Pergamon

European Journal of Cancer Vol. 32A, No. 8, pp. 1303–1309, 1996

Printed in Great Britain
0959–8049/96 $15.00+0.00

PII: S0959-8049(96)00103-7

Original Paper

Sex as a Prognostic Factor in Gastric Cancer

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The aim of this study was to assess whether survival of gastric cancer patients differed between males and females. Although it is well known that the incidence of gastric cancer is higher for men than for women, the existence of a sex-specific prognosis has seldom been addressed. Studies based on population registries have not assessed the role of stage and histology. Cases of histologically confirmed gastric carcinoma were obtained from three Spanish hospitals in Soria (n = 405), Barcelona (n = 249) and Mataró (n = 197). Differences in possible confounders were tested between men and women and survival analyses were performed separately by hospital. Cox's proportional hazards models were used to account for age, tumour stage, histology and tumour sub-location. Only in Mataró was a significant difference in the stage distribution observed between women and men, with a lower proportion of local stage tumours among women (P = 0.047). No statistically significant differences of histological type between men and women were observed in any of the centres. After adjusting for tumour stage and age, women were observed to have significantly better survival in Barcelona (female to male hazard ratio (HR) = 0.578, $P < 0.001$); this effect was marginal in Soria (HR = 0.788, P = 0.092) and non-significant in Mataró (HR = 0.895, P = 0.54). Age-adjusted hazard ratios were calculated within each tumour stage. For Barcelona, the effect of better prognosis among women was most marked at local stage (HR = 0.320, P = 0.013), and in Soria at the regional stage (HR = 0.426, P = 0.002). Although in Mataró all HRs were below unity, none were statistically significant. Little effect was observed at the disseminated stage. The other covariables exerted no influence. Women appear to have a better prognosis than men, and the difference could be tumour stage dependent. Confirmation of these findings would give a valuable insight into gastric cancer growth and ultimately be of use in planning treatment. **Copyright © 1996 Elsevier Science Ltd**

Key words: stomach neoplasms, carcinomas, tumour staging, hospital, sex, prognosis, survival
Eur J Cancer, Vol. 32A, No. 8, pp. 1303–1309, 1996

INTRODUCTION

THE ROLE that sex may have on cancer incidence is unquestionable for many neoplasms. For gastric cancer, a highly lethal and still one of the most frequent digestive tract cancers [1, 2], incidence is known to be higher for men [3–5], but a prognostic differential by sex has seldom been directly addressed [6]. From a selection of gastric cancer survival studies, some [7–13] indicated no differences by sex in survival, whereas others revealed better survival for women [3, 14–20]; no study, as far as we are aware, revealed better survival for men other than one conducted in Fukuoka, Japan, among patients with advanced gastric cancer [6]: although 10-year survival rates were very similar for both sexes overall, as well as among cases older than 50 years, survival was poorer for women than for men in the subgroup of patients under the age of 50 years.

Of late, incidence [3, 19] and mortality [21, 22] rates for gastric cancer have been decreasing in many areas of the world. It is not yet established whether the decrease in incidence has affected similarly the different histological types [2, 19, 23, 24]. Incidence figures from the U.S. over the period 1973 to 1989 show that the decline apparently differs by sex [3]; the decrease for women was 25.2% whilst in men it was 18.1%, a ratio of 1.4. Furthermore, this figure varied between age and ethnic groups, with a relative decrease of 2.6 in Caucasians aged under 65 years, whereas for Black people of the same age the figure is 0.4. The implication is that the underlying origins of the change are not just global ones affecting uniformly the entire population; instead, there may be components more specific to sex, race and probably to age.

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Received 28 Nov. 1995; revised 11 Mar. 1996; accepted 12 Mar. 1996.

Recent evidence suggests that sex hormone receptors may play a role in stomach cancer [25, 26]. The results of a Japanese study [26] revealed that gastric cancer patients with oestrogen receptors had significantly worse survival than those without; the difference was deemed to be possibly related to the effect of progesterone. Prevalence of receptors did not vary between men and women, although higher proportions were seen at lower ages. Seemingly therefore, whilst the stomach is not thought to be a target site for sex hormones, the tumour may well be hormone dependent [26]. Should this be the case, the sex of the individual could be expected to modify the effect of receptors on tumour growth via sex-specific hormone levels. Alternatively, the presence of sex hormone receptors may just be a marker of tumour aggressiveness and the sex of the individual would have no corresponding prognostic effect.

