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The cure of cancer: A European perspective

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ABSTRACT

Cancer survival analyses based on cancer registry data do not provide direct information on the main aim of cancer treatment, the cure of the patient. In fact, classic survival indicators do not distinguish between patients who are cured, and patients who will die of their disease and in whom prolongation of survival is the main objective of treatment.

In this study, we applied parametric cure models to the cancer incidence and follow-up data provided by 49 EUROCARE-4 (European Cancer Registry-based study, fourth edition) cancer registries, with the aims of providing additional insights into the survival of European cancer patients diagnosed from 1988 to 1999, and of investigating between-population differences.

Between-country estimates the proportion of cured patients varied from about 4–13% for lung cancer, from 9% to 30% for stomach cancer, from 25% to 49% for colon and rectum cancer, and from 55% to 73% for breast cancer. For all cancers combined, estimates varied between 21% and 47% in men, and 38% and 59% in women and were influenced by the distribution of cases by cancer site. Countries with high proportions of cured and long fatal case survival times for all cancers combined were characterised by generally favourable case mix. For the European pool of cases both the proportion of cured and the survival time of fatal cases were associated with age, and increased from the early to the latest diagnosis period. The increases over time in the proportions of Europeans estimated cured of lung, stomach and colon and rectum cancers are noteworthy and suggest genuine progress in cancer control. The proportion of cured of all cancers combined is a useful general indicator of cancer control as it reflects progress in diagnosis and treatment, as well as success in the prevention of rapidly fatal cancers.

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1. Introduction

Analyses of population-based cancer survival typically present and compare absolute and relative survival a given time – usually 5-years – after diagnosis. While 5-year survival is a useful indicator, it does not provide direct information on the main aim of cancer treatment, the cure of the patient. In fact classic survival indicators do not distinguish between patients who are cured, and have a life expectancy close to that of the rest of the population, and patients who

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will die of their disease and in whom prolongation of survival is the main objective of treatment. Another important shortcoming of the survival indicator is that increases in survival reflect not only gains in life expectancy, but also anticipation of diagnosis – the so-called lead time bias – which may not be accompanied by postponement of death. If it were possible to reliably estimate the proportion of patients cured of their disease, it would be possible to control for lead time bias, which is a characteristic only of patients who will die of their disease.

Methods for estimating the proportion of patients who are cured, and the survival time of those who are not, have been developed and applied to data from population-based cancer registries.[1] These indicators are best estimated on data from cancer registries that have been collecting data for a long period so that patient follow-up is sufficiently long. This is the case for many of the cancer registries participating in the EUROCARE studies[2–4] on the survival of European cancer patients. In fact, about half the cancer registries participating in EUROCARE-4 provided data on cohorts of patients followed-up for 16 years after diagnosis.

The aim of the present study was to use EUROCARE survival data to estimate the proportions of patients cured of their cancer in diverse European populations, to estimate the average time to death of cases not cured and to analyse between-country differences. To do this, we applied parametric cure models that allow the cured and not cured populations of cancer survivors to be distinguished.[5–7]

2. Data and methods

2.1. Data sources and estimation of relative survival

We selected 49 of the 83 cancer registries participating in EUROCARE-4 for analysis as they provided information on cancer patients diagnosed from 1st January 1988 to 31st December 1999 and followed up until 31st December 2003. Follow-up thus varied from four years, for patients diagnosed in 1999, to 16 years for those diagnosed in 1988. Table 1 shows the countries and cancer registries included in the analysis, with the percentages of national coverage, and the numbers of adult (15–99 years) patients diagnosed in 1988–1999, for all cancer sites combined. Only first primary malignant cancers, except non-melanoma skin cancers, were considered in the analysis.[8]

We also excluded cases known to the registries only by death certificate or discovered incidentally at autopsy. For nine countries, the entire population was covered by cancer registration. The other 40 registries, representing nine countries, covered variable proportions of their respective national populations, ranging from 1% in Germany (Saarland cancer registry) to 90% in the eight English regional registries (East Anglia, Mersey, Northern and Yorkshire, Oxford, South Western, Thames, Trent and West Midlands). Two specialist regional cancer registries (Côte d'Or and Zurich) provided data on digestive tract cancers only.

Cancer site-specific cumulative relative survival was estimated from incidence and vital status data using the SEER*-Stat software.[9] Relative survival – the ratio of the observed

Table 1 – Numbers of European adults (age 15–99 years) diagnosed with cancer in 1988–1999 and included in the analyses, by country and cancer registry, with percentage of national coverage.

