



WJG 20th Anniversary Special Issues (8): Gastric cancer

Gastric cancer research in Mexico: A public health priority

Clara Luz Sampieri, Mauricio Mora

Clara Luz Sampieri, Instituto de Salud Pública, Universidad Veracruzana, Av. Luis Castelazo Ayala, Col. Industrial Ánimas, 91190 Xalapa, Veracruz, México

Mauricio Mora, Facultad de Medicina, Universidad Veracruzana. Médicos y Odontólogos, Col. Virginia Cordero, 91120 Xalapa, Veracruz, México

Author contributions: Sampieri CL conceived and designed the study, performed the literature search and wrote the manuscript; Mora M co-wrote the manuscript; both authors have read and approved the final version to be published.

Supported by Consejo Nacional de Ciencia y Tecnología, No. CONACyT of Mexico; Research project approved for Clara Luz Sampieri, No. 86575

Correspondence to: Dr. Clara Luz Sampieri, Instituto de Salud Pública, Universidad Veracruzana. Av. Luis Castelazo Ayala, Col. Industrial Ánimas, 91190 Xalapa, Veracruz, México. csampieri@uv.mx

Telephone: +52-228-8418900 Fax: +52-228-8418935

Received: October 27, 2013 Revised: December 12, 2013

Accepted: January 8, 2014

Published online: April 28, 2014

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.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

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

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^[1]. It is considered a country of medium-high income, with a life expectancy at birth of 77 years^[1]. 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^[1]. 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^[2]. 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^[1].

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, 75.4 per 100000 habitants in 2011^[2], but also in the variety of individual and environmental risk factors with which it is associated^[3]. 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%); bronchopulmonary (6.4%); liver-intrahepatic bile duct (5.5%) and colon (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*^[4] (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)^[4]; (2) Tovar-Guzmán *et al*^[5] (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^[5]. Interestingly, these authors found a differential trend in mortality per gender, which probably reflected the regional socioeconomic conditions of the country^[5]. 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 56.02 (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*^[6] (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 10000 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)^[6]. 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^[6].

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^[2], and is a disease that is subject to epidemiological surveillance^[7], 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^[8].

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^[9]. 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^[9]. The intestinal type is normally diagnosed in older people and its development depends on environmental factors^[9]. In contrast, the diffuse type usually occurs in young people, and is associated with individual factors^[9]. 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 (RHNM, 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 inhabitants^[12].

The high mortality^[5,13], 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^[14]; 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^[14]; and (3) antioxidant micronutrients may play an etiological role^[14]. 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.*^[3], 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^[15]. Most cancers are not heredi-

tary in origin and potentially modifiable factors, such the consumption of alcohol and tobacco, diet and infections, can have an important effect on their development^[3].

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/ISSSTE). 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^[16]. 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^[16]. These research funds are administered by the National Council of Science and Technology (Consejo Nacional de Ciencia y Tecnología, CONACyT)^[17]. 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^[18].

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 ascribed to a Mexican institute; the studies had to have findings that could support the proposal of public policy directed towards the primary or secondary prevention of gastric cancer. The objectives of prevention were considered as follows: primary, avoiding the occurrence

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, 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 27659 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	From a total of 11276 cases of digestive system cancers, 3830 (34%) were of gastric cancer Increase in adjusted mortality rate Gender-based differential trend in the magnitude and prematurity of mortality	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 Zubiran/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.

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^[2,5,13,19], 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^[8], 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^[2,5,13]. 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^[5]. 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 2 Studies of risk and protection factors in gastric cancer in the Mexican population

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 Risk of gastric cancer: moderate to high capsaicin consumption synergistically in genetically susceptible individuals (IL-1B-31C allele carriers) infected with more virulent <i>H. pylori</i> (CagA positive) strains	158 gastric cancer 317 controls
[28]	2009	INSP Cuernavaca, Morelos	Protective effect against gastric cancer: higher intake of cinnamic acids, secoisolariciresinol and coumestrol. Main sources of these molecules: pears, mangos, beans, carrots, squash and legumes	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 <i>H. pylori</i> 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 ¹ Bethesda, MD, United States	Risk of gastric cancer: consumption of saturated fat and cholesterol Protective effect against gastric cancer: intake of yellow and orange vegetables.	220 gastric cancer 752 controls
[31]	1998	INSP Cuernavaca, Morelos	Risk of gastric cancer: consumption of fresh and processed meat, dairy products, fish and salty snacks 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

¹In 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.

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)^[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^[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^[25] and the high consumption of capsaicin^[27], saturated fat^[30], cholesterol^[30], and fresh^[26] and processed meat^[25,26]. Factors that protect against the development of the disease are: high consumption of fruit^[25,28] and vegetables^[28] (Table 2).

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^[34]. 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^[34].

H. pylori produces gastritis in almost all infected individuals, with a minority progressing towards chronic atrophic gastritis^[35]. Gastritis is an inflammation of the gastric mucosa, which does not imply serious complications^[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 peptic acid and increases the risk of developing gastric cancer^[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)^[36].