The possible role of sex hormone receptors and the sex-specific changes in incidence, together with the observation that diet only partly explains the mortality distribution [27–33], suggest that gastric cancer may be related to sex. Therefore, it is of interest to assess whether prognosis is also associated with sex. If prognosis was partly sex dependent, further aetiological clues would need to be examined: candidates could be genetic, lifestyle and hormone related factors. It is also possible that sex is related to survival through differing age, tumour spread at diagnosis, histology or tumour sub-location between men and women. The aim of this study was to assess whether survival of patients with gastric cancer differed between males and females from three different geographic areas of Spain, whilst taking into account other prognostic factors and potential confounders.

MATERIALS AND METHODS

Data from two hospital cancer registries were analysed: the Hospital del Mar in Barcelona, and the Hospital Sant Jaume in the town of Mataró. The third hospital from which data were obtained is the Hospital General del Insalud, in Soria. The latter covers an approximate population of 100000 inhabitants and has around 250 beds. The province of Soria, in the Spanish interior, is a region with one of the highest gastric cancer rates in Europe [22]. Between the years of 1981 and 1991 a total of 458 patients were diagnosed with gastric adenocarcinoma and were histologically confirmed. Of these, 405 (88%) had sufficient information surrounding disease evolution to be entered in the analyses. The Hospital del Mar Tumour Registry has been in operation since 1978; its procedures have been described in detail elsewhere [34–36]. It is a 450-bed teaching hospital primarily serving a mid–low income and densely populated area of the city of Barcelona. The registry provided 249 cases of histologically confirmed gastric cancer with valid follow-up. The Hospital Sant Jaume has approximately 160 beds and is located in the coastal town of Mataró, some 50 km to the north of Barcelona. It provided 197 cases of histologically confirmed gastric cancer diagnosed since 1982. Follow-up was carried out through the registry in Barcelona and Mataró, and through the admissions centre of the hospital in Soria; patients being lost to follow-up were traced by telephone. Only incident cases were included, i.e. those newly diagnosed during the study period. Along with the factor of primary interest (namely, sex), the influence of the following variables was assessed: age (in hospital-specific quintiles), tumour stage (local, regional or disseminated, derived from the TNM classification) [37, 38], histology (coded as intestinal, diffuse or other based on the ICD-O [39] and Lauren's gastric cancer classification [40–42] and the sub-location of the tumour (cardia or other, ICD-O).

Statistical methods

For within centre comparisons, each centre was analysed independently making use of the usual descriptive and univariate analysis such as the Student's t-test to compare group means for continuous variables, and the χ^2-test to assess the relationship between two categorical variables [43]. Between centre comparisons were also considered meaningful and appropriate; they were performed using χ^2-tests for discrete variables and analysis of variance for the continuous variables [43]. Although it was tempting to combine data from the three hospitals, pooled or stratified survival analyses were not performed because of: (a) the exploratory nature of the study; (b) sociodemographic and epidemiological differences among the three areas; (c) lack of sufficiently homogeneous data on clinical practice in the three hospitals; and (d) the heterogeneity of the observed effects (see Discussion).

Survival was measured as months after diagnosis, and considered simultaneously with the outcome of dead (uncensored) or living/lost to follow-up (censored). Kaplan–Meier survival curves by sex were plotted within each centre, and the separation of the survival curves was tested via the log-rank test [44]. Cox's proportional hazards modelling [44] was used for a multivariate model of the data, with the prior assumption of proportionality of the hazards over time being tested by using a time–interaction term.