Country	Cancer registry	Percentage of national coverage	Number of cases included in analysis
Austria	National	100	425,137
Czech Republic	West Bohemia	8	43,898
Denmark	National	100	315,442
Finland	National	100	232,231
France	Bas Rhin, Calvados, Cote d'Or digestive[a], Doubs, Haut Rhin, Isère, Somme, Tarn	9	173,378
Germany	Saarland	1	75,052
Iceland	National	100	11,469
Italy	Firenze, Genova, Modena, Parma, Ragusa, Romagna, Torino, Varese, Veneto	15	586,769
Netherlands	Amsterdam, Eindhoven	24	173,022
Norway	National	100	253,399
Poland	Cracow, Warsaw	6	97,585
Scotland	National	100	363,013
Slovenia	National	100	74,742
Spain	Basque country, Navarra, Tarragona	8	153,501
Sweden	National	100	472,031
Switzerland	Basel, Geneva, Grisons, St Gallen, Valais, Zurich[a]	43	85,910
England	East Anglia, Mersey, Northern and Yorkshire, Oxford, South Western, Thames, Trent, West Midlands	90	2,262,774
Wales	National	100	168,195
European pool	Pool of the 49 cancer registries listed above		5,967,548

a These registries provided data for digestive tract cancers only.

survival of cancer patients to the survival expected in the age- and sex-matched general population[10,11] – was calculated by the Hakulinen method by using age- and sex-specific life tables from each cancer registry area.[12] Relative survival was the input data for the cure models.

2.2. Cure models

Also known as mixture models,[5–7] cure models are parametric survival models that assume patients can be divided into cured cases, with the same mortality as the rest of the population of the same age and sex, and fatal cases, with an excess risk of death compared to the rest of the population. These models require the specification of a parametric excess mortality function for fatal cases. For this purpose, we used a Weibull distribution which represents the failure time of fatal cases. We applied cure models to relative survival data by country (as represented by our selected cancer registries), age class (15–44, 45–54, 55–64, 65–74 and 75–99 years) and diagnosis period (1988–1990, 1991–1993, 1994–1996 and 1997–1999) for the common cancer sites: breast (women only), lung, prostate, colon and rectum and stomach. We also applied the cure models to the relative survival estimated for all cancer sites combined, for men and women separately.

The general form of the cure model used is

$$RS(t) = [P + (1 - P) \times W(\lambda, \gamma, t)]. \quad (1)$$

where RS is the relative survival, t is the follow-up time, P is the proportion of cured patients, $W(\lambda, \gamma, t)$ is the Weibull cumulative survival of form $\exp(-(\lambda t)^{\gamma})$, and λ and γ are, respectively, the scale and shape parameters of the distribution. From model (1), the average time to death for fatal cases T can be calculated from λ and γ as

$$T = \frac{1}{\lambda} \times \Gamma\left[1 + \frac{1}{\gamma}\right] \quad (2)$$

where Γ is the gamma function. Model (1) was applied separately to the data stratified, first by country, then by age class and then by diagnosis period. The model produced satisfactory fits to the survival data for stomach, colon and rectum and lung cancers, but not for breast or prostate cancers. The reason for this can be appreciated by inspecting the cumulative relative survival curves of Fig. 1 derived from the data of the 49 cancer registries included in the analysis, for all adults, over the period 1988–1999. The curves for lung cancer, stomach cancer and colon and rectum cancer flatten out five-to-ten years after diagnosis. The survival when the curve flattens approximately indicates the proportion of patients who are cured (these survivors have a death risk similar to that of the healthy population). For breast and prostate cancers, on the other hand, relative survival decreased continuously with follow-up, and did not clearly flatten out in the follow-up time available. This behaviour indicates that excess mortality remains for these cancers at least 16 years after diagnosis.

Fitting model (1) to each diagnosis period is not appropriate in such situations, as very little information on the asymptotic value of relative survival is contained in the data for the most recent diagnosis periods. For these cancers, therefore (and also for all cancers combined), we were unable to estimate the proportions cured and the survival time of fatal cases for each diagnosis period. It was, however, possible to estimate these variables considering the patients in all diagnosis periods together, so the estimates produced refer to the mean year of all the diagnosis periods (1988–1990, 1991–1993, 1994–1996 and 1997–1999). To do this, we introduced an additional parameter β to the Weibull model to represent the relative excess risk of death by the diagnosis period. We thus obtained the following modified cure model:

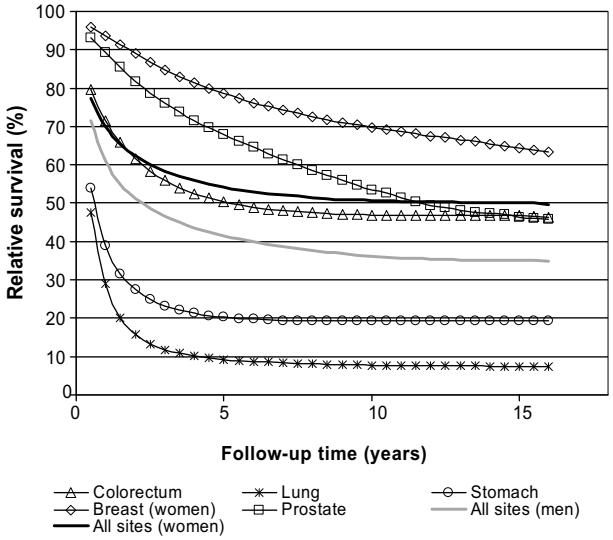

Fig. 1 – Curves showing relative survival for selected cancer sites in relation to length of follow-up in adult patients (15–99 years) diagnosed in the pool of 49 European cancer registries, during the period 1988–1999.

$$RS(t) = [P + (1 - P) \times W(\lambda, \gamma, t)]^{\exp\{\beta(p - p_{\text{mean}})\}} \quad (3)$$

where p is the diagnosis period and p_{mean} is the mean year of all the diagnosis periods (reference period). Using model (3) *time trends* for P (proportion of cured patients) and T (average time to death for fatal cases, Eq. (2)) are not available, since a single period effect β is estimated which refers to the entire period considered. The coefficient β is in fact a measure of the relative risk of dying of patients diagnosed in a given period between 1988 and 1999 compared to the reference period. As the follow-up time gets longer fatal cases die and β becomes the period effect of the proportion cured. A negative value of β corresponds to an increase in the chance of being cured of the cancer over the diagnosis period.

Using model (3) P and T were estimated at the mean year of diagnosis for breast cancer, prostate cancer and all cancers combined (men and women separately) for each country. The model was also applied to the European pool of breast cancer, prostate cancer and all cancer cases, for the diagnosis period 1988–1999, in order to estimate in P and T with age at diagnosis.

Table 2a – Estimated proportions (%) of cured patients, and life expectancy (years) for fatal cases for lung, stomach and colon and rectum cancers diagnosed in European adults (15–99 years) in the period 1988–1999 by country; with estimates also for the European pool of cancer cases (49 of the 83 cancer registries participating in the EUROCARE-4 study) by age at diagnosis and by diagnosis period.

