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Original Paper

The Prognostic Role of Gender in Survival of Adult Cancer Patients

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Many observations indicate that women have a much longer expectancy of life than men. Some population-based studies on cancer patients support the idea of the role of gender in predicting survival. However, the data are somewhat contrasting and inconclusive. The purpose of this paper was to evaluate the prognostic role of gender for cancer patients, making use of the large set of survival data made available by the EUROCARE II project for the period 1985–1989. By applying a multivariate approach the major confounders such as age, geographical area and cancer site were considered in analysing survival data on more than 1 million cancer cases collected by 45 population-based cancer registries in 17 European countries. The results were consistent with the general observation that in the industrialised countries women tend to survive longer than men. The multivariate analysis showed better survival from cancer in women than in men, estimated as an overall 2% lower relative risk of dying. The female advantage was particularly evident in young cases, reduced in patients in middle age groups and in the oldest patients completely reversed so that at this age men had the better prognosis. Longer survival for women was not present immediately after diagnosis, but the major advantage was seen after 3 years of follow-up. The risk of death for women was significantly lower for cancer of the head and neck, oesophagus, stomach, liver and pancreas. For bladder cancer, the risk of death was significantly greater for women. These results can be explained by gender differences in sub-site distributions (head and neck and stomach) and by the differences in the stage at diagnosis (presumably bladder). However, the consistency of the data, evident only when a vast set of data is analysed, suggest that women may be intrinsically more robust than men in coping with cancer. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

LIFE EXPECTANCY for women at birth exceeds that for men in almost all countries, exceptions being Bangladesh, Bhutan, India, Nepal and Pakistan; the anomaly of these countries generally being considered as an effect of strong discrimination against women [1]. In most industrialised countries, the greater life expectancy of women has been known for a long time [2]. In Sweden, the country with the longest reliable mortality statistics, female life expectation at birth has exceeded males since 1751 when data became available [1]. Some researchers predict that the gender gap will increase in the near future [3], whilst others suggest it will decrease slightly [4]. One view of the phenomenon is that it is biological and approaches the status of a law of nature. However, even if women do have an advantage over men in terms of psychological and biological robustness [2], the causes of this difference remain poorly understood.

The potential effect of gender as a predictor of life expectancy of cancer patients has not been sufficiently investigated.

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EUROCARE I, a project for estimating the survival of European cancer patients diagnosed during 1978–1985 [5] and other studies found that female gender is a favourable prognostic factor for survival, even after adjusting for competing mortality (i.e. when relative survival were considered) and age [6–9].

The aim of the present study was to evaluate gender differences in cancer survival in a large set of data collected across 45 population-based cancer registries in 17 European countries (EUROCARE II). By analysing such a large set of survival data, undesirable random effects will be reduced, facilitating identification of the potential prognostic role of gender after adjusting for competing mortality, age, geographical area and cancer site.

PATIENTS AND METHODS

Survival analysis was carried out on 1 188 469 malignant cancer adult patients (ICD9: 140–208 except 173) diagnosed from 1985 to 1989 in 17 European populations participating in EUROCARE II. Cases discovered at autopsy, first diagnosed with another malignant tumour or known on the basis of death certificates only (DCO) were not included. Cases were followed for a minimum of 5 years after diagnosis. Some registries (Denmark, Estonia, Finland, Slovakia, Slovenia and Iceland) cover the population of the entire country. The English and Scottish registries cover a large fraction of the U.K., whereas, Austria, France, Germany, Italy, The Netherlands, Poland, Spain, Sweden and Switzerland are represented by a number of local and regional registries.

Information on cancer site or subsite, coded according to the International Classification of Diseases (ICD) [10] was available from the registries. Survival time was considered as the time between diagnosis and death, irrespective of the specific cause of death. Reliable information on the cause of death is often lacking in population-based studies. Correction for mortality due to competing causes was obtained by computing the relative survival (the ratio of observed survival to the survival of the general population in which the cancer cases occurred). Gender, age, year and general mortality rates specific to the registry area were derived from official life tables provided by each cancer registry. Life expectancy at country level was derived from WHO 'Health For All' statistical database [11].