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^[37,38]; (2) association with modifiable factors^[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 Culiacan, Sinaloa	Association between alcohol consumption and <i>H. pylori</i> infection. No relationship between <i>H. pylori</i> and smoking and coffee consumption	269 <i>H. pylori</i> positive 269 <i>H. pylori</i> negative
[46]	2013	IMSS Mexico City	Association between <i>H. pylori</i> and p53 expression and between p53 and intestinal metaplasia	104 patients with no evidence of acute or clinically significant gastric pathology
[41]	2013	INSP Cuernavaca, Morelos	IgG2 response to CagA could be used as a novel serological marker to identify patients with <i>H. pylori</i> -associated gastric cancer	46 intestinal metaplasia 41 gastric cancer 50 controls
[47]	2013	INSP Cuernavaca, Morelos	No association between CagA and gastric cancer	67 gastric cancer 368 non atrophic gastritis 124 preneoplastic lesion
[48]	2012	UNAM Mexico City	Correlation of antibody subclass titers with Th1/Th2 markers may aid pathology characterization and diagnosis	14 gastric cancer 5 peptic ulcer 13 bleeding peptic ulcer 12 dyspepsia
[49]	2012	IMSS Mexico City	Failure to express <i>cag19</i> and <i>cag24</i> <i>in vivo</i> in precancerous lesions might serve as a biomarker of the risk of development of gastric cancer	11 gastric cancer 10 non atrophic gastritis 10 duodenal ulcer
[40]	2011	INSP Cuernavaca, Morelos	Vac-A neutralizing antibodies might serve as a biomarker of the risk of development of gastric cancer and duodenal ulcer	90 intestinal metaplasia 60 gastric cancer 52 duodenal ulcer 145 non atrophic gastritis
[43]	2009	UNAM Tlalnepantla, Estado de Mexico	Patients with chronic gastritis had a high incidence of infection by <i>H. pylori</i> ; 44% of the <i>H. pylori</i> strains may be considered as highly virulent since they possessed two or three of the virulence markers analyzed: <i>vacA s1 cagA babA2</i>	238 chronic gastritis
[50]	2009	IMSS Mexico City	30 genes are significantly associated with non-atrophic gastritis, duodenal ulcer, or gastric cancer and may serve as risk biomarkers	10 non atrophic gastritis 10 duodenal ulcer 9 gastric cancer
[51]	2008	UNAM Mexico City	<i>H. pylori</i> is uniformly distributed across the stomach in dyspepsia and has preference for fundus and corpus in gastric cancer. <i>H. pylori</i> genotype diversity across the systematic whole-organ and tumor is remarkable. There is insufficient evidence to support the association of one isolate with a specific disease, due to the multistrain nature of <i>H. pylori</i>	16 gastric cancer 14 dyspepsia
[38]	2008	INSP Cuernavaca, Morelos	<i>H. pylori</i> 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 126 precancerous lesions 65 gastric cancer 59 duodenal ulcer
[52]	2004	UANL Nuevo Leon, Nuevo Leon	Absence of the HLA-DQA1*0503 allele could be a host risk factor for the development of gastric cancer. Infection with <i>H. pylori</i> CagA ⁺ , VacA ⁺ strains represents a significant risk in terms of the development of gastric cancer	22 gastric cancer <i>H. pylori</i> positive 8 high grade dysplasia <i>H. pylori</i> positive 77 matched controls <i>H. pylori</i> positive
[37]	2004	INSP Cuernavaca, Morelos	There is no association between nitrite and ascorbic consumption or interactions of these nutrients with seropositivity to <i>H. pylori</i> CagA ⁺ . Seropositivity to <i>H. pylori</i> CagA ⁺ strains may be an independent factor in diffuse gastric cancer	211 gastric cancer 454 controls
[53]	2001	SU ¹ California, United States	In regions with a high prevalence of chronic atrophic gastritis, serological screening with CagA alone is an effective test for identifying eligible subjects	178 <i>H. pylori</i> positive 155 <i>H. pylori</i> CagA ⁺
[45]	1997	INSP Cuernavaca, Morelos	<i>H. pylori</i> infection present in 87.2% of cases and 82.5% of controls	109 gastric cancer 177 controls
[44]	1993	INCan Mexico City	In a high-risk population, precursor lesions for adenocarcinoma are universally associated with <i>H. pylori</i> infection	245 symptomatic patients

¹In 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/Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado; IMSS: Mexican Institute of Social Security/Instituto Mexicano del Seguro Social; INSP: National Institute of Public Health/Instituto Nacional de Salud Pública; EBV: Epstein-Barr virus; UNAM: National Autonomous University of Mexico/Universidad Nacional Autónoma de México; UANL: Autonomous University of Nuevo Leon/Universidad Autónoma de Nuevo León; SU: Stanford University; INCan: National Institute of Cancerology/Instituto Nacional de Cancerología.

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 <i>H. pylori</i> 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. Among Latin-American countries, Mexico has the lowest frequency of EBV associated gastric carcinoma	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.

infection^[40,41]; (4) contrasting socioeconomic, sanitary and climatological conditions of the country, which could affect the presence of the bacterium in the environment^[42]; and (5) the differential occurrence of bacterial strains in diseases associated with the development of gastric cancer^[43], precancerous lesions^[38,44] and gastric cancer^[38]. 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^[45] and, in high-risk populations, precursor lesions for gastric cancer are universally associated with *H. pylori* infection^[44].

