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Original Paper

Socioeconomic Status and Survival of Gastric Cancer Patients

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Survival differences in cancer patients according to socioeconomic status (SES) have been reported for several organs, but the relationship with gastric cancer prognosis has not been conclusively defined. The present study analysed the survival of 122 incident, histologically confirmed gastric cancer patients diagnosed between 1985 and 1987 in Genoa, Italy and enrolled in a multicentric case–control study on gastric cancer occurrence and dietary habits. Adjusting for age at diagnosis, tumour stage, histopathological grading and surgery (i.e. curative gastric resection), Cox's proportional hazards regression model showed statistically significant hazard ratio (HR) (relative risk) estimates below unity for education (> 5 versus ≤ 5 years of schooling, HR = 0.40, $P = 0.003$) and occupation (higher versus lower income job, HR = 0.59, $P = 0.030$). Also, the same final regression model revealed a positive prognostic effect for origin (Southern Italy migrants versus Genoa natives) (HR = 0.56, $P = 0.039$) and female gender (HR = 0.58, $P = 0.020$). High SES, origin from lower risk area for gastric cancer occurrence and female gender are positive prognostic categories for gastric cancer patients.

Key words: gastric neoplasm, cancer survival, socioeconomic status, migration, sex
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INTRODUCTION

THE ROLE of socioeconomic status (SES) on incidence, survival and mortality for cancer at various sites has been widely documented in the last 15 years [1–14]. In particular, most studies found cancer survival to be generally better for higher SES, although some degree of variation in results was noted. Variation usually concerned the definition of SES indicators [15], measures of SES based on ecological (aggregate) information [16] or individual data [17], cancer site [18] and lack of one or more important clinical and pathological factors strongly related to patients' prognosis [7, 19], namely tumour stage, histopathological grading, and surgery (i.e. curative gastric resection).

Although several socioeconomic indicators have been proposed as potential prognostic factors for cancer survival, income, occupation and education are deemed to adequately summarise all SES characteristics [15].

On the relationship between SES and gastric cancer survival, few studies are available. In fact, an extensive review of papers published since 1985 reveals only three studies [18–20] and these do not provide homogeneous results on the influence of socioeconomic factors. Accordingly, it is important to examine the natural history of this disease which, despite decreasing incidence and mortality rates in nearly all industrialised countries [21], remains one of the most lethal malignancies. In fact, in Italy, cancer registration data between 1983 and 1985 show 1-year observed survival probability less than 50% for both male (39%) and female (40%) patients [22].

The aim of this study was to investigate the effect of SES on the prognosis of patients with gastric cancer.

MATERIALS AND METHODS

A multicentric case–control study was carried out in Italy between June 1985 and December 1987, examining the effect of dietary habits on gastric cancer occurrence [23]. Briefly, a total of 1016 incident cases with histological diagnosis, confirmed by a panel of pathologists, and 1159 randomly selected controls were interviewed using a structured questionnaire to obtain detailed information on dietary habits and demographic, residential, occupational, medical, educational

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Table 1. *Distribution of cause of death certifications by socioeconomic factors*

Factors and levels	Causes of death ($n = 92$)				
	Gastric cancer (%)	Digestive cancer (%)	Other cancer (%)	Cardiovascular disease (%)	Unknown cause (%)
Education*					
≤ 5 years ($n = 20$)	17 (85.0)	1 (5.0)	1 (5.0)	0 (0.0)	1 (5.0)
> 5 years ($n = 72$)	62 (86.1)	5 (6.9)	2 (2.7)	3 (4.2)	0 (0.0)
Occupation					
Lower income job† ($n = 51$)	44 (86.3)	2 (3.9)	2 (3.9)	3 (5.9)	0 (0.0)
Higher income job‡ ($n = 41$)	35 (85.4)	4 (9.7)	1 (2.4)	0 (0.0)	1 (2.4)
Whole group ($n = 92$)	79 (85.9)	6 (6.5)	3 (3.3)	3 (3.3)	1 (1.1)

*Years of schooling. †Manual/unskilled workers and farmers. ‡Professionals, managers; clerical, service and trade workers.

and familial characteristics. The results of the study are reported elsewhere [24, 25]. Our investigation concerned all 122 cases referred to the Genoa centre (National Institute for Cancer Research) which were recruited and followed-up until 31 December 1995. The vital status for each subject was obtained from the Liguria Mortality Registry, whereas clinical and pathological information at diagnosis, such as disease stage, histopathological grading [26] and surgery, were extracted from the case–control study questionnaire and verified through the Genoa Cancer Registry, a population registry covering nearly 650 000 inhabitants per year and accredited by the World Health Organisation. Both registries have been active since 1985.