RESULTS

The patient profile is shown by centre in Table 1, revealing that patients diagnosed in Soria and Barcelona were of similar ages whereas those from Mataró were somewhat younger ($P = 0.078$). In all three centres, women were older than men ($P = 0.0002$). There was some variation in tumour staging among the centres ($P < 0.001$), which seems to be due mainly to the greater proportion of patients diagnosed with regional stage disease in Mataró (42.6%). Only in this latter centre was a significant difference in the stage distribution observed between women and men, with a lower proportion of local stage tumours among women ($P = 0.047$). There were but minor differences in the frequency of unstaged tumours between the two sexes in any of the three centres ($P > 0.55$ in all cases). The Soria data show a different classification of histology to that of Barcelona and Mataró: whilst a high proportion of cases (72.8%) were classified as intestinal type in Soria, the figures for Mataró (17.3%) and Barcelona (12.9%) were both low. The intestinal to diffuse ratio was higher in Soria (4.8) than in Barcelona (2.2) and Mataró (1.6); high intestinal to diffuse ratios are thought to represent increased presence of environmental/dietary risk factors [41]. No statistically significant differences of histological type between men and women were observed in any of the centres. The proportion of the cardia sub-location varied with centre ($P = 0.001$), being lowest for Soria (2.8%) and highest for Mataró (10.2%).

The 5-year survival rates are also presented in Table 1. The Kaplan–Meier sex-specific survival curves for each centre are given by tumour stage at diagnosis in Figures 1 and 2. There was little separation of the sex-specific survival curves for Soria and Mataró within local stage disease, whereas a higher death rate for men is evident in Barcelona ($P = 0.007$) (Figure 1). An unfavourable survival of men was also observed for

Table 1. Patient profile by sex and centre

	Soria		Barcelona		Mataró	
	Women	Men	Women	Men	Women	Men
Number	135	270	91	158	78	119
Age (years) mean	70.2	67.4	70.3	67.0	69.2	64.7
		$P=0.031$*		$P=0.043$*		$P=0.015$*
Tumour stage (%)						
Local	28.1	29.3	20.9	24.7	16.7	32.8
Regional	27.4	26.3	34.1	34.8	52.6	36.1
Disseminated	36.3	34.4	29.7	26.6	23.1	25.2
Missing	8.1	10.0	15.4	13.9	7.7	5.9
		$P=0.94$†		$P=0.76$†		$P=0.047$†
Sub-location (% cardia)	3.0	2.7	5.5	8.2	5.1	13.4
		$P=0.40$†		$P=0.42$†		$P=0.059$†
Histology (%)						
Diffuse	14.1	15.6	6.6	5.7	7.7	9.2
Intestinal	74.8	71.9	6.6	16.5	14.1	19.3
Others	8.9	11.5	86.8	77.8	78.2	71.4
		$P=0.67$†		$P=0.081$†		$P=0.56$†
Follow-up (months)						
Median	12	10	11	6.5	7.5	9
% Uncensored	65.9	70.4	74.7	81.6	67.9	64.7
% Survival (5 year)	25.9	28.0	26.4	12.6	17.9	28.6

*t-test for differences between two means. †χ^2 test. In the case of tumour stage, the missing data were left out of the calculation.

regional stage tumours in Soria ($P=0.004$) and less so in Barcelona ($P=0.137$) (Figure 2); no clear separation is apparent for Mataró patients ($P=0.526$). The disseminated stage revealed no separation of the sex-specific survival curves for any centre.

Results of the proportional hazard analyses are summarised in Table 2. Cox's modelling was deemed to be a suitable approach as no significant nor marginally significant interactions with time were detected for any of the variables. Clearly decreasing probability of survival with increasing tumour stage is seen in all the centres, the increase being most noticeable in Soria. The hazard ratio (HR) was also seen to increase with age for all the centres (data not shown). Histology had a marginally significant effect only in Barcelona, which then disappeared after tumour stage was accounted for; slightly lower risk of death was associated with the diffuse and intestinal histologies in comparison with the 'other' types. The cardia sub-location showed significantly worse survival in Soria only (HR = 2.6, $P=0.011$).

Model 2 in Table 2 gives the female to male hazard ratios by centre adjusted for stage and age; age adjustment was performed using centre-specific age quintiles. All hazard ratios were less than unity (i.e. favourable to women), with that of Barcelona being highly statistically significant (HR = 0.578, $P=0.001$) and that for Soria being marginally so (HR = 0.788, $P=0.092$). Further covariate adjustment did not noticeably alter these figures. Models 3–5 show the age-adjusted female to male hazard ratios separately for each stage. There was no statistically significant effect for sex at any of the stages in Mataró; whilst all hazard ratios were inferior to unity, the magnitude of the difference was slight, especially for the regional and disseminated stages. In Soria and Barcelona significant results were observed mainly in the earlier stages of the disease; substantially favourable prognosis was observed for women diagnosed with regional stage tumours in Soria (HR = 0.426, $P=0.002$) and with local stage tumours in Barcelona (HR = 0.32, $P=0.013$). Among disseminated tumours from Barcelona a weaker effect was seen (HR = 0.633, $P=0.12$). No effect was observed in the other centres among disseminated tumours.