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^[54] and its incidence in gastric cancer is low^[55,56] (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^[57]; tumor suppressor genes, for example p53^[58]; extracellular matrix remodeling genes; matrix metalloproteinases (MMPs), such as MMP-9^[59]; inflammatory molecules, TNF^[60] and IL-8^[61]; cell growth factors and their receptors, such as human epidermal growth factor receptor 2^[62]; and enzymes that participate in the metabolism of the methyl groups, such as methylenetetrahydrofolate reductase^[63] (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^[64], as well as following international recommendations in relation to the design and execution of studies^[65,66].

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^[75]. 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^[76]. Thus, individuals identified as being at highest risk can be monitored endoscopically to detect dysplasia and early cancer^[14]. 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^[76].

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^[77]. 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 5 Studies of molecular markers for 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
[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	HER2 amplification is suitable as a marker for screening gastric cancer histotype <i>MMP9</i> 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	UNAM 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	IMSS 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
[63]	2009	INSP Cuernavaca, Morelos	In subjects with high consumption of folate, choline and vitamin B6, and 5,10-methyle netetrahydrofolate reductase (MTHFR) 677 TT genotype, there is a reduction in diffuse gastric risk compared to MTHFR 677 CC + CT carriers. In subjects with low consumption of methionine and MTHFR 677 TT genotype, there is a reduced risk of diffuse gastric cancer compared to MTHFR 677 CC + CT carriers. Carriers of the MTHFR 677 TT genotype with a low consumption of folate have a significantly increased risk of development of intestinal gastric cancer	248 gastric cancer 478 controls
[69]	2007	UANL Monterrey, Nuevo Leon	There is no association between the MTHFR C677T polymorphism and development of gastric cancer	51 gastric cancer 83 controls
[57]	2007	INCMSZ Mexico City	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 677T allele may be a contributor to the high rate of morbidity and mortality in gastric cancer	201 gastric cancer 427 controls
[71]	2006	LSU ¹ 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 ⁺ <i>H. pylori</i> infection	183 gastric cancer 377 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	65 gastric cancer 182 controls
[72]	2005	UANL Monterrey, Nuevo Leon	Carrying the proinflammatory IL-1B-31*C allele is associated with increased risk of gastric cancer	63 gastric cancer 215 controls
[73]	2004	INCan Mexico City	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	20 gastric cancer 40 <i>H. pylori</i> -associated chronic gastritis 90 controls
[74]	2003	UANL Monterrey, Nuevo Leon	Carrying the pro-inflammatory IL-1B-31*C 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; INCMNSZ: National Institute of Medical Science and Nutrition Salvador Zubiran/Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán; UV: University of Veracruz/Universidad Veracruzana; UNAM: 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 Leon/Universidad Autónoma de Nuevo León; LSU: Louisiana State University; NYU: New York University; INCan: National Institute of Cancerology/Instituto Nacional de Cancerología.

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

CagA is an effective test for identifying eligible subjects^[45] and that, in high-risk populations, precursor lesions for gastric cancer are universally associated with *H. pylori* infection^[44]. Moreover, the scientific evidence provided by randomized trials in China^[78] and Mexico^[79] shows that,

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^[14]. 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 Gail model for breast cancer in the United States^[80] and the model of oral cancer risk factors in rural Sri Lanka^[81] 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^[80,81]. In China, good results have been obtained from the combined application of a questionnaire regarding risk factors for colorectal cancer and an immunochemical fecal occult blood test to identify subjects at risk of suffering cancer^[82]. 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.

