In 1984, Marshall and Warren discovered the etiological role of \(H. pylori\) in gastritis and peptic ulcers, for which they received the Nobel Prize in 2005\(^\text{40}\). Infection by \(H. pylori\) is mainly acquired in infancy via fecal-oral and oral-oral pathways, and it has been estimated that 50% of the world’s population could be infected with this bacterium, increasing to 80% of the population within some developing countries\(^\text{40}\).

\(H. pylori\) produces gastritis in almost all infected individuals, with a minority progressing towards chronic atrophic gastritis\(^\text{35}\). Gastritis is an inflammation of the gastric mucosa, which does not imply serious complications\(^\text{34}\); in contrast, chronic atrophic gastritis is characterized by a loss of the parietal and principal cells that drives a reduction in the secretion of pepsin and increases the risk of developing gastric cancer\(^\text{34}\).

The progression, severity and consequences of infection by \(H. pylori\) depend on an interaction of multiple factors. Those relating to the host include genetic background or physiological and immunological state. Factors relating to the bacteria include bacterial genomic plasticity, capacity for adaptation to the individual conditions of the host, modulation of the reaction to the host immune system response and production of various virulence factors, such as vacuolating cytotoxin and the cytotoxin-associated antigen A (CagA)\(^\text{40}\).

The study of the relationship between \(H. pylori\) and the development of gastric cancer is without doubt a complex process in Mexico, for many reasons: (1) the diversity of reported strains\(^\text{37,38}\); (2) association with modifiable factors\(^\text{39}\); (3) host effect in progression of the
Table 3: Studies of *Helicobacter pylori* in pathologies associated with the development of gastric cancer and gastric cancer in a Mexican population