All considered factors were subjected to univariate analysis for men and women separately. In order to provide an immediate comparison of survival between the sexes, the Relative Risk (RR) of death was calculated as the ratio of the relative survival rates, expressed as logarithms, for each gender. To assess the effects of follow-up, age, area (country) and cancer site simultaneously on survival, several multiple regression analyses were performed [12]. By this multivariate approach, it was possible to model relative survival using a method similar to that proposed by Cox for observed survival [13]. In these models, time from diagnosis, i.e. duration of follow-up, was a categorical variable taking values 1, 3, 5, 7, 9 and 11 years. Except gender-specific sites and the breast, all cancer sites were considered. Age at diagnosis was divided into 5 classes (15–44, 45–54, 55–64, 65–74, 75–99 years). The colon cancer site, the country Finland, age class 55–64 years and men were taken as the reference categories for the variables site, country, age and gender, respectively. Gender had no influence on relative survival for colon cancer in a previous study on EUROCARE I data in which Finland was taken as the reference category [14]. Thus, the variables considered in the present study had the following levels: 6 intervals of follow-up, 17 countries (England and Scotland were considered separately), 27 sites, 5 age classes and gender. However, in order to investigate the role of age on survival, a few models considered sub-groups of total patients with different sets of explanatory variables. Due to the very large number of patients considered, the general multivariate regression analysis produced several factors having formal statistical significance; only factors of specific interest were considered.

RESULTS

Life expectancy

In all countries participating in the EUROCARE II study, life expectancy at birth was higher for women than for men according to WHO 1992 data (Figure 1) [11]. Differences between the sexes ranged from around 4 years in Iceland, where the expectation of life for men was 76.8 years, to 11.2 years in Estonia, where the expectation of life for men was 63.6 years (Table 1). The three highest differences were observed in the Eastern European countries Estonia, Poland and Slovakia; whereas the three smallest differences were in the Northern European countries of Iceland, Denmark and Sweden. In Southern European countries and in The Netherlands, the difference between the sexes ranged between around 6 and 8 years.

Differences in life expectancy between the sexes were inversely associated with the RRs of dying (women versus men) for all cancer malignancies combined—correlation index: $r = -0.7$. However, by analysing the correlation of this difference with the RR of dying for several common tumours (Table 1), we found that for some tumours the correlation was negative (e.g. lung), for others it was positive (e.g. melanoma) and for others the association was weak (e.g. kidney).

Univariate analyses

Table 2 shows the RRs of dying for women compared with men by cancer site. The age-standardised 5-year relative survival by gender is also presented. Considering overall age-standardised survival, the risk of dying was similar for men and women for several common malignancies (for example, colon, rectum, gall bladder, pancreas, lung and leukaemia);

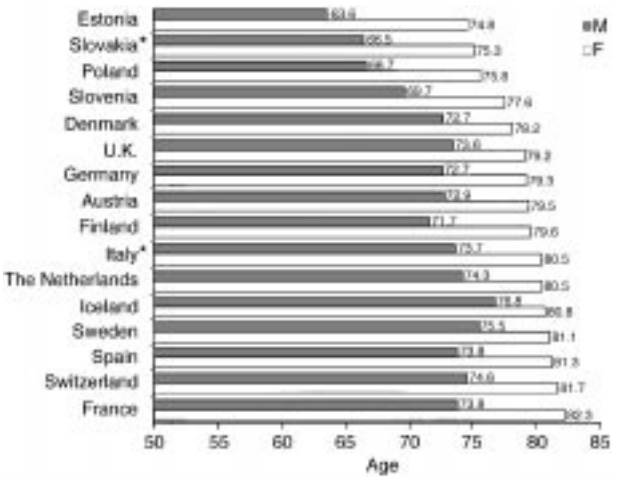

Figure 1. Life expectancy at birth ranked by female in Europe, 1992 according to the WHO [11]. *1991.