Country	Lung cancer						Stomach cancer						Colon and rectum cancers					
	Proportion of cured cases (%)			Life expectancy of fatal cases (years)			Proportion of cured cases (%)			Life expectancy of fatal cases (years)			Proportion of cured cases (%)			Life expectancy of fatal cases (years)		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Czech Republic	4.2*	3.6	4.8	0.93	0.86	1.01	8.5*	6.8	10.2	1.13	1.04	1.21	27.6*	24.1	31.1	2.44	2.26	2.61
Denmark	4.1*	3.7	4.5	0.71	0.65	0.76	11.5	10.8	12.1	0.82	0.76	0.88	37.1	35.1	39.1	2.46	2.34	2.59
England	6.3	5.9	6.6	0.58	0.54	0.63	12.4	11.8	13.0	0.68	0.63	0.74	39.9	37.9	41.9	2.12	2.01	2.24
Finland	5.6	5.1	6.0	1.00	0.94	1.05	21.8	20.8	22.9	0.93	0.84	1.02	47.1	44.4	49.8	2.53	2.31	2.75
France	10.3	9.7	10.8	1.14	1.08	1.20	23.8	22.8	24.8	1.10	1.02	1.19	49.4	47.4	51.3	2.64	2.45	2.83
Iceland	7.2*	6.1	8.2	0.91	0.80	1.02	14.1*	7.9	20.3	2.36	2.22	2.51	44.5*	39.6	49.4	3.14	2.74	3.54
Italy	7.0	6.4	7.6	0.99	0.92	1.07	25.4	24.2	26.6	1.05	0.95	1.15	45.8	43.1	48.4	2.58	2.37	2.79
Netherlands	9.9	9.3	10.4	1.01	0.96	1.07	18.6	18.1	19.2	0.88	0.83	0.93	48.0	46.6	49.4	2.49	2.37	2.61
Norway	6.7	6.2	7.3	0.82	0.76	0.88	18.4	17.5	19.2	0.85	0.78	0.93	46.1	44.0	48.2	2.69	2.52	2.85
Poland	4.4*	3.9	4.9	0.89	0.83	0.95	8.9*	7.8	10.0	0.80	0.72	0.88	24.8*	21.7	27.8	1.93	1.77	2.08
Scotland	5.1	4.7	5.5	0.65	0.60	0.70	10.8	10.1	11.4	0.78	0.73	0.84	39.2	36.8	41.5	2.36	2.23	2.49
Slovenia	6.7	6.2	7.1	0.86	0.80	0.91	13.7	12.5	14.9	1.03	0.96	1.10	31.9	29.3	34.5	2.22	2.06	2.38
Spain	10.0	9.5	10.5	0.84	0.78	0.89	26.8	25.9	27.7	0.85	0.76	0.94	43.9	41.9	45.9	2.30	2.15	2.46
Sweden	7.7	7.1	8.3	0.87	0.80	0.94	16.5	15.8	17.2	0.98	0.92	1.03	45.2	43.6	46.8	3.04	2.90	3.18
Switzerland	7.3*	6.5	8.0	1.06	0.98	1.14	21.7	20.4	23.0	1.03	0.92	1.14	46.3	42.8	49.8	3.11	2.79	3.42
Age class																		
15–44 years	16.2	15.9	16.5	0.95	0.91	0.99	23.8	22.9	24.8	1.44	1.35	1.52	47.4	46.2	48.6	3.03	2.89	3.16
45–54 years	10.8	10.6	11.1	0.95	0.93	0.98	21.3	20.4	22.2	1.40	1.33	1.48	43.0	42.0	44.0	2.97	2.87	3.07
55–64 years	7.8	7.6	8.0	0.94	0.91	0.97	17.4	16.7	18.0	1.22	1.16	1.28	41.0	39.7	42.2	3.10	2.99	3.22
65–74 years	5.9	5.7	6.1	0.78	0.76	0.80	14.6	14.0	15.3	1.02	0.97	1.07	40.7	39.5	42.0	2.68	2.60	2.77
75–99 years	3.5	3.3	3.6	0.56	0.55	0.58	12.5	12.0	13.0	0.67	0.63	0.70	40.3	39.0	41.6	1.57	1.53	1.62
Period																		
1988–1990	6.1	5.9	6.3	0.66	0.64	0.69	15.4	15.0	15.8	0.74	0.69	0.79	41.8	41.2	42.3	1.76	1.71	1.82
1991–1993	6.5	6.3	6.7	0.68	0.65	0.71	16.4	15.9	16.9	0.79	0.74	0.84	44.1	43.3	44.8	1.82	1.75	1.88
1994–1996	7.2	6.8	7.5	0.72	0.69	0.76	17.5	16.8	18.2	0.85	0.80	0.91	46.8	45.5	48.1	1.95	1.86	2.04
1997–1999	7.9	7.4	8.4	0.73	0.69	0.77	18.3	17.2	19.4	0.85	0.79	0.91	48.5	45.6	51.4	2.09	1.92	2.26

* Asterisk indicates estimates with associated coefficients of variation exceeding the limit of tolerance of 10%.

Table 2b – Estimated proportions (%) of cured cases, life expectancy (years) of fatal cases and relative excess risk of death (β-coefficient) for prostate cancer, breast cancer in women, all cancers men and all cancers women diagnosed in European adults (15–99 years) from 1988 to 1999 by country; with estimates for the European pool of cancer cases (49 of the 83 cancer registries participating in the EUROCARE-4 study) by age at diagnosis.