REFERENCES

- 1 Banco Mundial. [cited 2013 Oct 18]. Available from: URL: <http://datos.bancomundial.org/pais/mexico>
- 2 Instituto Nacional de Estadística y Geografía. Comunicado de prensa. 2013 [cited 2013 Oct 18]. Available from: URL: <http://www.inegi.org.mx/inegi/contenidos/espanol/prensa/aPropositom.asp?s=inegi&c=2859&ep=113>
- 3 Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res* 2008; **25**: 2097-2116 [PMID: 18626751 DOI: 10.1007/s11095-008-9661-9]
- 4 Tovar-Guzmán V, Hernández-Girón C, López-Ríos O, Lazcano-Ponce EC. Prostate cancer mortality trends in Mexico, 1980-1995. *Prostate* 1999; **39**: 23-27 [PMID: 10221262]
- 5 Tovar-Guzmán V, Hernández-Girón C, Barquera S, Rodríguez-Salgado N, López-Carrillo L. Epidemiologic panorama of stomach cancer mortality in Mexico. *Arch Med Res* 2001; **32**: 312-317 [PMID: 11440790]
- 6 Tovar-Guzmán V, Ortiz F, Jiménez F, Valencia G. Panorama epidemiológico de la mortalidad por cáncer cervicouterino en México (1980-2004). *Rev Fac Med UNAM* 2008; **51**: 47-51
- 7 Diario Oficial de la Federación. Norma Oficial Mexicana. [cited 2013 Oct 18]. Available from: URL: http://dof.gob.mx/nota_detalle.php?codigo=5288225&fecha=19/02/2013
- 8 Secretaría de Salud. Guía de práctica clínica. [cited 2013 Oct 18]. Available from: URL: http://www.cenetec.salud.gob.mx/descargas/gpc/CatalogoMaestro/167_GPC_CA_GASTRICO/Gpc_cancergastrico.pdf
- 9 Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675]
- 10 López-Carrillo L, Vega-Ramos B, Costa-Dias R, Rascón-Pacheco RA. Histological types of gastric cancer in Mexico. *Int J Epidemiol* 1997; **26**: 1166-1171 [PMID: 9447395]
- 11 López-Basave HN, Morales-Vásquez F, Ruiz-Molina JM, Namendys-Silva SA, Vela-Sarmiento I, Ruan JM, Rosciano AE, Calderillo-Ruiz G, Díaz-Romero C, Herrera-Gómez A, Meneses-García AA. Gastric cancer in young people under 30 years of age: worse prognosis, or delay in diagnosis? *Cancer Manag Res* 2013; **5**: 31-36 [PMID: 23580357 DOI: 10.2147/CMAR.S40377]
- 12 Registro Histopatológico de Neoplasias Malignas en México 2001. Secretaría de Salud (México), Dirección General de Epidemiología (DGEPI). [cited 2009 Sep 25]. Available from: URL: <http://www.dgepi.salud.gob.mx/divent/RHNM>.
- 13 Instituto Nacional de Estadística y Geografía. Comunicado de prensa. 2010 [cited 2013 Oct 18]. Available from: URL: <http://www.inegi.org.mx/inegi/contenidos/espanol/prensa/aPropositom.asp?s=inegi&c=2750&ep=27>
- 14 Correa P. Is gastric cancer preventable? *Gut* 2004; **53**: 1217-1219 [PMID: 15306570]
- 15 La Vecchia C, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. *Cancer* 1992; **70**: 50-55 [PMID: 1606546]
- 16 Consejo Nacional de Ciencia y Tecnología. Fondos y Apoyos. [cited 2013 Oct 18] Available from: URL: http://www.conacyt.gob.mx/FondosyApoyos/Sectoriales/InvestigacionBasicaAplicada/SSA/Documents/FOSISS_DEMANDAS_2013.pdf
- 17 Consejo Nacional de Ciencia y Tecnología. Página de inicio. [cited 2013 Oct 18]. Available from: URL: <http://www.conacyt.gob.mx/Paginas/InicioNueva.aspx>
- 18 Instituto Nacional de Cancerología. [cited 2013 Oct 18]. Available from: URL: <http://incan-mexico.org/incan/incan.jsp>
- 19 De Nicola L, Flores-Rodríguez J, Zamora-Varaona J. Tratamiento nutricional del paciente con cáncer gástrico. *Cancerología* 2007; **2**: 337-44
- 20 Roesch-Dietlen F, Jiménez-García VA, Remes-Troche JM, Rubio-Arce JF, López-Salinas A, Ruiz-Juárez I, Grube-Pagola P, Silva-Cañetas CF. [Epidemiologic behavior of malignant digestive tract tumors over a five year period in Veracruz, Mexico]. *Rev Gastroenterol Mex* 2012; **77**: 3-8 [PMID: 22450014]
- 21 González Trujillo JL, Vargas F, Torres Villalobos G, Milke P, Villalobos Pérez Jde J. [Variations in a 24-year period of colorectal and gastric cancer in Mexico]. *Rev Gastroenterol Mex* 2003; **68**: 120-125 [PMID: 15127648]
- 22 Meneses-García A, Ruiz-Godoy LM, Beltrán-Ortega A, Sánchez-Cervantes F, Tapia-Conyer R, Mohar A. [Main malignant neoplasms in Mexico and their geographic distribution]