Other individual characteristics were: sex, age at diagnosis, year of diagnosis, migration from Southern Italy (migrant versus Genoa native), education (years of schooling) and occupation (job title). Education and occupation were a priori dichotomised in the following manner: greater than 5 years of schooling (middle–high school and university) versus less than or equal to 5 years of schooling (illiterate and elementary school); higher income job (professionals, managers, clerical, service and trade workers) versus lower income job (manual/unskilled workers and farmers). Housewives were classified according to husband's and/or father's occupation.

The product-limit method [27] was applied to estimate survival probabilities, and the statistical significance of the differences among these was assessed by the logrank test [28]. Cox's proportional hazards regression model [29] was performed to assess the effect of each prognostic factor on survival adjusted for the possible confounding effect of all other factors included in the same model. Hazard ratio (HR) (relative risk) estimates were obtained by exponentiating regression coefficients, and their statistical significance was tested by the likelihood ratio test. Asymptotic standard errors of coefficients were used to calculate 95% confidence intervals (CIs) of HRs. The proportional hazards assumption was assessed by testing the statistical significance of time-dependent regression terms resulting from the interaction between each factor and survival time [29]. All statistical significance levels (P values) were two-tailed. Data analyses were performed using BMDP [30] and EGRET [31] biostatistical packages.

RESULTS

All patients were traced and 30 (24.6%) were still alive as of 31 December 1995. The observed distribution of cause of death certification was: 79 (85.9%) gastric cancer, 6 (6.5%) other digestive cancers, 3 (3.3%) unspecified cancers, 3 (3.3%) cardiovascular diseases and 1 (1.1%) unknown cause (Table 1) according to the 9th revision of the *International Classification of Diseases* [32]. Disease stage was unknown for 13 (10.7%) patients while histopathological grading was unknown for 52 (42.6%).

The median survival time was 11.20 months. The median follow-up time was 108.19 months (range: 91.90–120.51 months) and 6.11 months (range: 069–100.27 months) for censored and deceased patients, respectively.

Table 2 reports the results of univariate analysis for 1-, 3-, and 5-year product-limit survival probabilities, logrank test value and related significance level. As expected, clinical and pathological factors (disease stage, histopathological grading, surgery) appeared to be very important prognostic factors. Interestingly, education (Figure 1) and sex (Figure 2) were also highly related to gastric cancer survival, with a prognostic advantage in favour of higher educational level (> 5 years of schooling) and female gender.

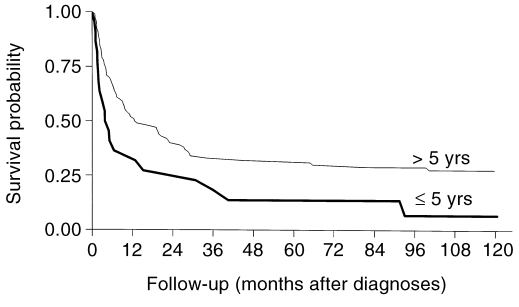

Figure 1. Product-limit survival curves of 122 gastric cancer patients diagnosed between 1 June 1985 and 31 December 1987 in Genoa, Italy and followed-up until 31 December 1995, according to educational level. > 5 years, greater than 5 years of schooling; ≤ 5 years, less than or equal to 5 years of schooling.

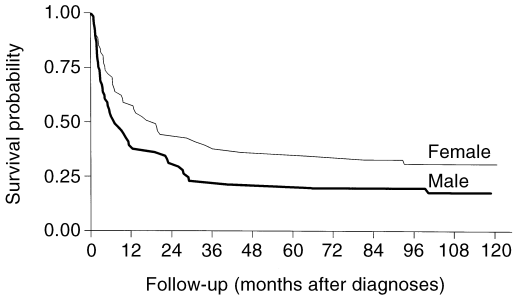

Figure 2. Product-limit survival curves of 122 gastric cancer patients diagnosed between 1 June 1985 and 31 December 1987 in Genoa, Italy and followed-up until 31 December 1995, according to sex.

