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Mortality due to gastric cancer in Andalusia: trends and geographic distribution

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Aims. To describe the evolution of mortality due to gastric cancer in Andalusia and the current geographic distribution of mortality.
Design. Descriptive, population-based study.
Setting. Andalusia (Southern Spain) during the period from 1975 to 1999.
Participants. Residents of the region of Andalusia.
Measurements. Crude rates adjusted for age (interval 35-64 years) of potential years of life lost (1-70 years), and cumulative rates (0-74 years), for mortality due to gastric cancer from 1975 to 1999. Linear regression coefficients were calculated from the model that best fit mortality rates standardized across the study period. Age-adjusted rates were calculated for the five-year period from 1995 to 1999 for primary health care districts.
Results. A sustained decrease in mortality (standardized rate per 100000 inhabitants) due to gastric cancer was seen in women (15.9 to 5.8) and men (33.9 to 14.5). The Sierra Norte (Seville province), Huelva and Córdoba districts, together with the Guadix district (Granada province), had the highest age-adjusted rates for the period from 1995 to 1999. Mortality rates were higher in men than in women throughout the period analyzed; the male:female ratio was consistently greater than 2.
Conclusions. Mortality due to gastric cancer decreased notably in Andalusia during the last quarter of the twentieth century, but the current geographic distribution of mortality rates varies across the region. Mortality rates in some primary health care districts were threefold as high as in other districts where mortality was low. Further analytical studies are needed to clarify the possible causes of these marked local differences.

Key words: Gastric cancer. Mortality. Spatial distribution. Andalusia.

MORTALIDAD POR CÁNCER DE ESTÓMAGO EN ANDALUCÍA: TENDENCIA Y DISTRIBUCIÓN ESPACIAL

Objetivo. Describir la evolución de la mortalidad por cáncer de estómago en Andalucía y su distribución geográfica actual.
Diseño. Estudio descriptivo de base poblacional.
Emplazamiento. Andalucía durante el período 1975-1999.
Participantes. Residentes en Andalucía.
Mediciones. Tasas brutas, ajustadas por edad, truncadas (35-64 años), de años potenciales de vida perdidos (1-70 años) y acumuladas (0-74 años) de mortalidad por cáncer de estómago entre 1975 y 1999. Coeficientes de regresión lineal del modelo que mejor se ajusta a las tasas estandarizadas a lo largo de todo el período. Tasas ajustadas por edad del quinquenio 1995-1999 en los distritos sanitarios de atención primaria.
Resultados. Se observa un descenso mantenido de la mortalidad por cáncer de estómago, y las tasas estandarizadas pasan de 15,9 a 5,8 en mujeres y de 33,9 a 14,5 en varones (por 100.000 individuos). Los distritos de las sierras norte de Sevilla, Huelva y Córdoba junto con Guadix, en Granada, presentaron las tasas más altas en el quinquenio 1995-1999 tras ajustar por edad. Los varones mantienen tasas más elevadas de mortalidad a lo largo del intervalo analizado, con razones de masculinidad siempre superiores a 2.
Conclusiones. La mortalidad por cáncer de estómago ha descendido notablemente en Andalucía a lo largo del último cuarto del siglo XX, pero la distribución geográfica actual de la misma no es homogénea y se observan distritos de atención primaria con tasas 3 veces superiores a las tasas de los distritos de baja mortalidad. Se necesitan estudios analíticos que aclaren las posibles causas de estas notables diferencias.

Palabras clave: Cáncer de estómago. Mortalidad. Distribución espacial. Andalucía.

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A commentary follow this article (pág. 640)

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Introduction

The stomach is the second most frequent site of cancer, accounting for 9.9% of all cases of cancer worldwide. This figure rises to 11.9% in men and decreases to 7.6% in women, among whom it is the fourth most frequent location after breast, colorectal and cervical cancer.[1]