Examination of the magnitude of the hazard ratios in each stage suggested that the effect of sex upon survival might differ by stage (Table 2). This was most clear in Soria where, indeed, the test for the sex–stage interaction was statistically significant ($P=0.008$). The statistical significance of the interaction test was low in Barcelona ($P=0.49$), where the HRs of all three stages were below unity; and, as expected, it was null in Mataró ($P=0.84$).

DISCUSSION

The results provide evidence for the existence of a differential prognosis for gastric cancer between men and women. However, this evidence is not consistent throughout the centres investigated, and in one centre (Mataró) no effect was detected. The relative heterogeneity of results may in part be due to differing implementation of classifications; for instance, tumour stage appeared to differ between men and women in Mataró, with more men diagnosed at an earlier stage. Despite the stratification by tumour stage, some residual confounding may have persisted, as the tumour stage classification was relatively broad. Furthermore, these differences may reflect some misclassification of tumour stage. Indeed correct classification has been related to better probability of survival; a recent report concluded that part of the decline in gastric cancer mortality may be due to better pre-operative staging of the tumour [45]. Whether this could explain the lack of effect of sex observed for Mataró remains arguable. Some differences among centres were also apparent in the histological classification: in Barcelona and Mataró only pure cases of intestinal or diffuse gastric cancer were classified as such,

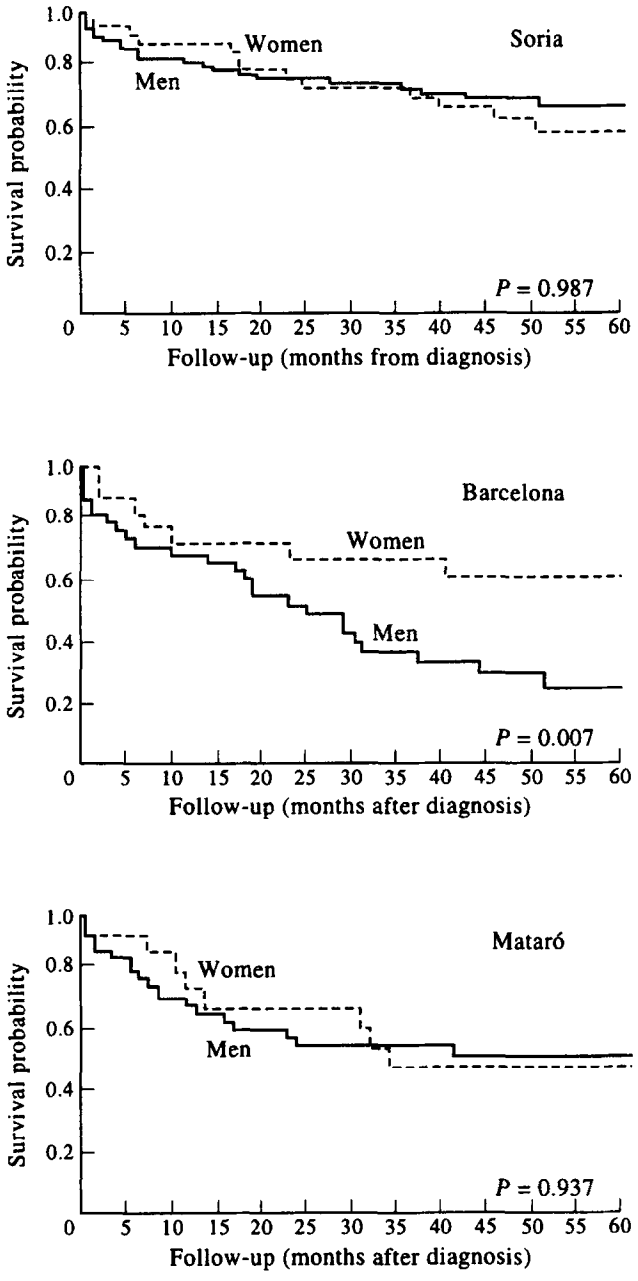

Figure 1. Sex-specific Kaplan–Meier survival curves by centre: local stage tumours.