Table 1. *Differences in life expectation between females and males. Estimated Relative Risk (RR) of dying from cancer for females versus males for those countries with a national cancer registry (EUROCARE* II*)*

Country	Differences between females and males in life-expectancy 1992 1 Years	Stomach cancer* 2 RR (f:m)	Colon cancer* 3 RR (f:m)	Lung cancer* 4 RR (f:m)	Melanoma of skin* 5 RR (f:m)	Kidney cancer* 6 RR (f:m)	Non-Hodgkin's lymphomas* 7 RR (f:m)	Leukaemia* 8 RR (f:m)	All malignant neoplasms* 9 RR (f:m)
Iceland	4.0	0.7	0.8	1.0	0.5	1.1	0.4	1.3	0.84
Denmark	5.5	0.9	0.9	1.0	0.5	1.1	0.8	1.1	0.74
Finland	7.9	1.0	0.9	0.9	0.6	0.8	0.8	1.0	0.70
Slovenia	7.9	0.9	0.9	1.0	0.5	0.7	0.7	0.8	0.64
Slovakia	8.6	1.0	1.0	0.8	0.6	0.9	0.8	1.0	0.77
Estonia	11.2	1.0	1.0	0.7	0.7	1.1	0.7	1.0	0.65
Correlation index '*r*' with data in column 1		0.77	0.75	− 0.87	0.88	− 0.23	0.52	− 0.63	− 0.75

*Cases diagnosed from 1985–1989.

Table 2. *Five-year age-standardised relative survival (%) and Relative Risk (RR) of dying at different ages of cancer for females versus males by age group (years) (EUROCARE* II*)*

ICD 9—cancer site	Age group (years) 15–44	45–54	55–64	65–74	75–99	Age standardised 5-year relative survival Male	Female	RR (f:m)
			RR (f:m)					
141 Tongue	0.8	0.7	0.6	0.7	0.9	37	50	0.7
143–145 Oral cavity	0.7	0.8	0.9	0.5	0.7	41	53	0.7
146 Oropharynx	0.9	0.8	0.6	0.9	0.8	30	45	0.7
147 Nasopharynx	1.1*	1.2*	0.9	1.3*	0.7	34	32	1.1*
148 Hypopharynx	1.1*	1.0	1.2*	1.1*	0.4	22	23	1.0
141–143–148 Head and neck	0.7	0.7	0.7	0.5	0.8	34	48	0.7
150 Oesophagus	0.7	0.7	0.7	0.8	0.9	7	12	0.8
151 Stomach	1.1*	0.8	0.9	0.9	0.9	19	24	0.9
152 Small intestine	0.9	1.4*	1.3*	1.0	1.3*	37	30	1.2*
153 Colon	1.0	0.8	0.9	1.0	1.1*	47	46	1.0
154 Rectum	0.6	0.9	0.9	1.0	1.1*	42	43	1.0
155 Liver	0.9	1.1*	1.2*	0.9	0.9	4	5	0.9
156 Gall bladder	2.3*	1.2*	1.2*	0.8	1.0	12	12	1.0
157 Pancreas	0.7	0.8	1.1*	1.2*	1.0	4	4	1.0
160 Nasal cavities	0.4	1.3*	0.7	0.7	1.6*	42	45	0.9
161 Larynx	0.5	0.9	0.8	0.8	1.6*	63	65	0.9
162 Lung	0.7	0.9	1.0	1.0	1.1*	9	10	1.0
163 Pleura	1.1*	0.5	0.8	1.5*	0.9	7	8	0.9
170 Bone	0.7	0.9	1.1*	0.6	1.2*	45	51	0.9
171 Soft tissues	0.9	0.5	0.9	1.0	2.0*	59	59	1.0
172 Melanoma of skin	0.5	0.6	0.5	0.6	0.5	68	81	0.5
174-5 Breast	2.0*	0.7	1.0*	1.3*	0.5	69	73	0.9
188 Bladder	1.3*	1.4*	1.2*	1.2*	1.2*	65	60	1.2*
189 Kidney	0.9	0.7	0.9	1.0	1.1*	47	49	0.9
190.6 Choroid (melanoma)	0.2	0.6	1.5*	1.1*	1.0	69	71	0.9
191 Brain	0.9	1.0	0.7	0.8	1.2*	17	20	0.9
103 Thyroid	0.1	0.5	0.6	0.7	0.4	65	78	0.6
200, 202 Non-Hodgkin's lymphoma	0.8	0.9	0.8	0.8	1.2*	45	48	0.9
201 Hodgkin's disease	0.8	0.6	0.9	1.2*	1.5*	71	73	0.9
203 Multiple myeloma	1.2*	1.0	0.9	1.0	1.2*	29	27	1.1*
204.0 Acute lymphatic leukaemia	0.8	0.6	1.3*	0.6	0.7	23	29	0.8
204.1 Chronic lymphatic leukaemia	1.4*	0.4	0.5	0.8	0.9	60	66	0.8
205.0 Acute myeloid leukaemia	1.1*	1.0	0.7	1.0	1.2*	10	10	1.0
205.1 Chronic myeloid leukaemia	0.7	0.6	1.1*	0.9	1.2*	30	33	0.9
204–208 Leukaemia	1.0	0.8	0.9	1.0	1.0	33	34	1.0
140–208 All malignant neoplasms	0.7	0.5	0.6	0.7	0.9	41	53	0.7