| Ref. | Year | Institute of adscription of corresponding author-city | Main finding | Quantity and type of groups studied |
|------|------|------------------------------------------------------|--------------|------------------------------------|
| [39] | 2013 | ISSSTE | Association between alcohol consumption and *H. pylori* infection. | 269 *H. pylori* positive |
|      |      | Culiacan, Sinaloa | No relationship between *H. pylori* and smoking and coffee consumption | 269 *H. pylori* negative |
| [46] | 2013 | IMSS | Association between *H. pylori* and p53 expression and between p53 and intestinal metaplasia | 104 patients with no evidence of acute or clinically significant gastric pathology |
| [41] | 2013 | INSP | IgG2 response to CagA could be used as a novel serological marker to identify patients with *H. pylori*-associated gastric cancer | 46 intestinal metaplasia |
| [47] | 2013 | INSP | No association between CagA and gastric cancer | 41 gastric cancer |
|      |      | Cuernavaca, Morelos | 50 controls |
| [48] | 2012 | UNAM | Correlation of antibody subclass titers with Th1/Th2 markers may aid pathology characterization and diagnosis | 67 gastric cancer |
|      | Mexico City | 368 non atrophic gastritis |
| [49] | 2012 | IMSS | Failure to express cag19 and cag24 in *in vitro* in precancerous lesions might serve as a biomarker of the risk of development of gastric cancer | 14 gastric cancer |
| [50] | 2011 | INSP | Vac-A neutralizing antibodies might serve as a biomarker of the risk of development of gastric cancer and duodenal ulcer | 90 intestinal metaplasia |
|      | Cuernavaca, Morelos | 50 controls |
| [51] | 2009 | UNAM | Patients with chronic gastritis had a high incidence of infection by *H. pylori*; 44% of the *H. pylori* strains may be considered as highly virulent since they possessed two or three of the virulence markers analyzed: vacA s1 cagA b2a2 | 238 chronic gastritis |
|      | Tlalnepantla, Estado de Mexico | 11 gastric cancer |
| [50] | 2009 | IMSS | 30 genes are significantly associated with non-atrophic gastritis, duodenal ulcer, or gastric cancer and may serve as risk biomarkers | 10 non atrophic gastritis |
|      | Mexico City | 10 duodenal ulcer |
| [51] | 2008 | UNAM | *H. pylori* is uniformly distributed across the stomach in dyspepsia and has preference for fundus and corpus in gastric cancer. *H. pylori* genotype diversity across the systematic whole-organ and tumor is remarkable. | 16 gastric cancer |
|      | Mexico City | There is insufficient evidence to support the association of one isolate with a specific disease, due to the multistain nature of *H. pylori* | 14 dyspepsia |
| [38] | 2008 | INSP | *H. pylori* infection and CagA are risk markers for intestinal metaplasia. In gastric cancer, prevalence of these risk markers decreases, probably reflecting the fact that infection reduces when advanced atrophy and metaplasia develops | 368 non atrophic gastritis |
|      | Cuernavaca, Morelos | 126 precancerous lesions |
| [52] | 2004 | UANL | Absence of the HLA-DQA1*0503 allele could be a host risk factor for the development of gastric cancer. | 65 gastric cancer |
|      | Nuevo Leon, Mexico | 59 duodenal ulcer |
| [52] | 2004 | INSP | Infection with *H. pylori* CagA+, VacA+ strains represents a significant risk in terms of the development of gastric cancer | 22 gastric cancer *H. pylori* positive |
|      | Cuernavaca, Morelos | 8 high grade dysplasia *H. pylori* positive |
| [37] | 2004 | INSP | There is no association between nitrite and ascorbic consumption or interactions of these nutrients with seropositivity to *H. pylori* CagA+. Seropositivity to *H. pylori* CagA+ strains may be an independent factor in diffuse gastric cancer | 211 gastric cancer |
|      | Cuernavaca, Morelos | 454 controls |
| [38] | 2001 | SU | In regions with a high prevalence of chronic atrophic gastritis, serological screening with CagA alone is an effective test for identifying eligible subjects | 178 *H. pylori* positive |
|      | California, United States | 155 *H. pylori* CagA+ |
| [45] | 1997 | INSP | *H. pylori* infection present in 87.2% of cases and 82.5% of controls | 109 gastric cancer |
|      | Cuernavaca, Morelos | 177 controls |
| [44] | 1993 | INCan | In a high-risk population, precursor lesions for adenocarcinoma are universally associated with *H. pylori* infection | 245 symptomatic patients |

*In collaboration with INCan, UNAM Mexico City and the Colegio de la Frontera Sur, San Cristobal de las Casas, Chiapas. *H. pylori*: *Helicobacter pylori*; ISSSTE: Institute of Social Security and Services of State Employees; IMSS: Mexican Institute of Social Security; INSP: National Institute of Public Health; IMSS: National Institute of Health/Instituto Nacional de Salud Pública; EBV: Epstein-Barr virus; UANL: National Autonomous University of Mexico/Universidad Nacional Autónoma de México; SU: Stanford University; INCan: National Institute of Cancerology/Instituto Nacional de Cancerología.*
infection; (4) contrasting socioeconomic, sanitary and climatological conditions of the country, which could affect the presence of the bacterium in the environment; and (5) the differential occurrence of bacterial strains in diseases associated with the development of gastric cancer, precancerous lesions and gastric cancer. Of the studies selected according to the criteria used in this review, 16/48 (33%) focused on the relationship between H. pylori and the development of gastric cancer, and have made a considerable contribution towards the understanding of this complex phenomenon (Table 3).

Contributions made by studies conducted in Mexico that could support the design of strategies for the prevention and control of gastric cancer (Table 3) include the knowledge that, in regions with a high prevalence of chronic atrophic gastritis, serological screening with CagA is an effective test for identifying eligible subjects and, in high-risk populations, precursor lesions for gastric cancer are universally associated with H. pylori infection.

The role of the Epstein-Barr virus (EBV) in relation to the development of gastric cancer in Mexico has been little studied; however, pediatric patients co-infected with EBV and H. pylori produce more severe clinical charts and its incidence in gastric cancer is low (Table 4).