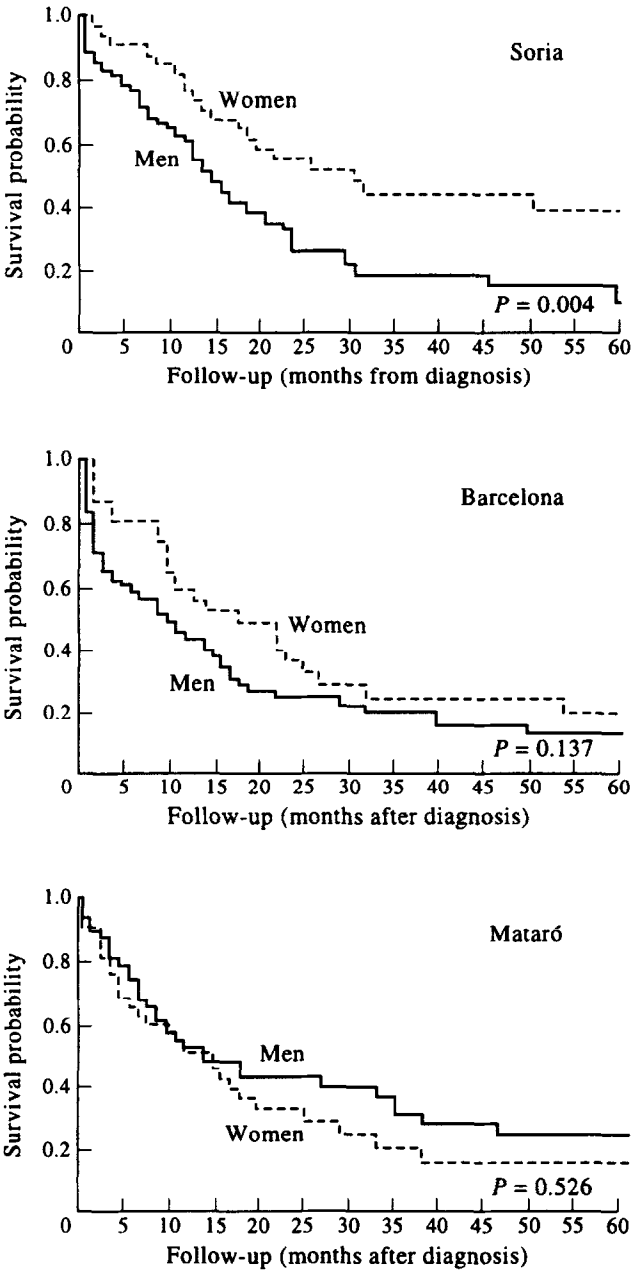

Figure 2. Sex-specific Kaplan–Meier survival curves by centre: regional stage tumours.

whereas in Soria broader criteria were used [40–42]. Unfortunately, in this study, an external review of pathology slides was not feasible. Nonetheless, histology was observed to have practically no effect both on survival and on the effect of sex. Some [18, 19, 46]—but not all [2, 47, 48]—previous reports also found similar survival rates among intestinal and diffuse gastric tumours.

Initially, the possibility of conducting a combined analysis of all patients from the three hospitals was considered: it could provide global estimates and highly significant *P*-values, and it would be easy to perform. However, we chose the more conservative approach of analysing each hospital separately, which did not mask differences among centres. Pooling data from different areas may become more appropriate when clinical and data collection procedures are highly uniform and, particularly, when homogeneous effects are observed across the areas.