*Relative risk higher for women than for men.

Table 3. Five-year age-standardised relative survival (%) of European cancer patients by gender and country (EUROCARE II)

	Oesophageal cancer		Stomach cancer		Colon cancer		Pancreas cancer		Lung cancer		Melanoma of skin		Kidney cancer		Non-Hodgkin's lymphoma		Hodgkin's disease		Leukaemia		All neoplasms	
Country	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Northern Europe																						
Iceland	–	–	19	32	44	52	5	–	12	13	64	81	44	39†	45	72	–	–	25	18†	47	53
Finland	7	9	19	20	48	50	2	3	10	12	76	85	45	52	39	47	71	77	34	33	38	50
Sweden*	–	–	18	17†	52	55	2	3	9	10	85	90	49	48†	47	52	74	71	32	34	50	58
Denmark	2	9	12	15	39	43	2	2	6	6	72	83	36	33†	43	49	69	71	29	27	42	52
U.K.																						
Scotland	5	10	10	12	41	41	4	3†	6	6	74	88	36	35†	40	43	65	67	28	24†	29	38
England	7	12	11	13	41	41	3	3	7	7	70	83	39	37†	43	47	70	74	28	29	42	51
Western Europe																						
The Netherlands*	7	18	18	22	59	56†	3	3	12	11†	76	83	53	45†	40	46	76	–	30	36	35	51
Germany*	8	–	25	27	50	50	–	2	9	14	67	83	47	55	44	50	76	66†	39	39	49	59
Austria*	24	–	23	31	55	44†	5	–	10	15	97	86†	55	76	61	64	85	–	43	41†	47	54
Switzerland*	11	11	21	25	52	49†	2	3	10	11	83	94	53	45†	49	52	76	76	44	36	51	62
France*	7	–	24	26	52	54	–	7	12	16	71	81	57	56†	54	53†	70	85	45	50	42	59
Southern Europe																						
Spain*	8	–	25	28	50	49†	5	5	12	–	70	84	51	52	51	48†	–	68	39	40	47	57
Italy*	6	13	20	27	47	47	4	3†	9	10	55	78	52	55	44	48	69	71	24	30	38	52
Eastern Europe																						
Slovenia	4	–	12	16	33	38	2	4	6	7	48	69	39	52	37	49	69	80	27	35	24	40
Slovakia	7	16	18	20	39	38†	9	9	12	19	55	69	43	45	35	42	58	66	36	35	32	42
Poland*	4	–	8	10	26	23†	3	4	6	9	43	60	33	33	32	31†	62	70	14	10	22	34
Estonia	–	–	15	16	37	38	4	0†	5	14	55	67	32	28†	21	32	41	51	40	41	22	37
Europe	7	12	19	24	47	46†	4	4	9	10	68	81	47	49	45	48	71	73	33	34	41	53

* < 20% of the national population covered. †5-year relative survival is lower for women than for men.

whilst the risk was slightly smaller for women with, for example, stomach, larynx and kidney cancer and non-Hodgkin's lymphomas (RR = 0.9). For melanoma of the skin and thyroid the risk for women was definitely lower (RR = 0.5 and RR = 0.6, respectively), whilst for bladder cancer and cancer of the small intestine, the risk was higher (RR = 1.2) in women. For cancers of the upper respiratory tract (except for nasopharynx) women also had a lower risk of dying (see head and neck, RR = 0.7). When survival by age was analysed, RRs were found to be generally lower for younger women than men (< 74 years at diagnosis), whilst in elderly patients women had a higher RR of dying for several cancer sites (see Table 2).