Table 2. One, 3- and 5-year survival probabilities of 122 gastric cancer patients estimated by the product-limit method in relation to socioeconomic, demographic, clinical and pathological factors

Factors and levels	Total	Survival probability (%)			Log rank test	P*
		1 year	3 years	5 years		
Disease stage					46.33	< 0.01
0 + IA + IB	26	80.8	76.9	76.9		
II	12	75.0	41.7	41.7		
IIIA + IIIB	34	55.9	32.4	17.6		
IV	37	18.9	2.7	2.7		
Unknown	13	30.8	7.7	7.7		
Histophathological grading					7.47	0.02
G1 + G2	40	57.5	42.5	40.0		
G3	30	36.7	13.3	10.0		
Unknown	52	50.0	32.7	30.8		
Surgery					24.74	< 0.01
Yes	98	57.1	38.8	35.7		
No	24	16.7	4.2	0.0		
Sex					4.13	0.04
Male	61	39.3	23.0	21.3		
Female	61	59.0	39.3	36.1		
Age at diagnosis					0.77	0.68
≤ 60 years	31	41.9	32.3	29.0		
61–70 years	59	54.2	32.2	30.5		
> 70 years	32	46.9	28.1	25.0		
Year of diagnosis					0.22	0.90
1985	27	55.6	29.6	25.9		
1986	52	44.2	32.7	30.8		
1987	43	51.2	30.2	27.9		
Migration from Southern Italy					0.97	0.33
Genoa native	97	48.5	29.9	26.8		
Migrant	25	52.0	36.0	36.0		
Education†					5.71	0.02
≤ 5 years	22	36.4	22.7	13.6		
> 5 years	100	52.0	33.0	32.0		
Occupation					2.49	0.11
Lower income job‡	50	44.0	22.0	20.0		
Higher income job§	72	52.8	37.5	34.7		
Whole group	122	49.2	31.1	28.7		

*Two-sided significance level. †Years of schooling. ‡Manual/unskilled workers and farmers. §Professionals, managers; clerical, service, and trade workers.

The results of multivariate analyses are reported in Table 3. Model 1 represents the joint effect of education, occupation, migration and sex on survival after adjustment for the confounding effect of age at diagnosis, tumour stage, histopathological grading and surgery. In this modelling, all factors appear to be significant predictors. Specifically, a protective effect was found for higher educational level (HR = 0.40; CI = 0.22–0.70), higher income job (HR = 0.59; CI = 0.37–0.94) (Figure 3), south to north migration (HR = 0.56; CI = 0.32–0.97) (Figure 4) and female gender (HR = 0.58; CI = 0.37–0.92).

Other models in which education was differently categorised were also fitted. According to the distribution of Italian educational degrees, a three level (≤ 5 years, illiterate and elementary school; 6–8 years, middle school; > 8 years, high school and university) and a four level (≤ 5 years; 6–8 years; 9–12 years, high school; > 12 years, university) factor were used, but significantly different results were not obtained (data not shown).

Models 2 and 3 (Table 3) show results of Cox's regression performed by excluding either education (model 2) or occupation (model 3) from the analyses. Minimal changes were found in the HRs related to regression terms included in the model, particularly as far as the two main socioeconomic indicators were concerned, indicating a very low degree of correlation between the two factors in predicting survival.

Finally, statistical evaluation of time-dependent terms via the likelihood ratio test showed no violation of the proportional hazards assumption.

DISCUSSION

The major finding of this study is that, taking into account the relevant role of clinical and pathological factors (tumour stage, histopathological grading and surgery) relative to disease onset, differences in SES represented by educational level (years of schooling) and type of occupation (job title) had prognostic significance on gastric cancer patients' survival. Specifically, subjects with a higher income occupation and a higher educational level showed a better life expectancy.

Although mechanisms whereby SES might influence survival are complex and still debated, an attempt to explain the observed differences might be based on the following issues: (1) mortality due to other causes; (2) early cancer detection;

Table 3. Joint effect of education (years of schooling), occupation (job title), migration from Southern Italy and sex on survival of 122 *gastric cancer patients evaluated by multivariate Cox's regression model (see text)*