- bution, 1993-2002]. *Rev Invest Clin* 2003; **64**: 322-329 [PMID: 23227582]
- 23 **Torres J**, Correa P, Ferreccio C, Hernandez-Suarez G, Herrera R, Cavazza-Porro M, Dominguez R, Morgan D. Gastric cancer incidence and mortality is associated with altitude in the mountainous regions of Pacific Latin America. *Cancer Causes Control* 2013; **24**: 249-256 [PMID: 23224271 DOI: 10.1007/s10552-012-0114-8]
 - 24 **Hu JF**. Estimation of cancer latency using data from a case-control study with time-related factors--estimated latency for consumption of alcohol and tobacco in relation to gastric cancer. *Zhonghua Zhong Liu Zazhi* 1992; **14**: 119-122 [PMID: 1618079]
 - 25 **Verdalet-Olmedo M**, Sampieri CL, Morales-Romero J, Montero-L de Guevara H, Machorro-Castaño AM, León-Córdoba K. Omission of breakfast and risk of gastric cancer in Mexico. *World J Gastrointest Oncol* 2012; **4**: 223-229 [PMID: 23444276 DOI: 10.4251/wjgo.v4.i11.223]
 - 26 **Ward MH**, López-Carrillo L. Dietary factors and the risk of gastric cancer in Mexico City. *Am J Epidemiol* 1999; **149**: 925-932 [PMID: 10342801]
 - 27 **López-Carrillo L**, Camargo MC, Schneider BG, Sicinski LA, Hernández-Ramírez RU, Correa P, Cebrian ME. Capsaicin consumption, Helicobacter pylori CagA status and IL1B-31C& gt; T genotypes: a host and environment interaction in gastric cancer. *Food Chem Toxicol* 2012; **50**: 2118-2122 [PMID: 22414649 DOI: 10.1016/j.fct.2012.02.043]
 - 28 **Hernández-Ramírez RU**, Galván-Portillo MV, Ward MH, Agudo A, González CA, Orate-Ocaña LF, Herrera-Goepfert R, Palma-Coca O, López-Carrillo L. Dietary intake of polyphenols, nitrate and nitrite and gastric cancer risk in Mexico City. *Int J Cancer* 2009; **125**: 1424-1430 [PMID: 19449378 DOI: 10.1002/ijc.24454]
 - 29 **López-Carrillo L**, López-Cervantes M, Robles-Díaz G, Ramírez-Espitia A, Mohar-Betancourt A, Meneses-García A, López-Vidal Y, Blair A. Capsaicin consumption, Helicobacter pylori positivity and gastric cancer in Mexico. *Int J Cancer* 2003; **106**: 277-282 [PMID: 12800206]
 - 30 **López-Carrillo L**, López-Cervantes M, Ward MH, Bravo-Alvarado J, Ramírez-Espitia A. Nutrient intake and gastric cancer in Mexico. *Int J Cancer* 1999; **83**: 601-605 [PMID: 10521793]
 - 31 **Rascón Pacheco RA**, López Carrillo L. Consumption of foods prepared with corn, wheat and rice and its relationship to gastric cancer incidence in Mexico. *Arch Latinoam Nutr* 1998; **48**: 221-224 [PMID: 9951534]
 - 32 **López-Carrillo L**, López-Cervantes M, Ramírez-Espitia A, Rueda C, Fernández-Ortega C, Orozco-Rivadeneira S. Alcohol consumption and gastric cancer in Mexico. *Cad Saude Publica* 1998; **14** Suppl 3: 25-32 [PMID: 9819462]
 - 33 **López-Carrillo L**, Hernández Avila M, Dubrow R. Chili pepper consumption and gastric cancer in Mexico: a case-control study. *Am J Epidemiol* 1994; **139**: 263-271 [PMID: 8116601]
 - 34 **Bartnik W**. Clinical aspects of Helicobacter pylori infection. *Pol Arch Med Wewn* 2008; **118**: 426-430 [PMID: 18714738]
 - 35 **Oh JD**, Kling-Bäckhed H, Giannakis M, Xu J, Fulton RS, Fulton LA, Cordum HS, Wang C, Elliott G, Edwards J, Mardis ER, Engstrand LG, Gordon JI. The complete genome sequence of a chronic atrophic gastritis Helicobacter pylori strain: evolution during disease progression. *Proc Natl Acad Sci USA* 2006; **103**: 9999-10004 [PMID: 16788065]
 - 36 **Hatakeyama M**, Higashi H. Helicobacter pylori CagA: a new paradigm for bacterial carcinogenesis. *Cancer Sci* 2005; **96**: 835-843 [PMID: 16367902]
 - 37 **López-Carrillo L**, Torres-López J, Galván-Portillo M, Muñoz L, López-Cervantes M. Helicobacter pylori-CagA seropositivity and nitrite and ascorbic acid food intake as predictors for gastric cancer. *Eur J Cancer* 2004; **40**: 1752-1759 [PMID: 15251166]
 - 38 **Camorlinga-Ponce M**, Flores-Luna L, Lazcano-Ponce E, Herrera R, Bernal-Sahagún F, Abdo-Francis JM, Aguirre-García J, Muñoz N, Torres J. Age and severity of mucosal lesions influence the performance of serologic markers in Helicobacter pylori-associated gastroduodenal pathologies. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 2498-2504 [PMID: 18768521 DOI: 10.1158/1055-9965.EPI-08-0289]
 - 39 **Sánchez-Cuén JA**, Cabrales AB, Magaña GB, Garay FJ. Helicobacter pylori infection and its association with alcohol consumption: a case-control study. *Rev Gastroenterol Mex* 2013; **78**: 144-150 [PMID: 23932770 DOI: 10.1016/j.rgmx.2013.06.003]
 - 40 **Ayala G**, Flores-Luna L, Hernández-Amaro D, Mendoza-Hernández G, Chihu-Amparán L, Bernal-Sahagún F, Camorlinga M, Lazcano-Ponce E, Torres J. Association of circulating VacA-neutralizing antibodies with gastric cancer and duodenal ulcer. *Cancer Causes Control* 2011; **22**: 1425-1434 [PMID: 21779758 DOI: 10.1007/s10552-011-9817-5]
 - 41 **de la Cruz-Herrera CF**, Flores-Luna L, Gutierrez-Xicotencatl L, Chihu-Amparan L, Sánchez-Aleman MA, Lazcano-Ponce E, Torres J, Ayala G. IgG2 response and low IgG titre specific to Helicobacter pylori CagA as serological markers for gastric cancer. *J Med Microbiol* 2013; **62**: 591-598 [PMID: 23288428 DOI: 10.1099/jmm.0.050567-0]
 - 42 **Fernandez-Eguiarte A**, Zavala-Hidalgo J, Romero-Centeno R. Atlas Climático Digital de México. 2009 [cited 2009 Sep 25]. Available from: URL: <http://www.atmosfera.unam.mx/uniatmos/atlas/>
 - 43 **Paniagua GL**, Monroy E, Rodríguez R, Arroniz S, Rodríguez C, Cortés JL, Camacho A, Negrete E, Vaca S. Frequency of vacA, cagA and babA2 virulence markers in Helicobacter pylori strains isolated from Mexican patients with chronic gastritis. *Ann Clin Microbiol Antimicrob* 2009; **8**: 14 [PMID: 19405980 DOI: 10.1186/1476-0711-8-14]
 - 44 **Guarner J**, Mohar A, Parsonnet J, Halperin D. The association of Helicobacter pylori with gastric cancer and preneoplastic gastric lesions in Chiapas, Mexico. *Cancer* 1993; **71**: 297-301 [PMID: 8422620]
 - 45 **López Carrillo L**, Fernández Ortega C, Robles Díaz G, Rascón Pacheco RA, Ramírez Iglesias T. Helicobacter pylori infection and gastric cancer in Mexico. A challenge for prevention and population control. *Rev Gastroenterol Mex* 1997; **62**: 22-28 [PMID: 9190649]
 - 46 **Morales-Fuentes GA**, Zarate-Osorno A, Quiñónez-Urrego EE, Antonio-Manrique M, Martínez-García CL, Figueroa-Barojas P, Zamorano-Orozco Y, Leal-Osuna SE, Martínez-Camacho C, Mejía-Cuán LA, Rivera-Nava CA, Sánchez-Chávez X, Ramírez-Ramírez MA. [p53 expression in the gastric mucosa of patients infected with Helicobacter pylori]. *Rev Gastroenterol Mex* 2013; **78**: 12-20 [PMID: 23374541 DOI: 10.1016/j.rgmx.2012.11.001]
 - 47 **Flores-Luna L**, Camorlinga-Ponce M, Hernandez-Suarez G, Kasamatsu E, Martínez ME, Murillo R, Lazcano E, Torres J. The utility of serologic tests as biomarkers for Helicobacter pylori-associated precancerous lesions and gastric cancer varies between Latin American countries. *Cancer Causes Control* 2013; **24**: 241-248 [PMID: 23184121 DOI: 10.1007/s10552-012-0106-8]
 - 48 **Martínez-Becerra F**, Castillo-Rojas G, Ponce de León S, López-Vidal Y. IgG subclasses against Helicobacter pylori isolates: an important tool for disease characterization. *Scand J Immunol* 2012; **76**: 26-32 [PMID: 22686508 DOI: 10.1111/j.1365-3083.2012.02699.x]
 - 49 **Avilés-Jiménez F**, Reyes-Leon A, Nieto-Patlán E, Hansen LM, Burgueño J, Ramos IP, Camorlinga-Ponce M, Bermúdez H, Blancas JM, Cabrera L, Ribas-Aparicio RM, Solnick JV, Torres-López J. In vivo expression of Helicobacter pylori virulence genes in patients with gastritis, ulcer, and gastric cancer. *Infect Immun* 2012; **80**: 594-601 [PMID: 22124657 DOI: IAI.05845-11]
 - 50 **Romo-González C**, Salama NR, Burgeño-Ferreira J, Ponce-Castañeda V, Lazcano-Ponce E, Camorlinga-Ponce M, Torres