Appraising the role of sex as a prognostic factor in gastric cancer requires to control for age and stage: age essentially counteracts the sex effect (as women tend to be diagnosed at a later age), and tumour stage may interact with the sex effect. For cases diagnosed with disseminated stage the effect of sex would be minimal as it is the distant spread of the tumour that dominates the course of the disease. Also, local stage tumours are more amenable to control, and therefore the effect of sex would be less apparent. Consequently, it is in the regional stage where other prognostic factors could be expected to play a greater role and be more statistically identifiable. This notion is confirmed in the SEER project: in the United States women have higher relative survival and this is most remarkable within regional stage tumours [3]. In a study conducted by Curtis

*Table 2. Results of survival analyses by centre**

	Soria	Barcelona	Mataró
1. Stage			
Local	1.0	1.0	1.0
Regional	3.17 (2.15–4.68)	2.22 (1.46–3.38)	2.36 (1.43–3.92)
Disseminated	13.3 (8.89–19.8)	4.51 (2.89–7.03)	6.56 (3.77–11.4)
	$P < 0.001$†	$P < 0.001$	$P < 0.001$
2. Sex‡	0.788 (0.578–1.04)	0.578 (0.414–0.807)	0.895 (0.601–1.33)
	$P = 0.092$	$P = 0.001$	$P = 0.54$
3. Local stage			
Sex§	0.589 (0.302–1.147)	0.320 (0.130–0.789)	0.773 (0.286–2.09)
	$P = 0.12$	$P = 0.013$	$P = 0.61$
4. Regional stage			
Sex§	0.426 (0.249–0.727)	0.614 (0.368–1.03)	0.971 (0.563–1.67)
	$P = 0.002$	$P = 0.062$	$P = 0.91$
5. Disseminated stage			
Sex§	1.16 (0.795–1.70)	0.633 (0.357–1.12)	0.960 (0.502–1.84)
	$P = 0.44$	$P = 0.12$	$P = 0.90$

*Except for *P*-values, all figures are hazard ratios (and 95% confidence limits). †All *P*-values are derived from the Likelihood ratio test. ‡Female to male hazard ratios; age- and stage-adjusted. §Female to male hazard ratios for given tumour stage; age-adjusted.

and associates [49] marginally better survival was observed for women only after having accounted for age and stage, and this sex difference was not present at the local stage. A study among Canadian gastric cancer patients [50], whilst not examining directly the role of sex on prognosis, did provide results by sex; from the sex-specific survival curves one observes a notably (not statistically tested) higher death rate among men diagnosed at regional stage compared to women of the same stage, whereas no such difference is evidenced at local or disseminated stages. Additional tests of the sex–stage interaction should be performed in future studies.

Access to more precise data on surgical treatment, diagnostic work-up, and staging and histological procedures would have been useful in this study. Unfortunately, much of this information was not routinely collected by the three registries. Nevertheless, we deem it unlikely that such limitations biased our conclusions. With regards to gender differences in treatments administered, we know of no evidence supporting the idea that men receive less or worse treatment. If something, some studies indicate that men may be more frequently operated upon [19, 51]; surgery remains the standard treatment [2, 52] and may serve as a reasonable palliative measure [53]. A study of 2773 patients with gastric cancer from the Rotterdam Cancer Registry found virtually identical resection rates in males and females, yet a significantly lower postoperative mortality among females [20]. Nevertheless, future studies aimed at refuting our findings could include information on therapeutic and palliative care. Data on gender differences in access to care, use of diagnostic technology and other aspects of clinical practice would also be warranted [24, 54, 55].

Between 6% and 15% of the tumours included in this study were unstaged, or the stage was not recorded. Even long-established registries will have a number of missing data, particularly if their case ascertainment is wide. In the SEER programme, for example, 12–16% of cases of stomach cancer are unstaged [3]. An ever larger figure of cases with no pathological stage size was reported by the patient care study of the American College of Surgeons (ACS) [47]. Conversely, complete data may be more common in less representative case-series. Importantly, there were but minor differences in the frequency of unstaged tumours between the two sexes in any of the three centres. Indeed, providing absolute reassurance that there were no biases related to stage migration and the "Will Rogers phenomenon" [56, 57] would require an in-depth study of potential differences in the diagnostic work-up and staging procedures among males and females [24, 54, 55].