	Model 1		Model 2		Model 3	
Factors and levels	HR	95% CI	HR	95% CI	HR	95% CI
Education*						
≤ 5 years	1.00	Ref.	—	—	1.00	Ref.
> 5 years	0.40	0.22–0.70	—	—	0.37	0.21–0.66
LRT (*P*†)	9.00	(0.003)	—	—	10.3	(0.001)
Occupation						
Lower income job‡	1.00	Ref.	1.00	Ref.	—	—
Higher income job§	0.59	0.37–0.94	0.56	0.36–0.89	—	—
LRT (*P*)	4.73	(0.030)	6.02	(0.014)	—	—
Migration from Southern Italy						
Genoa native	1.00	Ref.	1.00	Ref.	1.00	Ref.
Migrant	0.56	0.32–0.97	0.60	0.34–1.05	0.55	0.32–0.97
LRT (*P*)	4.26	(0.039)	3.53	(0.060)	4.78	(0.029)
Sex						
Male	1.00	Ref.	1.00	Ref.	1.00	Ref.
Female	0.58	0.37–0.92	0.70	0.45–1.07	0.59	0.37–0.93
LRT (*P*)	5.44	(0.020)	2.70	(0.100)	5.32	(0.021)
Model LRT (*P*)	77.3	(< 0.001)	68.3	(< 0.001)	72.6	(< 0.001)

HR, Hazard ratio (relative risk) estimate adjusted for disease stage, histopathological grading, surgery and age at diagnosis; 95% CI, 95% confidence interval for HR; LRT, likelihood ratio test; Ref., reference category. *Years of schooling. †Two-sided significance level of LRT. ‡Manual/unskilled workers and farmers. §Professionals, managers; clerical, service, and trade workers.

(3) host related factors and tumour biology; (4) quality of medical care.

It is well known that mortality from other causes unduly lowers the observed survival probabilities. In this study, almost all causes of death were known and Table 1 shows the distribution according to socioeconomic factors. Noteworthy is the nearly homogeneous distribution of the percentage of gastric cancer death certification across educational and occupational categories. Because a large percentage of deaths for digestive tract cancers can very likely be attributed to gastric cancer, an overall and relatively constant 92% of all deaths were certified as due to gastric cancer. Even if imbalances are evident with respect to the certification of other causes of death (other cancers, cardiovascular disease and unknown causes), the differences, based on few patients, appear to be small and therefore unable to modify the results of Cox's regression analysis.

Delay in diagnosis has been proposed as a cause accounting for the influence of SES on survival prediction. It has been claimed that prolonged survival with more affluent SES might be due to earlier gastric cancer detection with or without (lead time bias) prognostic improvements [7, 22]. In our study, early detection cannot be considered a relevant explanation, since the extent of disease was taken into account by the multivariate regression model. Although this is consistent with the findings highlighted by other authors [33], the role of tumour stage, in these circumstances, might be underestimated because of both the 10% of unknown stages and the broad categories in which the covariate had been rearranged. Accordingly, neither a partial effect of early detection within the same tumour stage category nor a residual confounding (incomplete confounder adjustment) effect [34] can be completely ruled out. Both effects may lead to a decrease of the role of tumour stage on the study outcome and an increase of the predictive behaviour of the other covariates, socioeconomic factors included.

A differential biological behaviour and host characteristics have been postulated as plausible explanations for SES gradients in life expectancy for various cancer sites [8, 35, 36]. Socioeconomically deprived people may have weaker host

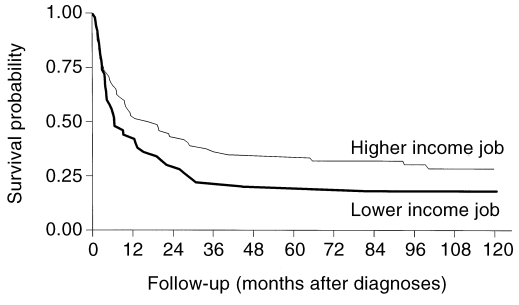

Figure 3. Product-limit survival curves of 122 gastric cancer patients diagnosed between 1 June 1985 and 31 December 1987 in Genoa, Italy and followed-up until 31 December 1995, according to occupation (job title). Higher income job, professionals, managers; clerical, service and trade workers; Lower income job, manual/unskilled workers and farmers.