Table 3 shows the 5-year relative survival by gender for selected cancer sites by country. The advantage for women was present in almost all countries with available data for oesophagus, stomach, lung, melanoma, non-Hodgkin's lymphoma, Hodgkin's disease and all cancers combined. Survival was sometimes worse in women with colon cancer, kidney cancer or leukaemia.

Multivariate analyses

Table 4 presents the models fitted to all the data, including those with main factors and those with an interaction with gender of the first grade. All the models were highly significant except for the last model, which included interaction of gender with country. This can be explained by the low statistical power for analysing gender-differences in individual countries.

Table 5 presents the estimated risk of dying for women relative to men and the interactions with follow-up, site and age. The relative risk of interactions helps us to understand where the differences in survival between the genders were

Table 4. Regression analyses of relative survival rates in cancer patients in Europe: stepwise procedure (EUROCARE II)

Models No.	Factors included in the model	Deviance	Degrees of freedom	Comparisons among models	Deviance difference	Degree of freedom difference	*P* value
1	Follow-up	216816	24247				
2	Follow-up + site	72038	24221	1–2	144778	26	< 0.0001
3	Follow-up + site + age	53137	24217	2–3	18901	4	< 0.0001
4	Follow-up + site + age + country	47091	24201	3–4	6046	16	< 0.0001
5	Follow-up + site + age + country + gender	47012	24200	4–5	63	1	< 0.0001
Models with interaction							
6	(model 5) + follow-up.gender	46574	24195	6–5	454	5	< 0.0001
7	(model 5) + site.gender	46310	24174	7–5	718	26	< 0.0001
8	(model 5) + age.gender	46775	24196	8–5	253	4	< 0.0001
9	(model 5) + country.gender	46993	24184	9–5	35	16	0.004

Table 5. Selected relative risk and the associated P value for models 5, 6, 7, 8 of Table 4 (EUROCARE II)

Model	Factor	Relative risk*	*P* value
Model 5: follow-up, site, age country, gender	Gender	0.98	0.01
Model 6: follow-up, site, age country, gender and follow-up.gender	Gender	1.00	n.s.
	Follow-up (3 years)	0.83	< 0.001
	Follow-up (5 years)	0.81	< 0.005
	Follow-up (7 years)	0.84	n.s.
	Follow-up (9 years)	0.87	n.s.
	Follow-up (11 years)	0.81	n.s.
Model 7: follow-up, site, age country, gender and site.gender	Gender	1.01	n.s.
	Lip	0.87	n.s.
	Salivary glands	0.69	n.s.
	Head and neck	0.77	0.01
	Oesophagus	0.85	< 0.001
	Stomach	0.92	0.01
	Small intestine	0.90	n.s.
	Rectum	1.00	n.s.
	Liver	0.91	0.03
	Gall bladder	1.08	n.s.
	Pancreas	0.94	0.05
	Nasal cavities	1.01	n.s.
	Larynx	1.15	n.s.
	Lung	0.99	n.s.
	Pleura	1.02	n.s.
	Bone	0.74	n.s.
	Soft tissues	1.04	n.s.
	Melanoma of skin	0.58	n.s.
	Bladder	1.50	< 0.001
	Kidney	1.00	n.s.
	Choroid (melanoma)	0.68	n.s.
	Brain	1.01	n.s.
	Thyroid gland	0.84	n.s.
	Non-Hodgkin's lymphoma	0.94	n.s.
	Hodgkin's disease	0.95	n.s.
	Multiple myeloma	0.89	n.s.
	Leukaemia	1.01	n.s.
Model 8: follow-up, site, age, country, gender and age.gender	Gender	0.95	< 0.01
	15–44 age class	0.86	0.02
	45–54 age class	0.95	n.s.
	65–74 age class	1.01	n.s.
	75 + age class	1.07	< 0.001

*Colon, Finland, 55–64 years and men were the reference categories for the variables site, country, age and gender, respectively. n.s., not significant.