Country	Breast cancer women									Prostate cancer								
	Proportion of cured cases (%)			Life expectancy of fatal cases (years)			β coefficient (relative excess risk of death)			Proportion of cured cases (%)			Life expectancy of fatal cases (years)			β Coefficient (relative excess risk of death)		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Czech Republic	54.7	51.3	58.1	4.34	3.80	4.88	–0.06	–0.05	–0.07	27.7*	16.5	38.8	5.98	4.56	7.41	–0.06	–0.05	–0.07
Denmark	63.1	60.3	65.9	5.17	4.54	5.81	–0.03	–0.03	–0.04	13.6*	10.3	16.9	4.81	4.50	5.12	–0.01	–0.01	–0.02
England	67.4	64.8	70.0	4.58	3.96	5.20	–0.07	–0.06	–0.08	44.0	39.7	48.3	4.81	4.22	5.40	–0.10	–0.10	–0.11
Finland	73.2	70.2	76.1	5.81	4.81	6.80	–0.05	–0.04	–0.06	49.0*	44.0	53.9	6.47	5.49	7.45	–0.11	–0.10	–0.12
France	72.8	70.0	75.6	5.76	4.84	6.68	–0.05	–0.04	–0.06	63.3	57.9	68.7	6.32	4.86	7.77	–0.09	–0.08	–0.10
Iceland	71.7	65.5	77.9	6.89	4.64	9.15	–0.09	–0.08	–0.11	60.5	56.5	64.5	5.12	4.30	5.93	–0.07	–0.06	–0.08
Italy	69.9	67.3	72.5	6.08	5.26	6.90	–0.07	–0.06	–0.08	56.7*	50.4	62.9	5.93	4.57	7.30	–0.13	–0.12	–0.14
Netherlands	68.1	66.5	69.6	5.29	4.89	5.70	–0.06	–0.06	–0.07	56.7	54.0	59.4	5.70	5.15	6.26	–0.11	–0.10	–0.11
Norway	66.1	63.5	68.6	5.69	5.01	6.36	–0.06	–0.05	–0.07	40.1*	33.7	46.4	6.67	5.56	7.77	–0.08	–0.07	–0.09
Poland	55.3	52.0	58.5	4.83	4.23	5.42	–0.09	–0.08	–0.09	19.4*	5.4	33.4	7.45	5.78	9.12	–0.11	–0.10	–0.11
Scotland	66.3	63.7	68.9	4.39	3.80	4.98	–0.06	–0.05	–0.07	43.7*	39.1	48.3	4.81	4.17	5.45	–0.07	–0.06	–0.08
Slovenia	54.8	52.3	57.4	4.99	4.52	5.45	–0.04	–0.04	–0.05	22.0*	13.2	30.8	5.60	4.59	6.61	–0.07	–0.06	–0.08
Spain	72.9	71.6	74.2	4.11	3.77	4.45	–0.09	–0.08	–0.09	51.9	47.6	56.2	4.54	3.86	5.21	–0.12	–0.11	–0.12
Sweden	73.4	70.9	76.0	5.75	4.87	6.62	–0.04	–0.03	–0.05	37.3*	31.5	43.1	7.91	6.82	9.01	–0.06	–0.05	–0.06
Switzerland	69.2	67.0	71.4	4.99	4.42	5.57	–0.05	–0.04	–0.06	56.3*	49.2	63.3	6.52	4.93	8.10	–0.11	–0.10	–0.12
Age class																		
15–44 years	65.2	64.4	66.1	4.90	4.72	5.09	–0.04	–0.04	–0.04	41.5	39.0	44.1	2.27	2.02	2.52	–0.04	–0.03	–0.05
45–54 years	72.2	71.1	73.3	5.26	4.93	5.58	–0.07	–0.07	–0.08	43.5	39.9	47.0	4.85	4.33	5.36	–0.13	–0.12	–0.13
55–64 years	69.1	67.6	70.7	5.71	5.25	6.17	–0.08	–0.07	–0.08	51.4	47.8	55.0	5.75	5.07	6.43	–0.12	–0.11	–0.13
65–74 years	56.7	52.4	60.9	7.73	6.58	8.89	–0.04	–0.03	–0.04	43.0	37.2	48.7	6.92	5.83	8.00	–0.09	–0.09	–0.10