In general, women have a longer life expectancy than males and, hence, a greater relative survival. Thus, it would seem appropriate to compute relative survival rates. However, the use of relative survival may not eliminate sex-related differences in mortality. Factors such as smoking, drinking and occupational exposures, which affect competitive mortality, may be more frequent in male cases than in the general population whose mortality rates are used for computing relative survival; for females, such a difference is likely to be much smaller [58]. Furthermore, gastric cancer is a highly lethal disease. Hence, life expectancy of those that survive the disease or would have died from another cause before the disease is cured would have little effect on prognosis. In addition, the Kaplan–Meier curves (Figures 1 and 2) show some clear differences in survival in favour of women. It should be remembered that women were older than men at diagnosis (a fact consistently observed in population-based European registries [58] and in the hospital-based study of the ACS [47]); this would counteract to a significant extent the differential life-expectancy. The curves in Figures 1 and 2 are not adjusted by age. The weighted analysis of European registries conducted by the Eurocare Study [58] comprised both observed and relative survival rates from stomach cancer: use of relative survival did not generally diminish the differences favouring women, which are apparent in the pooled analysis of the 12 participating countries and, to differing degrees, in several individual nations such as Denmark, Holland, France, Germany, Italy, Poland and Scotland. Furthermore, the European pooled figures clearly show that the sex difference in survival (a) persists (sometimes, increased) even after 10 year of diagnosis, and (b) has not substantially

changed since the late 1970s [58]. Although the Eurocare database permits the analysis of the sex effect in the different age groups, information on stage and histology was not collected. In addition to gastric cancer, that study found that survival was better for females in several other cancers [58].

A real sex-effect would be expected to be observed better among patients diagnosed with regional stage disease, which is what was observed for the Soria data. A spurious difference would be more observable at local stage, as the overall life expectancy would be relatively more important among such patients. However, for regional stage disease, life expectancy seems unlikely to be important when one considers that 50% of such patients died within 18 months of diagnosis. Accordingly, any effect of competitive mortality is likely to be negligible in the regional stage; local stage results should be viewed somewhat more cautiously. On a similar note, any influence of the differing life expectancies on the sex effect would produce a significant interaction between sex and age on survival. No such interaction was detected in our data.

Several hypotheses could be tentatively proposed from these results. For instance, tumour growth may be affected by hormones and the presence of hormone receptors [25, 26]. It would be of interest to study how hormonal levels may change prognosis; an approach would be to calculate male to female hazard ratios for given ages and observe how they change with age, scrutinising any peaks or troughs occurring around ages of hormonal change. The previously cited U.S. data [3] is also indicative that sex-specific exposures and habits may affect gastric cancer incidence. Such habits could in turn affect tumour development; for example, evidence is available that vitamin A exerts an antiproliferative action [59]. Furthermore, women might be genetically more resistant to uncontrolled cell growth. The interdependence of the effects upon survival of clinical, morphological and genetic markers should probably receive greater attention; for example, in an Italian study, the finding that male gastric cancer patients had lower survival than females did not remain statistically significant when DNA ploidy, vascular invasion and stage were accounted for [18]. The possibility that histological patterns differ between sexes [48], and that they influence prognosis, also deserves further research. Finally, sex-related socioeconomic factors should also be considered, since marital status, occupation and residential area have been found to influence the prognosis of patients with gastric cancer [60, 61].

Gastric cancer is one of the cancers most related to man's interaction with the environment, as there are many ways to cause upsets to the stomach's normal functioning [59, 62–64]. To evaluate further the role of sex, large studies are needed, ones which have highly standardised assessment of stage [65], histology and sub-location. Many clinical trials, as well as observational studies, could be re-analysed to assess the influence of sex upon survival [20, 24, 45, 47, 48, 52, 57, 66, 67]. Additional information on sex hormone receptor status and serum hormone levels would allow the testing of specific hypotheses on mechanisms. Also, smoking, drinking, dietary habits and other environmental exposures prior to and after diagnosis ought to be considered. Should the differential prognosis by sex be verified, refined versions of behavioural, environmental, hormonal and genetic hypotheses would need to be tested. The results may give valuable insights into the mechanisms of gastric tumour growth, and ultimately could be of use in devising more effective treatment strategies.

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Acknowledgements—This work was partly funded by Fondo de Investigación Sanitaria (grant 92/0311) and by the Fundación Salud 2000 (grant Serono). The authors wish to thank A. Tieso and A. Lázaro, of the Research Unit of the Hospital General del Insalud of Soria for help in the preparation of the Soria data. They also acknowledge helpful assistance from the staff of the registries of the Hospital Sant Jaume at Mataró and of the Hospital del Mar in Barcelona. The valuable comments on previous versions of the manuscript from J. Vioque, M. Gallén, G. López-Abente, I. Izarzugaza, J. Belloc and F. Macià are also gratefully acknowledged.