The incidence of gastric cancer differs in developing countries, where the annual rate of new cases in men approaches that of lung cancer, and in developed countries, where there are more cases of prostate and colorectal cancer than of gastric cancer.[2] In women the differences between developing and developed countries are smaller, but nonetheless evident. In fact, 38% of all cases of gastric cancer occur in The People´s Republic of China, where –as occurs in other parts of Southeast Asia– it is the most frequent type in both sexes. Gastric cancer is also the most frequent type (with rates higher than those for lung cancer) in tropical areas of South America. Within Europe the highest rates are reported for Eastern countries.[1] The mortality rate/incidence ratio in men ranges from 0.40 in Japan to 0.89 in Central Asian countries, as compared to 0.86 in Europe. In women these figures range from 0.44 in Japan to 0.92 in temperate areas of South America, as compared to 0.83 in Europe.[1] The World Health Organization (WHO) database indicates large variations for sexes and countries in age-adjusted mortality rates.[3] During the period from 1995 to 1998, mortality rates surpassed 25 per 100,000 in men and 10 per 100,000 in women in the European countries of Belarus, Estonia, Russia, Latvia, Lithuania and the Ukraine. Age-adjusted rates in Spain for 1995 -- the last year for which data are available-- were 12.2 per 10^5 in men and 5.5 per 10^5 in women, i.e., higher than in Denmark, France, Finland, Greece, Iceland, Ireland, Luxembourg, The Netherlands, Norway, Sweden and the United Kingdom.[3] In the neighboring country of Portugal, these rates are almost twice as high as in Spain but now show a tendency to decrease, as in the rest of the world.[4]

There are several possible explanations for this trend. First, freezing and refrigeration technology has reduced the consumption of salted and smoked foods, preserved with techniques that have been associated in ecological studies with a high incidence of gastric cancer.[5] In addition, current farming systems and improvements in transportation have increased the consumption of fresh fruits and vegetables throughout the year, another trend associated with a reduced risk of gastric cancer.[6]

Some authors have recently speculated that green tea might be associated with a lower risk of gastric cancer. However, although there is a consensus regarding the protective effect of a diet rich in fruits, vegetables and whole grain cereals, and regarding the increased risk associated with a diet rich in salt and salted or smoked foods, and possibly with the habitual consumption of barbecued meat and fish,[6] the protective effect of green tea has yet to be widely accepted.[7] Alcohol consumption is another likely risk factor for cancer located specifically in the gastric cardia.[8]

The relationship between gastric cancer and *Helicobacter pylori* infection is also under investigation.[9] Current studies are attempting to clarify whether antibiotic treatment aimed at eradicating the infection has a protective effect on the appearance or malignant evolution of gastric adenocarcinoma, or whether such treatment acts, as some have suggested, as a risk factor for gastric cancer in light of the fact that some strains of *H. pylori* (cagA+) appear to protect against the appearance of adenocarcinoma of the gastric cardia.[10] Intervention-based studies of the effects of treatment of *H. pylori* infection in patients in whom evolution of gastric cancer differ[11] will help to clarify this relationship.

A genetic susceptibility to the appearance of gastric cancer was found in studies of isolated ethnic groups[12] and patients´ relatives[13], after possible confounding factors such as diet were taken into consideration. Finally, although the end of the 1980s saw reports of a relationship between ethylene oxide exposure and increased mortality from gastric cancer,[15,16] more recent studies that measured mortality[17] and incidence[18] in cohorts with occupational exposure failed to confirm this association.

The aim of the present study was to describe the trends in mortality due to gastric cancer in Andalusia (southern Spain) during the final quarter of the twentieth century, and to provide information on the current geographic distribution of the disease in the primary care health districts that currently comprise this region.

Material and methods

Deaths from gastric cancer --code 151 in CIE 8-9 and code C16 in CIE 10-- were recorded from national (INE, Instituto Nacional de Estadística) and regional (IEA, Instituto de Estadística de Andalucía) statistical databases for the periods 1971-1991 and 1992-1999. Data for 1999 were considered provisional at the time of the this study. The inclusion criterion was residence in Andalusia, and the populations used in our analyses were based on estimates provided by the IEA. To describe temporal trends we calculated crude and age-adjusted (direct method, using the European population as the reference population) mortality rates, truncated rates for 35 and 64 years of age, and potential years of life lost between 1 and 70 years (PYLL).[19] To calculate approximate figures for the risk of dying from gastric cancer in the absence of other causes we calculated cumulative rates for the ages 0 to 74 years[20] as a percentage. To quantify changes in trends during the period from 1975 to 1999 we developed linear regression models with year of death as the independent variable and adjusted mortality rate as the dependent variable, and estimated re-