75–99 years	49.9	44.7	55.1	7.12	6.15	8.10	–0.03	–0.02	–0.03	26.8	16.6	37.0	8.40	6.76	10.04	–0.05	–0.04	–0.05
	All cancers men									All cancers women								
Czech republic	26.6*	24.3	28.9	1.60	1.49	1.71	–0.05	–0.04	–0.05	47.3	43.4	51.2	1.78	1.50	2.06	–0.04	–0.03	–0.06
Denmark	29.3*	24.9	33.7	2.03	1.82	2.25	–0.02	–0.01	–0.03	48.8	44.7	52.9	2.19	1.86	2.51	–0.02	–0.01	–0.03
England	34.5	32.0	37.0	1.36	1.23	1.50	–0.03	–0.03	–0.04	49.8	46.6	53.0	1.49	1.23	1.75	–0.03	–0.01	–0.04
Finland	36.8*	32.9	40.7	2.61	2.42	2.80	–0.04	–0.04	–0.05	58.0	53.8	62.2	2.15	1.71	2.59	–0.04	–0.02	–0.06
France	32.6	29.8	35.4	2.91	2.76	3.07	–0.02	–0.02	–0.03	58.6	54.6	62.6	2.68	2.21	3.15	–0.02	0.00	–0.03
Iceland	46.6	43.4	49.8	2.24	2.00	2.48	–0.04	–0.03	–0.05	55.1	49.9	60.3	2.46	1.94	2.98	–0.04	–0.02	–0.05
Italy	37.0	34.6	39.4	1.82	1.68	1.96	–0.04	–0.03	–0.04	54.4	50.4	58.5	2.17	1.78	2.56	–0.04	–0.02	–0.05
Netherlands	35.6*	33.1	38.0	2.01	1.88	2.14	–0.03	–0.03	–0.04	52.7	48.1	57.2	2.68	2.28	3.08	–0.02	–0.01	–0.03
Norway	37.8	32.4	43.3	2.83	2.55	3.11	–0.03	–0.02	–0.04	54.7	50.9	58.4	2.08	1.73	2.43	–0.02	–0.01	–0.04
Poland	21.3	19.3	23.2	1.39	1.29	1.48	–0.05	–0.04	–0.05	38.0	34.2	41.8	1.71	1.46	1.95	–0.05	–0.04	–0.06
Scotland	30.8	27.8	33.7	1.44	1.31	1.58	–0.03	–0.02	–0.04	44.8	41.3	48.3	1.44	1.17	1.70	–0.02	–0.01	–0.04
Slovenia	23.7*	21.1	26.4	1.72	1.59	1.85	–0.03	–0.03	–0.04	44.9	40.5	49.2	2.22	1.90	2.53	–0.04	–0.02	–0.05
Spain	36.3	35.0	37.7	1.64	1.56	1.72	–0.03	–0.02	–0.03	55.8	52.8	58.8	1.79	1.49	2.09	–0.03	–0.02	–0.04
Sweden	37.3*	31.3	43.3	4.25	3.84	4.67	–0.03	–0.02	–0.04	56.1	52.2	60.0	2.35	1.99	2.72	–0.02	–0.01	–0.04
Switzerland	39.9	36.4	43.4	2.51	2.30	2.72	–0.04	–0.03	–0.05	55.7	51.5	59.8	2.48	2.06	2.91	–0.03	–0.02	–0.05
Age class																		
15–44 years	60.9	60.0	61.8	2.32	2.22	2.42	–0.03	–0.03	–0.04	65.4	64.6	66.3	4.13	3.95	4.30	–0.03	–0.03	–0.03
45–54 years	36.7	35.8	37.5	2.04	1.98	2.09	–0.03	–0.02	–0.03	58.0	56.7	59.4	4.04	3.85	4.23	–0.04	–0.03	–0.04
55–64 years	31.0	29.8	32.3	2.23	2.17	2.29	–0.04	–0.03	+0.04	48.6	47.1	50.1	3.38	3.25	3.50	–0.03	–0.03	–0.04
65–74 years	28.4	26.6	30.3	2.52	2.45	2.58	–0.04	–0.03	–0.04	37.1	35.2	39.0	2.76	2.68	2.84	–0.02	–0.01	–0.02
75–99 years	27.3	25.1	29.5	2.08	2.04	2.13	–0.02	–0.02	–0.03	33.2	32.0	34.3	1.36	1.33	1.39	–0.01	–0.01	–0.02