more significant. Overall, gender was significant at the 1% level in model 5 (which included only the main effects): women had a 2% protection after adjusting for time from diagnosis, cancer site, age and country. Interaction of gender with years of follow-up, indicated that the lower risk of women was not present at 1 year of follow-up (suggesting that the advantage was not present at the time of diagnosis) but was rather present after 3–5 years of follow-up. During subsequent years of follow-up, up to 11 years, differences in survival were again non-significant. Interactions with site (model 7) revealed the following sites for which between-gender survival differences were significant: head and neck, oesophagus, stomach, liver, pancreas and bladder. Only for bladder was the risk of death for women significantly higher than for men. This effect was also seen in age-stratified univariate analyses, whilst the lower risk for women in pancreatic cancer had been completely obscured in the univariate analysis (Table 2).

Model 8 (Table 5) revealed a complex risk pattern for the interaction of gender with age. Young age was a greater protective factor for women than men, whilst among elderly patients, women were at significantly higher risk than men. This result is consistent with that of the univariate analyses. The disadvantage in the older age groups for women remained in models in which only the elderly patients were considered (data not shown). The major determinant of this phenomenon was bladder cancer but, in a model on data from the elderly in which bladder cancer was excluded, women still had a significantly higher risk than men.

DISCUSSION

Women generally have a much longer life expectancy than men. Several earlier observations suggested that this female advantage is present in cancer patients, even after adjusting for competing mortality [5, 6, 9]. The purpose of the present study was to evaluate the role of gender as a potential predictor of survival in cancer patients, making use of the very large population-based data-set of the EUROCARE II. To our knowledge, this is the first time that gender has been analysed as predictor of survival in cancer patients adjusting

by a multivariate approach for the major confounders (competing mortality, age, geographical areas, and cancer site).

Our findings provide further evidence of better overall cancer survival in women than men. In principle the female survival advantage could be due to one or more of the following factors:

(1) Greater attention of women to their bodies and to disease, resulting in earlier diagnosis and more effective treatment;
(2) Over-correction or under-correction in one gender or other for competing mortality;
(3) A different mix of cases between the genders due to exposure to different risk factors; and
(4) Biological superiority of women in responding to diseases, treatments or both.

Culture-mediated factors may influence differences in illness behaviour between women and men, resulting in differences in the use of health services. Illness behaviour refers to a person's perception of symptoms, assessment of their importance and readiness to take health action [15]. Women may report more symptoms and at an earlier stage of the disease because they are more interested in health and have more knowledge about health than men do [16]. Women may also be more likely to seek help for symptoms [17]. It is apparently more socially acceptable for women to report discomforts to family and friends. This willingness to talk about symptoms influences medical care. Women may seek help sooner for a health problem, having being urged by friends or their own feelings to seek the opinion of a medical professional. Women may also give more details about their problem during this contact, thus, improving their chances of early cancer diagnosis and of receiving appropriate treatment, thus improving survival [18]. However, in the SEER Cancer Incidence Public-Use Database [19], which includes incidence data from US cancer registries covering approximately 10% of the North American population, the percentage of cases with non-invasive cancer for the most common sites do not differ greatly between women and men. In our findings, after diagnosis, the risk of death in women compared with men changed during the years of follow-up (i.e. the risk pattern in relation to time from diagnosis was non-proportional between men and women). A survival difference between genders was not present 1 year after diagnosis. If women tend to anticipate their diagnoses, one would expect to find a considerable gender difference in this period soon after diagnosis. Therefore, our results do not support the idea that diagnosis in women is systematically anticipated earlier than in men because women pay more attention to their bodies and their health.