TABLE 1 **Mortality from gastric cancer in women in Andalusia from 1975 to 1999**

Año	Casos	TB	TED	TT	Ttru	TA	APVP
1975	460	14,70	15,90	14,55	10,58	1,08	71,04
1976	429	13,63	14,26	14,14	9,72	0,93	73,42
1977	408	12,87	13,40	13,74	10,06	0,88	68,55
1978	434	13,58	14,06	13,34	11,42	0,94	78,76
1979	419	13,00	13,11	12,94	9,29	0,88	71,27
1980	440	13,54	13,39	12,53	9,08	0,88	75,52
1981	418	12,71	12,37	12,13	8,87	0,83	75,20
1982	428	12,85	12,30	11,73	8,18	0,80	67,43
1983	363	10,77	10,20	11,33	6,58	0,72	52,37
1984	346	10,16	9,52	10,92	7,27	0,63	50,60
1985	361	10,51	9,55	10,52	4,93	0,60	35,15
1986	403	11,65	10,59	10,12	7,01	0,64	54,63
1987	390	11,21	10,02	9,72	7,53	0,64	51,91
1988	334	9,55	8,48	9,31	6,05	0,56	51,35
1989	318	9,06	7,71	8,91	5,27	0,51	40,33
1990	312	8,87	7,63	8,51	5,86	0,54	43,01
1991	339	9,59	8,06	8,11	6,92	0,54	49,01
1992	301	8,46	7,05	7,70	5,58	0,44	51,22
1993	296	8,28	6,58	7,30	4,48	0,45	34,35
1994	299	8,32	6,68	6,90	5,17	0,46	38,57
1995	320	8,86	6,80	6,50	4,26	0,41	35,92
1996	309	8,51	6,67	6,09	5,45	0,42	39,05
1997	317	8,68	6,84	5,69	6,54	0,46	51,83
1998	287	7,82	5,91	5,29	4,96	0,40	40,31
1999	280	7,59	5,82	4,88	5,26	0,39	40,40

CR: crude rate; ASR: age-standardized rate, direct method (standard European population); TR: theoretical rate; TrR: truncated rate for ages 35 and 64 years; CumR: cumulative rate, ages 0 to 74 years, and PYLL: potential years of life lost between ages 1 and 74 years.

gression coefficients for men and women. The SPSS (v. 8.0) was used for all calculations, and a 5% level of significance was used for tests of the independence of variables and for intercept and slope values other than zero. Normal distribution of the data was checked in all cases. Age-adjusted mortality rates per primary health care district during the period from 1995 to 1999, grouped in quintiles, were used to illustrate the geographic distribution of mortality from gastric cancer. Maps were created with the MapMaker program.

Results

The mortality rate for gastric cancer in Andalusia decreased markedly between 1975 and 1999 (tables 1 and 2). Crude rates decreased to half the initial value in women and to two-thirds this value in men. Age-adjusted rates showed even larger changes, decreasing from 15.9 to 5.8 deaths per 100,000 in women and from 33.9 to 14.5 per 100,000 in men. The overall decrease was 63.5% in women and 57.2% in men. The male:female ratio remained higher than 2 in almost all years of study. Indicators of premature death --truncated rates and PYLL-- also fell in both sexes, and cumulative rates decreased from 1.08% to 0.39% in women, and from 2.48% to 1.07% in men. Figure 1 shows age-adjusted rates, regression equations and trends for both sexes according to the linear model, which best fit the changes in rates. These expressions can be used to estimate theoretical mortality rates.

Figures 2 and 3 illustrate the current geographic distribution of mortality from gastric cancer in all health care districts. In some districts in the provinces of Granada (Guadix), Seville, Huelva and Córdoba (Sierras Norte), mortality from gastric cancer in men was threefold as high as in those districts with the lowest rates. These local contrasts were even more striking for women.