- J. Differences in genome content among *Helicobacter pylori* isolates from patients with gastritis, duodenal ulcer, or gastric cancer reveal novel disease-associated genes. *Infect Immun* 2009; **77**: 2201-2211 [PMID: 19237517 DOI: IAI.01284-08]
- 51 **López-Vidal Y**, Ponce-de-León S, Castillo-Rojas G, Barreto-Zúñiga R, Torre-Delgado A. High diversity of *vacA* and *cagA* *Helicobacter pylori* genotypes in patients with and without gastric cancer. *PLoS One* 2008; **3**: e3849 [PMID: 19050763 DOI: 10.1371/journal.pone.0003849]
- 52 **Garza-González E**, Bosques-Padilla FJ, Pérez-Pérez GI, Flores-Gutiérrez JP, Tijerina-Menchaca R. Association of gastric cancer, HLA-DQA1, and infection with *Helicobacter pylori* CagA+ and VacA+ in a Mexican population. *J Gastroenterol* 2004; **39**: 1138-1142 [PMID: 15622476]
- 53 **Ley C**, Mohar A, Guarner J, Herrera-Goepfert R, Figueroa LS, Halperin D, Parsonnet J. Screening markers for chronic atrophic gastritis in Chiapas, Mexico. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 107-112 [PMID: 11219766]
- 54 **Cárdenas-Mondragón MG**, Carreón-Talavera R, Camorlinga-Ponce M, Gomez-Delgado A, Torres J, Fuentes-Pananá EM. Epstein Barr virus and *Helicobacter pylori* co-infection are positively associated with severe gastritis in pediatric patients. *PLoS One* 2013; **8**: e62850 [PMID: 23638154 DOI: 10.1371/journal.pone.0062850]
- 55 **Herrera-Goepfert R**, Reyes E, Hernández-Avila M, Mohar A, Shinkura R, Fujiyama C, Akiba S, Eizuru Y, Harada Y, Tokunaga M. Epstein-Barr virus-associated gastric carcinoma in Mexico: analysis of 135 consecutive gastrectomies in two hospitals. *Mod Pathol* 1999; **12**: 873-878 [PMID: 10496595]
- 56 **Herrera-Goepfert R**, Akiba S, Koriyama C, Ding S, Reyes E, Itoh T, Minakami Y, Eizuru Y. Epstein-Barr virus-associated gastric carcinoma: Evidence of age-dependence among a Mexican population. *World J Gastroenterol* 2005; **11**: 6096-6103 [PMID: 16273633]
- 57 **Medina-Franco H**, Ramos-De la Medina A, Vizcaino G, Medina-Franco JL. Single nucleotide polymorphisms in the promoter region of the E-cadherin gene in gastric cancer: case-control study in a young Mexican population. *Ann Surg Oncol* 2007; **14**: 2246-2249 [PMID: 17549573]
- 58 **Pérez-Pérez GI**, Bosques-Padilla FJ, Crosatti ML, Tijerina-Menchaca R, Garza-González E. Role of p53 codon 72 polymorphism in the risk of development of distal gastric cancer. *Scand J Gastroenterol* 2005; **40**: 56-60 [PMID: 15841715]
- 59 **Sampieri CL**, de la Peña S, Ochoa-Lara M, Zenteno-Cuevas R, León-Córdoba K. Expression of matrix metalloproteinases 2 and 9 in human gastric cancer and superficial gastritis. *World J Gastroenterol* 2010; **16**: 1500-1505 [PMID: 20333791]
- 60 **Partida-Rodríguez O**, Torres J, Flores-Luna L, Camorlinga M, Nieves-Ramírez M, Lazcano E, Perez-Rodríguez M. Polymorphisms in TNF and HSP-70 show a significant association with gastric cancer and duodenal ulcer. *Int J Cancer* 2010; **126**: 1861-1868 [PMID: 19626584 DOI: 10.1002/ijc.24773]
- 61 **Garza-Gonzalez E**, Bosques-Padilla FJ, Mendoza-Ibarra SI, Flores-Gutierrez JP, Maldonado-Garza HJ, Perez-Perez GI. Assessment of the toll-like receptor 4 Asp299Gly, Thr399Ile and interleukin-8 -251 polymorphisms in the risk for the development of distal gastric cancer. *BMC Cancer* 2007; **7**: 70 [PMID: 17462092]
- 62 **Cruz-Reyes C**, Gamboa-Dominguez A. HER2 amplification in gastric cancer is a rare event restricted to the intestinal phenotype. *Int J Surg Pathol* 2013; **21**: 240-246 [PMID: 23564704 DOI: 10.1177/1066896913481055]
- 63 **Galván-Portillo MV**, Cantoral A, Oñate-Ocaña LF, Chen J, Herrera-Goepfert R, Torres-Sanchez L, Hernandez-Ramirez RU, Palma-Coca O, López-Carrillo L. Gastric cancer in relation to the intake of nutrients involved in one-carbon metabolism among MTHFR 677 TT carriers. *Eur J Nutr* 2009; **48**: 269-276 [PMID: 19288150 DOI: 10.1007/s00394-009-0010-5]