International studies have suggested certain molecules as markers in gastric cancer: some of these findings have been confirmed in Mexico, for example, adhesion molecules, such as E-cadherin; tumor suppressor genes, for example p53; extracellular matrix remodeling genes; matrix metalloproteinases (MMPs), such as MMP-9; inflammatory molecules, TNF and IL-8; cell growth factors and their receptors, such as human epidermal growth factor receptor 2; and enzymes that participate in the metabolism of the methyl groups, such as methylenetetrahydrofolate reductase (Table 5). However, most of these molecules have failed to become popular as prognostic tools in gastric cancer, probably because of limitations in their reliability, sensitivity and specificity. However, these are problems that could be solved by adopting methods to optimize reproducibility: avoiding sampling variability, increasing the sample size of tumors, extending the number of genes analyzed and creating partnership platforms to study multicenter trials, as well as following international recommendations in relation to the design and execution of studies.

**DISCUSSION**

As part of the Mexican Ministry of Health, the National Council for the Prevention and Treatment of Cancer in Infancy and Adolescence (Consejo Nacional para la Prevención y el Tratamiento del Cáncer en la Infancia y la Adolescencia) directs actions for the prevention of cancer in people below 18 years of age. However, a specific program for gastric cancer is required, based on national health indicators and featuring a consensus for the timely detection of the disease. Experience in countries with a high incidence of gastric cancer, such as China and Japan, has shown that mass screening of the asymptomatic population using endoscopy and actions of vigilance in higher risk subjects have been cost-effective strategies: they have been able to detect between 50% and 80% of cases in the early stages. Thus, individuals identified as being at highest risk can be monitored endoscopically to detect dysplasia and early cancer. In countries where the incidence of gastric cancer is not so high, for example the United States and Canada, mass screening with endoscopy is not recommended: analysis of cost-effectiveness shows no justification for the application these programs.

In Mexico, no studies have been conducted on the prevalence of gastric cancer in each stage of the disease. One retrospective cohort study conducted in the INCan in Mexico City in 2001 reported that, in a set of 834 patients with gastric cancer, only 21 (2.5%) were diagnosed in the early stages of the disease. It is important to clarify that these data relating to the incidence of early stage gastric cancer came from a reference hospital, for which reason they should not be taken to reflect the national trend. To elucidate trends in gastric cancer per stage in Mexico, implementation of a system of epidemiological vigilance is necessary at each different level of care. Data

**Table 4: Studies of the Epstein-Barr virus in pathologies associated with the development of gastric cancer and gastric cancer in a Mexican population**

| Ref. | Year | Institute of adscription of corresponding author-city | Main finding | Quantity and type of groups studied |
|------|------|-------------------------------------------------------|--------------|-----------------------------------|
| [54] | 2013 | IMSS Mexico City | Co-infection with EBV and H. pylori in pediatric patients is associated with severe gastritis | 333 pediatric patients with chronic abdominal pain |
| [56] | 2005 | INCan Mexico City | EBV was detected in 7.3% of cases, all pertaining to patients > 50 years of age. | 330 gastric cancer |
| [55] | 1999 | INCan Mexico City | EBV is detected in 8.15% cases, six occur in males and five in females | 135 gastric cancer |