TABLE 2 **Mortality from gastric cancer in men in Andalusia from 1975 to 1999**

Año	Casos	TB	TED	TT	Ttru	TA	APVP
1975	685	22,86	33,93	31,56	25,29	2,48	178,39
1976	667	22,07	32,21	30,76	24,77	2,27	161,30
1977	675	22,12	31,35	29,96	27,24	2,37	191,13
1978	678	21,99	30,84	29,17	26,76	2,25	180,10
1979	653	20,96	29,22	28,37	21,66	2,18	155,09
1980	638	20,26	28,02	27,57	22,75	2,00	152,38
1981	615	19,28	26,40	26,77	20,14	1,80	134,89
1982	594	18,36	24,35	25,97	20,91	1,84	139,93
1983	576	17,58	23,10	25,17	21,10	1,65	137,89
1984	576	17,39	22,53	24,37	17,00	1,73	119,68
1985	620	18,55	23,76	23,57	19,45	1,80	137,36
1986	553	16,43	20,82	22,78	16,26	1,56	105,33
1987	557	16,45	20,62	21,98	18,10	1,53	136,97
1988	552	16,23	19,74	21,18	16,94	1,44	115,92
1989	529	15,51	18,58	20,38	16,11	1,33	114,51
1990	544	15,92	18,95	19,58	16,14	1,36	104,54
1991	534	15,55	18,03	18,78	16,89	1,32	118,28
1992	466	13,48	15,41	17,98	15,05	1,13	99,49
1993	547	15,74	17,80	17,19	15,43	1,28	106,81
1994	544	15,57	17,31	16,39	17,64	1,23	124,94
1995	522	14,87	15,95	15,59	14,70	1,23	95,36
1996	501	14,20	15,26	14,79	13,22	1,13	88,47
1997	525	14,80	15,49	13,99	13,16	1,14	84,95
1998	529	14,84	15,25	13,19	13,33	1,19	88,68
1999	500	14,01	14,51	12,39	11,92	1,07	82,49

CR: crude rate; ASR: age-standardized rate, direct method (standard European population); TR: theoretical rate; TrR: truncated rate for ages 35 and 64 years; CumR: cumulative rate, ages 0 to 74 years, and PYLL: potential years of life lost between ages 1 and 74 years.

Discussion

Our results document a notable decrease in mortality from gastric cancer in Andalusia, although the stomach remains the third most frequent site of cancer in men and the fourth most frequent site in women[21]. This trend is consistent with observations for the general population in Spain, where mortality rates peaked in the mid-1960s but have declined steadily since then[3] to their current values. The reasons for this decrease, also reported in other European countries, are associated with a decrease in the incidence, and with more recent increases in survival. For decades, survival among patients with gastric cancer was so low --less than 10% after 5 years-- that the trend in mortality was assumed to accurately reflect the decreased incidence[22] recorded in cancer registries in Spain and in other western countries. Recently published estimates[23] of survival are slightly higher and have undoubtedly contributed to these decreases in mortality: European 5-year survival rates are 19.3% for men and 23.6% for women overall, and range from 8.4% and 10.1% respectively in Poland to 24.3% for Spanish men and 3.1% for Icelandic women. The trend found in Andalusia is therefore not unexpected. With regard to the current geographic distribution of mortality, the large local differences between primary health care districts call into question the reliability of the information and the stability, for small areas, of mortality indexes that measure infrequent events. However, concordance studies of the causes of death which compared death certificates with clinical information for deceased patients have found official death statistics to be highly reliable both in Spain[24] and in other countries[25] where levels of development, reporting regulations and epidemiological coding practices are similar. Discrepancies in oncological statistics were found mainly for uterine cancers and mesotheliomas[26], and overall discrepancies in mortality figures for cancer decreased by 35% between the