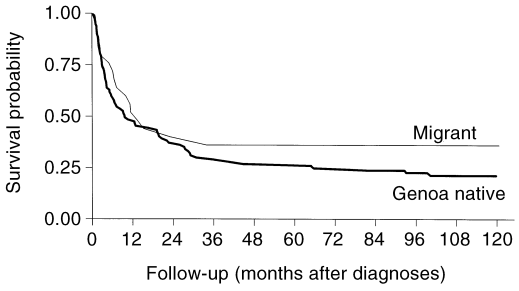

Figure 4. Product-limit survival curves of 122 gastric cancer patients diagnosed between 1 June 1985 and 31 December 1987 in Genoa, Italy and followed-up until 31 December 1995, according to migration from Southern Italy.

resistance attributable to unhealthy conditions at the time of and after diagnosis: heavier cigarette/alcohol consumption and poorer nutrition, destitute living conditions in run-down urban areas, more severe cardiovascular and respiratory comorbidities. There is evidence that such circumstances may indeed impair the immunological response to various diseases, including cancer [9], and lead to different biological behaviour due to higher grade of malignancy and more aggressive histological subtype [19, 20]. Unfortunately, Lauren's histological classification [37] was not available and lack of information (43%) on histopathological grading, which is an ideal indicator of tumour aggressiveness, prevents us from confirming the aforementioned hypothesis.

Impediments to health care services, along with poorer quality of medical care [38], adverse psychological attitude towards disease due to the lack of social assistance, inability to understand or lack of medical information, may also result in a worse survival outcome for socioeconomically disadvantaged people.

Although the effect of radiotherapy and chemotherapy was unknown, it seems very unlikely that the lack of these variables biased our results. The only available information on therapy was that related to surgery, which was included in regression modelling as a confounder. In fact, prospective, controlled clinical trials have failed to demonstrate prognostic benefits of these therapies, even after a curative resection [39]. Radical gastrectomy remains the only chance of cure to date. Thus, if socioeconomic related differences reflect a different quality of surgical treatment, this may have an impact on patients' prognosis.

Although a degree of overlap between occupation and education is expected [15], the regression analyses of instantaneous death rates (Table 3, models 2 and 3) indicated independence between the two factors in predicting survival. The small sample size of this study (122 gastric cancer patients) may have omitted the extreme categories of occupation (very low and very high), as defined in the case–control design (2175 cases and controls), leading to a frequency distribution characterised mainly by intermediate categories in which a nearly homogeneous distribution of years of schooling can be observed.

The other important findings of our study were the positive effect on survival of migration from Southern Italy and female gender. The role of migration on cancer occurrence has already been highlighted by other studies [40–43]. While south to north migration in Italy is a historical synonym of escape from poverty, in this setting it may represent a surrogate of specific protective factors typical of a geographical area characterised by lower gastric cancer occurrence figures [44].

The scientific literature has numerous studies suggesting that factors which influence cancer incidence may also affect subsequent survival [35, 45, 46]. Among these factors, a Mediterranean diet, based mainly on fresh fruit and raw vegetables [47], particularly during the first years of life, is considered to have a protective role in gastric cancer occurrence [25, 48–50]. Therefore, we believe that dietary habits acquired before diagnosis might also last after disease onset and affect its course.

Other factors, for example, lower environmental/occupational exposure to carcinogens due to a historical absence of industrial development in Southern Italy, cannot be ruled out as potential protective characteristics. Carcinogenesis is considered a multistep process wherein the carcinogen induces damage in susceptible cells [51]. Several genes are considered to be causally involved in the metastasis process [52], and there is evidence suggesting that as the exposure to carcinogens increases, so does the number of altered genes related to cancer development [53]. Therefore, type and dose of involved carcinogens before diagnosis and/or during disease course might modulate cancer prognosis through specific biological pathways.

In a very recent study on gastric cancer patients [54], a positive significant effect of female gender on survival outcome, of a similar magnitude to that observed in our study, was described. Although the stomach is not a target organ for sex hormones, some studies [55] have asserted that gastric cancer may be a site of receptors for these hormones and have found a statistically significant better survival for patients with negative status of oestrogenic receptors [56]. Therefore, a plausible explanation of this finding may be an underlying different prevalence of sex hormone receptors by gender which modulates tumour aggressiveness. Furthermore, a different distribution of smoking habits by sex might represent an additional explanation for the estimated prognostic advantage in the female subgroup.

In conclusion, the favourable prognosis in gastric cancer associated with SES provides further evidence for the increasing role of social class in the survival of several malignancies. This observation strengthens the concept that host-related and environmental factors may be as important as tumour-related factors in affecting disease outcome, particularly when the role of postsurgical treatment is marginal as it is in gastric cancer patients. As some of these factors are potentially modulatable, our findings may have important implications for the planning of future health service strategies and for the allocation of financial resources for the management of this disease.

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