- 64 **Sampieri CL**, León-Córdoba K, Remes-Troche JM. Matrix metalloproteinases and their tissue inhibitors in gastric cancer as molecular markers. *J Cancer Res Ther* 2013; **9**: 356-363 [PMID: 24125966 DOI: 10.4103/0973-1482.119302]
- 65 **Altman DG**, McShane LM, Sauerbrei W, Taube SE. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration. *PLoS Med* 2012; **9**: e1001216 [PMID: 22675273 DOI: 10.1371/journal.pmed.1001216]
- 66 **Moore HM**, Kelly AB, Jewell SD, McShane LM, Clark DP, Greenspan R, Hayes DF, Hainaut P, Kim P, Mansfield E, Potapova O, Riegman P, Rubinstein Y, Seijo E, Somiari S, Watson P, Weier HU, Zhu C, Vaught J. Biospecimen reporting for improved study quality (BRISQ). *J Proteome Res* 2011; **10**: 3429-3438 [PMID: 21574648 DOI: 10.1021/pr200021n]
- 67 **Torres-Jasso JH**, Bustos-Carpinteyro AR, Marín ME, Santiago E, Leoner C, Flores-Luna L, Torres J, Sánchez-Lopez JY. Analysis of the polymorphisms EGFR-r521K and ERBB2-1655V in Mexican patients with gastric cancer and premalignant gastric lesions. *Rev Invest Clin* 2013; **65**: 150-155 [PMID: 23844533]
- 68 **Rendón-Huerta E**, Teresa F, Teresa GM, Xochitl GS, Georgina AF, Veronica ZZ, Montañó LF. Distribution and expression pattern of claudins 6, 7, and 9 in diffuse- and intestinal-type gastric adenocarcinomas. *J Gastrointest Cancer* 2010; **41**: 52-59 [PMID: 19960275 DOI: 10.1007/s12029-009-9110-y]
- 69 **Zúñiga-Noriega JR**, Velasco-Campos Mdel R, Aguirre-Rodríguez A, Villarreal LM, Garza-González E, Maldonado-Garza HJ, Bosques-Padilla FJ. [C677T polymorphism of the MTHFR gene and the risk of developing distal gastric cancer in a Mexican population]. *Rev Gastroenterol Mex* 2007; **72**: 355-358 [PMID: 18595323]
- 70 **Lacasaña-Navarro M**, Galván-Portillo M, Chen J, López-Cervantes M, López-Carrillo L. Methylenetetrahydrofolate reductase 677C > T polymorphism and gastric cancer susceptibility in Mexico. *Eur J Cancer* 2006; **42**: 528-533 [PMID: 16359859 DOI: 10.1016/j.ejca.2005.10.020]
- 71 **Sicinschi LA**, Lopez-Carrillo L, Camargo MC, Correa P, Sierra RA, Henry RR, Chen J, Zabaleta J, Piazuelo MB, Schneider BG. Gastric cancer risk in a Mexican population: role of *Helicobacter pylori* CagA positive infection and polymorphisms in interleukin-1 and -10 genes. *Int J Cancer* 2006; **118**: 649-657 [PMID: 16114018 DOI: 10.1002/ijc.21364]
- 72 **Garza-González E**, Bosques-Padilla FJ, El-Omar E, Hold G, Tijerina-Menchaca R, Maldonado-Garza HJ, Pérez-Pérez GI. Role of the polymorphic IL-1B, IL-1RN and TNF-A genes in distal gastric cancer in Mexico. *Int J Cancer* 2005; **114**: 237-241 [PMID: 15540224 DOI: 10.1002/ijc.20718]
- 73 **Herrera-Goepfert R**, Zúñiga J, Hernández-Guerrero A, Rodríguez-Reyna T, Osnalla N, Ruiz-Morales J, Vargas-Alarcón G, Yamamoto-Furusho JK, Mohar-Betancourt A, Hernández-Pando R, Granados J. [Association of the HLA-DQB*0501, allele of the major histocompatibility complex with gastric cancer in Mexico]. *Gac Med Mex* 2004; **140**: 299-303 [PMID: 15259342]
- 74 **Garza-González E**, Hold G, Pérez-Pérez GI, Bosques-Padilla FJ, Tijerina-Menchaca R, Maldonado-Garza HJ, el-Omar E. [Role of polymorphism of certain cytokines in gastric cancer in Mexico. Preliminary results]. *Rev Gastroenterol Mex* 2003; **68**: 107-112 [PMID: 15127646]
- 75 **Secretaría de Salud**. Programa para la prevención y el tratamiento del cáncer en la infancia y adolescencia. [cited 2013 Oct 18]. Available from: http://www.censia.salud.gob.mx/contenidos/cancer/interm_cancer.html. CENSIA
- 76 **Dicken BJ**, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. *Ann Surg* 2005; **241**: 27-39 [PMID: 15621988]
- 77 **Oñate-Ocaña LF**, Cortés Cárdenas S, Herrera-Goepfert R, Aiello-Crocifoglio V, Mondragón-Sánchez R, Ruiz-Molina JM. [Early gastric carcinoma. Analysis of 21 cases]. *Rev Gastroenterol Mex* 2001; **66**: 14-21 [PMID: 11464624]