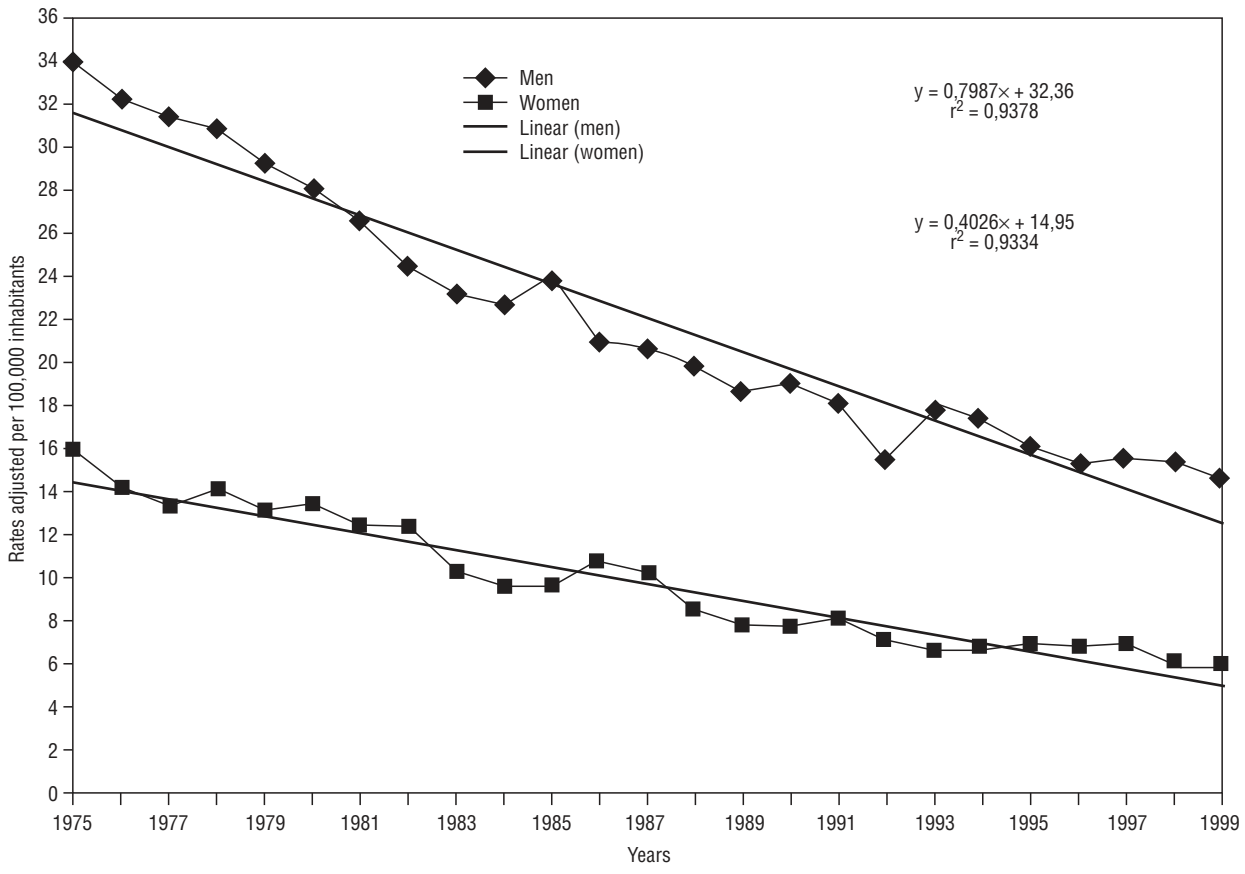

FIGURE 1 Evolution of mortality rates for gastric cancer in Andalusia from 1975 to 1999.

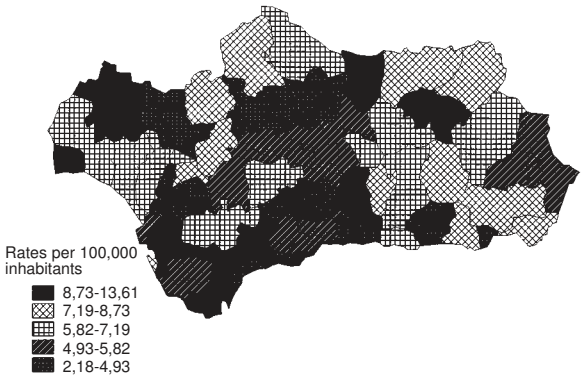

FIGURE 2 Mortality rates for gastric cancer in women in Andalusia from 1975 to 1999.

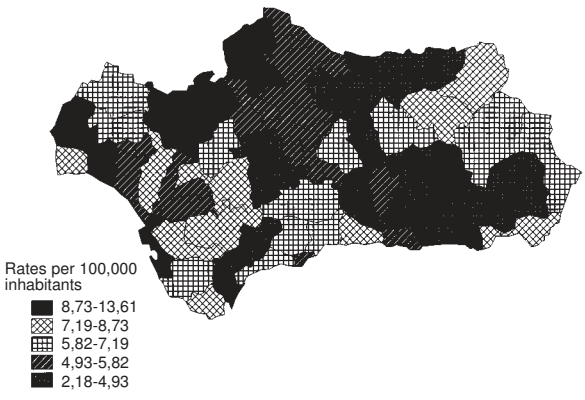

FIGURE 3 Mortality rates for gastric cancer in men in Andalusia from 1975 to 1999.