*H. pylori: Helicobacter pylori; IMSS: Mexican Institute of Social Security/Instituto Mexicano del Seguro Social; INCan: National Institute of Cancerology/Instituto Nacional de Cancerología; EBV: Epstein-Barr virus.*
The -160 C/A polymorphism of E-cadherin has a direct effect on the risk of diffuse gastric cancer. HER2 amplification is restricted to intestinal gastric cancer. MMP9 expression is enhanced in gastric cancer compared to normal mucosa, and has potential as a molecular marker. Claudin 6, 7, and 9 expression is related to gastric carcinogenesis, and detection of these is a useful prognostic marker in intestinal and diffuse gastric cancer. HLA-DQ alleles may be conferring susceptibility for the development of gastric cancer compared to chronic gastritis and the healthy condition. The IL-8-251*A allele could be related to the development of gastric cancer. Carriers of the MTHFR 677 TT genotype with a low consumption of folate have a significantly increased risk of development of intestinal gastric cancer. There is an association of major histocompatibility complex HLA-DQA1*0601 and HLA-DQB1*0501 alleles in gastric cancer compared to chronic gastritis and the healthy condition. These HLA-DQ alleles may be conferring susceptibility for the development of gastric cancer. The IL-1B-31 promoter polymorphism is a useful marker for the risk of gastric cancer of corresponding risk compared to chronic gastritis and the healthy condition. There is an association of major histocompatibility complex HLA-DQA1*0601 and HLA-DQB1*0501 alleles in gastric cancer compared to chronic gastritis and the healthy condition. These HLA-DQ alleles may be conferring susceptibility for the development of gastric cancer.

Table 5: Studies of molecular markers for the development of gastric cancer and gastric cancer in a Mexican population

| Ref. | Year | Institute of adscription | Main finding | Quantity and type of groups studied |
|------|------|--------------------------|--------------|-----------------------------------|
| [67] | 2013 | UG Guadalajara, Jalisco  | EGFR-R521K and ERBB2-1655V polymorphisms are not suitable as markers for identifying individuals at risk of developing gastric cancer | 155 gastric cancer  121 controls  103 general population |
| [62] | 2013 | INCMSZ Mexico City  | HER2 amplification is restricted to intestinal gastric cancer. | 269 gastric cancer |
| [59] | 2010 | UV Xalapa, Veracruz  | MMF9 expression is enhanced in gastric cancer compared to normal mucosa, and has potential as a molecular marker. | 6 gastric cancer 11 superficial gastritis |
| [68] | 2010 | UANL Mexico City  | Claudin 6, 7, and 9 expression is related to gastric carcinogenesis, and detection of these is a useful prognostic marker in intestinal and diffuse gastric cancer. | 70 gastric cancer |
| [60] | 2010 | INSP Mexico City  | Polymorphisms in TNF and HSP70 have a severity dose-response as risk markers from preneoplastic lesions to gastric cancer, probably because of their association with an intense and sustained inflammatory response. | 228 non atrophic gastritis 98 intestinal metaplasia 63 gastric cancer 58 duodenal ulcer 132 controls 248 gastric cancer 478 controls |
| [63] | 2009 | INSP Cuernavaca, Morelos | In subjects with high consumption of folate, choline and vitamin B6, and 5,10-methylene nitrotrihydrofolate reductase (MTHFR) 677 TT genotype, there is a reduction in diffuse gastric risk compared to MTHFR 677 CC + CT carriers. | 51 gastric cancer 83 controls |
| [57] | 2007 | UANL Monterrey, Nuevo Leon | The -160 C/A polymorphism of E-cadherin has a direct effect on the risk of diffuse gastric cancer at a young age. | 39 gastric cancer younger than 45 years of age 78 controls |
| [61] | 2007 | UANL Monterrey, Nuevo Leon | The IL-8-251*A allele could be related to the development of gastric cancer. | 78 gastric cancer 259 controls |
| [70] | 2006 | INSP Cuernavaca, Morelos | High prevalence of MTHFR 677TT allele may be a contributor to the high rate of morbidity and mortality in gastric cancer. | 201 gastric cancer 427 controls 185 gastric cancer 377 controls |
| [71] | 2006 | LSU New Orleans, United States | Identification of the IL-1B-31 promoter polymorphism is a useful marker for the risk of intestinal type gastric cancer in subjects with CagA+ H. pylori infection. | 65 gastric cancer 182 controls |
| [58] | 2005 | NYU2 New York, United States | Carrying the Arg/Arg genotype in the codon 72 exon 4 of p53 is associated with risk of development of gastric cancer. | 63 gastric cancer 215 controls |
| [72] | 2005 | UANL Monterrey, Nuevo Leon | Carrying the proinflammatory IL-1B-31C allele is associated with increased risk of gastric cancer. | 20 gastric cancer 40 H. pylori-associated chronic gastritis 90 controls |
| [74] | 2003 | UANL Monterrey, Nuevo Leon | Carrying the pro-inflammatory IL-1B-31C allele is associated with an increased risk of gastric cancer and high-grade dysplasia. | 33 gastric cancer 8 high-grade dysplasia 25 controls |