In a Swedish population-based study on 6262 youth cancer patients the overall death rate was 22% lower in women compared with men [6]. With this difference in the risk of death at around the age of sexual maturity, it was suggested that female sex hormones might be able to prevent the establishment of distant metastases in certain malignant diseases. In the Eindhoven Cancer Registry, in cases diagnosed at the age of 70 years or more, the prevalence of serious co-morbidity (classified as [20]) was higher for men than for women (J.W.W. Coebergh, Eindhoven Cancer Registry, The Netherlands) in several malignant neoplasms. In the younger age group, the proportion of cancer patients with co-morbidity was also higher in men than in women, but not as high as in the oldest age class. In our study we found that age was an important predictor of the gender difference in cancer survival. In young patients, the female advantage was evident as a 14% lower risk of death in the 15–44 age-class compared to men (see Table 5). However, the gender effect began to change for patients aged 65 years or more. Also, in the oldest patient group (over 75 years), women had a significantly higher risk of death than men. These findings should be considered with caution. In the older age group where information is often imprecise the adjustment for competing mortality could be biased. This is particularly for men who have higher general mortality than women (Figure 1). However, when the same models were applied only to data from subjects aged 75 years or more, the higher risk for women compared with men at the older ages was confirmed. This overall complex effect of age in determining survival differences between men and women is difficult to interpret, particularly in the light of the data on the different prevalence of co-morbidity between genders mentioned above [JWW Coebergh, Eindhoven Cancer Registry, The Netherlands]. However, it is noteworthy that neither our findings on age, nor the r coefficients given in Table 1, support the idea that biases in the correction of competing mortality can explain the female survival advantage. In fact, this survival advantage is present for the ages in which the effect of the adjustment for competing mortality is low.

In our multivariate analysis, the risk of death for women was lower than for men for the following cancer sites: head and neck, oesophagus, stomach, liver and pancreas. By contrast, for bladder cancer, women had a poorer prognosis than men. This survival difference for bladder cancer was an important explanatory factor in determining the higher death risk for women compared with men in the elderly. The influence of gender on survival for some of these cancers could be due to differences in sub-site distribution. The distribution of stomach cancer by sub-site was: 15% of male cases and 8% of female cases were cardias (ICD-9: 1510) (which have a poor prognosis); 26% of male and 27% of female cases were classified as 'other sub-sites' (ICD-9: 1511–1517), and 59% of male cases and 65% of female cases were 'not otherwise specified' (ICD-9: 1518–1519). The longer survival for bladder cancer among men could be explained by a higher frequency of non-invasive cancer in men than women [21]; however, further investigation is required to better interpret this interesting result.

In the EUROCARE I study, carried out on approximately 800 000 cancer patients from 11 European countries, women generally had longer relative survival than men, although for cancers of the kidney, colon, nasopharynx, oesophagus and acute myeloid leukaemia, women had worse survival [7]. However, when age-adjusted relative survival was considered, the only cancer for which women still had a worse prognosis was cancer of the colon [8]. The female advantage was suggested to be related to a more favourable distribution of subsites (for head and neck cancer) or histology (for lung cancer), different stage distribution gender differences in disease-specific prognostic factors and it was suggested that the female survival advantage could result from the approach used to correct for competing mortality [7]. In fact, factors such as smoking, drinking and occupational exposure, which heavily influence both cancer incidence and competing mortality are likely to be more frequent in male cases than in the general population, whose mortality is used for calculating

relative survival. This could result in an underestimation of real survival in men. In an Italian population-based project (ITACARE) on more than 90 000 cancer patients, the prognosis was consistently better for women than for men, except for bladder cancer [9]. For all cancer combined, women had a much better prognosis than men with a RR of death of 0.6. However, after excluding breast cancer and sex-specific cancer, the age-adjusted RR of death for women compared with men was 0.9. Part of the female advantage was explained as being due to the higher frequency in men of the smoking-related cancers (e.g. lung, pancreas and oesophagus) which have poor prognoses. Furthermore, differing histotype and sub-site distributions between men and women were considered capable of at least partially explaining sex-differences in survival of certain sites [22]. This was the case for melanoma (which is more often superficial spreading melanoma in women and occurs more often in the limbs of women) and for head and neck cancer, which shows differences in the distributions by sub-site and stage between the genders.

It is possible that genetic and environmental factors and their complex interrelations, which may influence the cancer prognosis [23], play a role in determining the survival differences between the genders found in this study. For example, genes on the X chromosome have been shown to influence immune functioning. The presence of two alleles of these genes in women (two X chromosomes) may confer increased resistance to infectious diseases and protect women from potential worsening of the disease status [23, 24]. There is considerable evidence that women may be biologically more durable than men: from conception to menopause, women have lower infant mortality, lower death rates from congenital anomalies and lower overall death rates [25]. The results of this present study lend support to the idea that women are also intrinsically more robust in combating cancer.

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APPENDIX

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