Discussion
Key points

What is known about the subject

- **Mortality rates for gastric cancer have decreased in developed countries during the last quarter of the twentieth century, although the stomach remains the second most frequent site of cancer worldwide.**

What this study contributes

- **We documented a large decrease in mortality from gastric cancer in Andalusia (Southern Spain) during the 1990s.**
- **The current geographic distribution of mortality rates in the region varies between primary health care districts.**
- **The highest mortality rates for both men and women, after adjustment for differences in age structure of the population in each district, are threefold as high as the lowest rates.**

late 1970s and 1980s. To ensure stability of the measurements, mean rates were calculated for the 5-year period from 1995 to 1999; when the window of time was enlarged, mortality rates stabilized even for areas with a low population, as are the primary health care districts compared in this study.

Attempts to compare areas of high and low mortality have led to the development of sophisticated statistical techniques[28] which are useful in searching for patterns in geographical distribution, but which undoubtedly distract attention from the actual data.[29] This was the reason which led us to present our findings as age-adjusted mortality rates. In overall terms, the incidence[30] and mortality rates in Andalusia are too low to warrant the use of early detection programs such as those currently in use in Japan, which involve double-contrast barium x-rays followed by gastroscopic examination for all inhabitants older than 40 years. This approach has indeed succeeded in detecting gastric cancer in its early stages, and has reduced mortality and incidence rates.[1] However, in Andalusia a more reasonable approach might be to develop preventive measures for those areas were mortality is high. Before such measures are attempted, previous studies will be needed to analyze morbidity, dietary patterns, genetic susceptibility and the prevalence of *H. pylori* infection, and statistical analyses of these data will need to take into account possible confounding factors such as occupational exposure and socioeconomic level..

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COMMENTARY

Gastric cancer: reducing the gap

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Gastric cancer is the second most frequent cause of death from cancer worldwide, with a mortality rate (adjusted for the world population, AWP) of 15.62 per 100,000 inhabitants, and is more frequent among men.[1] However, during the last ten years the characteristics of and attitudes toward this type of cancer have changed. This shift has come about thanks to a number of factors, which include: *a)* a decrease in the incidence of and mortality from gastric cancer; *b)* the identification of *Helicobacter pylori* and other environmental agents as causal factors; *c)* an increase in the incidence of cancer of the gastric cardia (and a decrease in cancer of the distal stomach, antrum and corpus); *d)* advances in the knowledge of the molecular biology of the tumor; *e)* a new TNM classification which makes it possible to estimate prognosis more accurately, along with awareness of the importance of lymph node involvement in prognosis; *f)* new treatment modalities, and *g)* in some countries such as Japan where the incidence if gastric cancer is high, the use of population screening.[2]

Spain, together with other southern European countries (i.e., Portugal and Italy), as well as Austria and Germany, ranks among the countries in Europe with the highest incidence (7.57 per 100,000 inhabitants, AWP) and mortality rates (5.37 per 100,000 inhabitants, AWP). These figures are higher than the European averages of 6.67 and 5.13 per 100,000 (both AWP), respectively.[1]

Mortality from gastric cancer, as shown in the study published in this issue by Ruiz Ramos et al,[3] particularly mortality in Andalusia, has decreased in recent decades. In Spain this decrease began at the end of the 1960s, i.e., somewhat later than in other countries. By 1974 lung cancer had replaced gastric cancer as the leading cause of death from all types of cancer.

The geographic distribution of gastric cancer in Spain, as shown in the study by Ruiz Ramos,[3] and based on an analysis of mortality from gastric cancer in Spain in 1996, reveals that rates vary from one part of the country to another. Within Spain there is a gradient from inland areas toward the coast, with highest rates recorded for the autonomous community of Castilla and León (AWP rate 22.42 per 100,000 in men in Burgos province) and lowest rates on the Mediterranean coast (AWP rate 8.13 per 100,000 men in Almería province). The reasons for this decrease in the incidence of gastric cancer are not entirely known, but changes in dietary habits have been clearly implicated. The higher consumption of fresh fruits and vegetables along with the lower consumption of foods preserved by salting, pickling or smoking, together with improvements in the preservation of fresh foods, partly explain the decrease.[4] The distribution of these dietary factors, along with smoking and drinking patterns, appear to be involved in the geographical differences in the incidence of gastric cancer in Spain. Some authors have also suggested that lower socioeconomic level, latitude and altitude are factors that might account for part of these differences.