- 78 **Wong BC**, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004; **291**: 187-194 [PMID: 14722144 DOI: 10.1001/jama.291.2.187]
- 79 **Ley C**, Mohar A, Guarner J, Herrera-Goepfert R, Figueroa LS, Halperin D, Johnstone I, Parsonnet J. Helicobacter pylori eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 4-10 [PMID: 14744726 DOI: 10.1158/1055-9965.EPI-03-0124]
- 80 **Pankratz VS**, Hartmann LC, Degnim AC, Vierkant RA, Ghosh K, Vachon CM, Frost MH, Maloney SD, Reynolds C, Boughey JC. Assessment of the accuracy of the Gail model in women with atypical hyperplasia. *J Clin Oncol* 2008; **26**: 5374-5379 [PMID: 18854574 DOI: 10.1200/JCO.2007.14.8833]
- 81 **Amarasinghe HK**, Johnson NW, Lalloo R, Kumaraarachchi M, Warnakulasuriya S. Derivation and validation of a risk-factor model for detection of oral potentially malignant disorders in populations with high prevalence. *Br J Cancer* 2010; **103**: 303-309 [PMID: 20628386 DOI: 10.1038/sj.bjc.6605778]
- 82 **Meng W**, Cai SR, Zhou L, Dong Q, Zheng S, Zhang SZ. Performance value of high risk factors in colorectal cancer screening in China. *World J Gastroenterol* 2009; **15**: 6111-6116 [PMID: 20027686 DOI: 10.3748/wjg.15.6111]

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





百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045