1In collaboration with INSP; 2In collaboration with UANL. H. pylori: Helicobacter pylori; UG: University of Guadalajara/Universidad de Guadalajara; INCMSZ: National Institute of Medical Science and Nutrition Salvador Zubirán/Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; UV: University of Veracruz/Universidad Veracruzana; INAM: National Autonomous University of Mexico/Universidad Nacional Autónoma de México; IMSS: Mexican Institute of Social Security/Instituto Mexicano del Seguro Social; INSP: National Institute of Public Health/Instituto Nacional de Salud Pública; UANL: Autonomous University of Nuevo León/Universidad Autónoma de Nuevo León; LSU: Louisiana State University; NYU: New York University; INCan: National Institute of Cancerology/Instituto Nacional de Cancerología.

CagA is an effective test for identifying eligible subjects and that, in high-risk populations, precursor lesions for gastric cancer are universally associated with H. pylori infection. Moreover, the scientific evidence provided by randomized trials in China and Mexico shows that, from such a system would generate indicators permitting the design of programs of prevention and control. In terms of gastric cancer prevention in Mexico, it should be considered that, in regions of high-prevalence of chronic atrophic gastritis, serological screening with...
while curing *H. pylori* infection produces a modest deceleration of the precancerous process, it does not prove that eradication of *H. pylori* decreases cancer risk. Understanding the modifiable factors associated with gastric cancer in the local population is also of great importance in terms of prevention of the disease (Table 2).

One window of opportunity in Mexico could be conducting studies in which questionnaires are used to identify risk profiles in specific groups of the population. This could be done with the aim of monitoring more closely those people that have an elevated risk of developing gastric cancer. In this context, the Gaill model for breast cancer in the United States and the model of oral cancer risk factors in rural Sri Lanka indicate the utility of this type of strategy, because it allows the relatively simple and cost-effective identification of people with a high risk of developing cancer, who can then be subjected to special control.[82,83] In China, good results have been obtained from the combined application of a questionnaire regarding risk factors for colorectal cancer and an immunochromic fecal occult blood test to identify subjects at risk of suffering cancer.[84] In Mexico, a risk model for gastric cancer would be difficult to establish because of the wide variety of factors associated with its development and to the broad diversity of socio-cultural, climatological and dietary conditions that exist in the country. Another challenge would be the validation of such a model, because it implies a prolonged period of monitoring of a large cohort of subjects, who would have to submit to invasive study by endoscopy. The creation of research networks is necessary within Mexico, which should include the health sector and the academic community, to approach this health problem with a multidisciplinary focus and propose actions for its prevention and control within a national context.

The few studies of gastric cancer in the Mexican population included in this review reveal little or no linkage between the scientific community and the health sector to resolve this health problem. Public policies in health research should direct initiatives for the formation of research networks that include experts from different disciplines. Such networks could generate, among other academic products, an official Mexican standard (*Norma oficial Mexicana*) for the prevention, detection, treatment and control of gastric cancer. This review should serve as a guide to identify the national research groups interested in the study of gastric cancer in the Mexican population.

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P-Reviewers: Mewes PW, Singh SR S-Editor: Wen LL L-Editor: Stewart GJ E-Editor: Wang CH