Other factors that should be taken into account in the distribution and risk of gastric cancer are the prevalence of *H. pylori* infection and the many partial gastrectomies done to treat ulcers more than 10 years ago. Gastric cancer occurs in only a small percentage of patients with *H. pylori* infec-

Chart. Gastric cancer

- In the general population, a variety of risk factors have been related with gastric cancer. Diet is a risk factor that has been implicated clearly in this disease. The association with *H. pylori* is not well documented, and eradication of the infection in the general population is not warranted.
- The delay between onset of the signs and symptoms that lead to a suspicion of gastric cancer and the actual diagnosis could be reduced if family physicians promptly requested or referred patients for endoscopic examination.
- The population at high risk (eg, patients who have undergone partial gastrectomy) may benefit from eradication of *H. pylori* and periodic endoscopic follow-up.
- Diagnosis of gastric cancer in an early stage has improved the outcomes of surgical treatment.

tion, hence generalized eradication with antibiotic treatment is not justified in view of its cost and the risk of resistance.[4] Nonetheless, eradication of the infection is recommended for patients who have had a partial gastrectomy.

Despite the marked decrease in the incidence of and mortality from gastric cancer, in most patients the tumor is diagnosed when it has reached an advanced stage and is inoperable. In western countries the tumor is advanced and the prognosis is poor in more than 80% of the patients at the time of diagnosis.[5] Against this background treatment can only be palliative, except in those cases when chemotherapy is used with the intention of shrinking the tumor to facilitate potentially curative surgical treatment in patients with a locally advanced tumor in the absence of metastases.

Early detection of the tumor has improved treatment outcomes in countries such as Japan and Korea, as well as in some Western hospitals.[6] In these countries survival after surgery is high (better than 90% after 5 years) thanks to the early diagnosis of the tumor. Complete resection is the treatment mode that has yielded the best results. Technological advances in the diagnosis and treatment of gastric cancer have contributed to the development of less invasive and hence less expensive treatments such as endoscopic mucosal resection and laparoscopy.

In Spain, gastric cancer is considered a disease with a poor prognosis, with a 5-year survival rate of 30%. Suspicious signs and symptoms for gastric cancer, such as weight loss, anemia, dysphagia and vomiting, can fail to lead to a correct diagnosis for months even when patients seek medical attention for their symptoms.[5] In some cases the inappropriate use of anti-ulcer medication camouflages the true diagnosis of cancer for some time. Once the cancer is diagnosed, it is often too late to consider surgery as a treatment option.

The delay in diagnosing gastric cancer might be avoided in part if family physicians could promptly request or refer their patients for endoscopic examination. Endoscopy should be advised for all patients older than 45 years who present initially with dyspeptic symptoms, as they make up the subgroup of patients at greatest risk for gastric cancer.[6]

Some studies have shown that the availability of endoscopic examinations can ensure an earlier diagnosis of suspected cancer, a possibility that would detect the disease at an earlier stage.[5] A prompt request for this procedure or referral to a secondary or tertiary center, along with awareness of the urgency of the situation by hospital practitioners, would speed the diagnosis. Differences in the diagnostic process in patients with suspected gastric cancer might also account for some of the geographic differences noted in the article by Ruiz Ramos et al.

In summary, to decrease the incidence of gastric cancer and reduce the gaps between different areas, preventive measures are needed for the general population, and early detection strategies are in order for the population at high risk. Primary care physicians need to be alerted to the potential significance of suspicious symptoms, to improve the chances of an early diagnosis. An efficient system of diagnosis for patients in whom gastric cancer is highly suspected, and the appropriate use of surgical procedures and other treatments, would translate as improvements in survival. Agreed-upon protocols and clinical practice guidelines for gastric cancer are instruments that are likely to facilitate an early diagnosis.

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