* Asterisk indicates estimates with associated coefficients of variation exceeding the limit of tolerance of 10%.

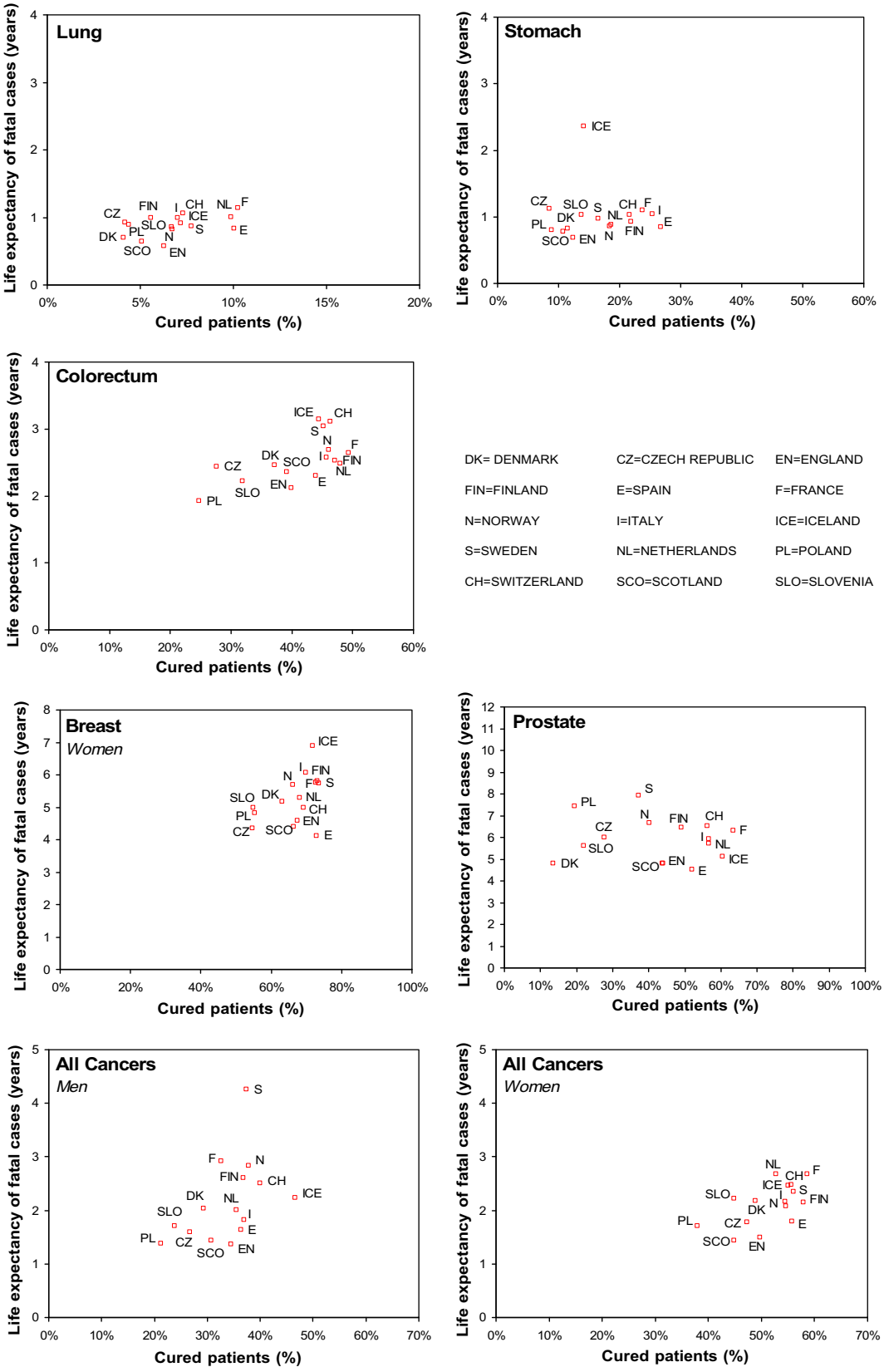

Fig. 2 – Graphs showing, for selected cancer sites, the proportion of cured patients (horizontal axis) and life expectancy of fatal cases (vertical axis) in adult European patients (age 15–99 years) diagnosed from 1988 to 1999 by a pool of 49 European cancer registries.

To provide an indication of the dispersion of the *P* and *T* estimates, we calculated the coefficient of variation (ratio of the standard deviation to the mean). The coefficient gives the variation as a proportion (independent of the unit of measurement) of the total, and can be used to compare variation between groups that have different means. Estimates of *P* and *T* for which coefficients of variation exceeded 10% are indicated with an asterisk in Table 2a and 2b.

3. Results

The results are presented as graphs in which the horizontal axis represents the proportion of cured patients (*P*), and the vertical axis represents the life expectancy of fatal cases (*T*) expressed in number of years. Each point on the graph is therefore a pair of coordinates (*P*, *T*) specific for either a country (Fig. 2), an age class (Fig. 3) or a diagnosis period (Fig. 4). Numerical values of *P* and *T* estimates (with 95% confidence intervals (CI)) are given in Table 2a and 2. Estimates of β parameter (with 95% CI) are also included in Table 2b. Due to inconsistencies in the long-term follow-up data for the cancer registries of Austria, Saarland and Wales,[13] the corresponding country-specific estimates (for Austria, Germany and Wales, respectively) were not shown.

For lung cancer, the average time to death for fatal cases was around one year for most countries, but somewhat shorter for Denmark, England and Scotland (Fig. 2 and Table 2a). For this cancer, therefore, differences in survival were mainly due to the differences in the proportion of cured patients: about 4% for the Czech Republic, Denmark and Poland; and about 10% for France, the Netherlands and Spain. The other countries were in the range 5–9%. As shown in Fig. 3, both survival indicators for lung cancer in the European pool decreased with an increasing age at diagnosis: the proportion cured decreased fourfold on passing from the youngest to the oldest age class; the average time to death for patients not cured remained constant (one year) up to age 55 and lowered for the two oldest age classes. Lung cancer survival improved slightly with time between 1988 and 1999 (Fig. 4) for the European pool, mostly because the proportion of cured patients increased from 6% to about 8%.

For stomach cancer, survival by country was similar to that observed for lung cancer (Fig. 2), in that between-country survival variation was almost completely explained by the variation (from about 9% to 27%) in the proportion of cured cases. Average time to death was about a year for most countries. The only outlier was Iceland, with average time to death of about 2 years, and cured proportion of 14%. Both survival indicators for stomach cancer decreased with advancing age (Fig. 3), but the decrease was particularly sharp for the proportion of cured patients. Both survival indicators also increased over the period 1988–1996 (Fig. 4); however, patients diagnosed in the last three years for which data are available (1997–1999) showed major improvements in proportion of cured, while survival time remained constant.

For colon and rectum cancers, the average time to death for the fatal cases was between two and three years, and the proportion of cured cases ranged from 25% to 49%. Country-specific colon and rectum cancer survival fell into two broad patterns: (a) countries with homogeneous (between 2 and 2.4 years) fatal case survival times and large differences (25–40%) in the proportion of cured cases and (b) countries with more variable fatal case survival times (2–3 years) and higher proportions of cured cases (44–49%). As regards the influence of age at diagnosis on the European pool of colon and rectum cancer cases (Fig. 3), 47.4% of patients aged 15–44 years were estimated cured, while those aged 55 or more had similar proportions of cured cases (between 40% and 42%) to those aged 45–54 (43%). For the 58–60% of the fatal cases, survival time was constant (at about three years) for younger patients (up to age 64) and decreased to 1.6 years in old patients (75–99 years). Colon and rectum cancer survival improved over time in the European pool, the proportion cured increased from about 42% in 1988–1990 to about 48% in 1997–1999.

The proportion of women estimated cured of breast cancer (Fig. 2) was around 70% for most European countries, although a few countries had very low proportions of cured women (from 63% to 55%). The survival time for the fatal breast cancer cases was generally in the range 4–7 years. As regards age, the 15–64 age range had the highest proportions cured (ranging from 65% in those of 15–44 years to 72% in those of 45–54 years) and the lowest life expectancy for the fatal cases (about 5–6 years), while those aged 65 and over had a lower proportion cured (50–60%) and better life expectancy for the fatal cases (about 7–8 years). For breast cancer, the β coefficient (see Table 2b) had a negative sign indicating that patients diagnosed in the more recent periods were more likely to be cured than patients diagnosed in the past. This effect was stronger in patients of age 45–64 years (β –0.07 and –0.08 for age classes 45–54 and 55–64, respectively) than in patients of other age groups (β between –0.03 and –0.04) and particularly marked in Iceland, Poland and Spain (β –0.09).

For prostate cancer (see Table 2b), estimates of proportion of cured and survival time of fatal cases for most countries had a wide dispersion (coefficient of variation greater than 10%). There was also a marked between-country variation (range 14–63%) in the proportion of cured cases, while the life expectancy for the fatal cases was in the contained range of 5–8 years. The most favourable estimates were for the 45–74 age range, with a cured proportion of between 43% and 51% and fatal case survival time of about 5 to about 7 years. The youngest cases (15–44 years) fared poorly overall with only 42% cured and short fatal case survival (2.3 years). An even lower proportion cured was estimated for men aged 75–99 years, but this was mitigated somewhat by a long fatal case survival time (8.4 years). However, this latter estimate had a large coefficient of variation (Table 2b). For prostate cancer, the β coefficient had a negative sign for all countries, and for each age group of the European pool. Patients aged 45–64 years benefited more from being recently diagnosed (β –0.13 and –0.12 for age classes 45–54 and 55–64, respectively) than patients in other age groups (β between –0.04 and –0.09). This period effect was estimated as greater in Italy (β –0.13) and Spain (β –0.12) than the other countries included in the analysis.

The proportion of men cured of all cancers combined ranged from 21% in Poland to 47% in Iceland, and the life expectancy for fatal cases varied from about 1 year in Poland to about 3 years in France. Sweden was an outlier with a very

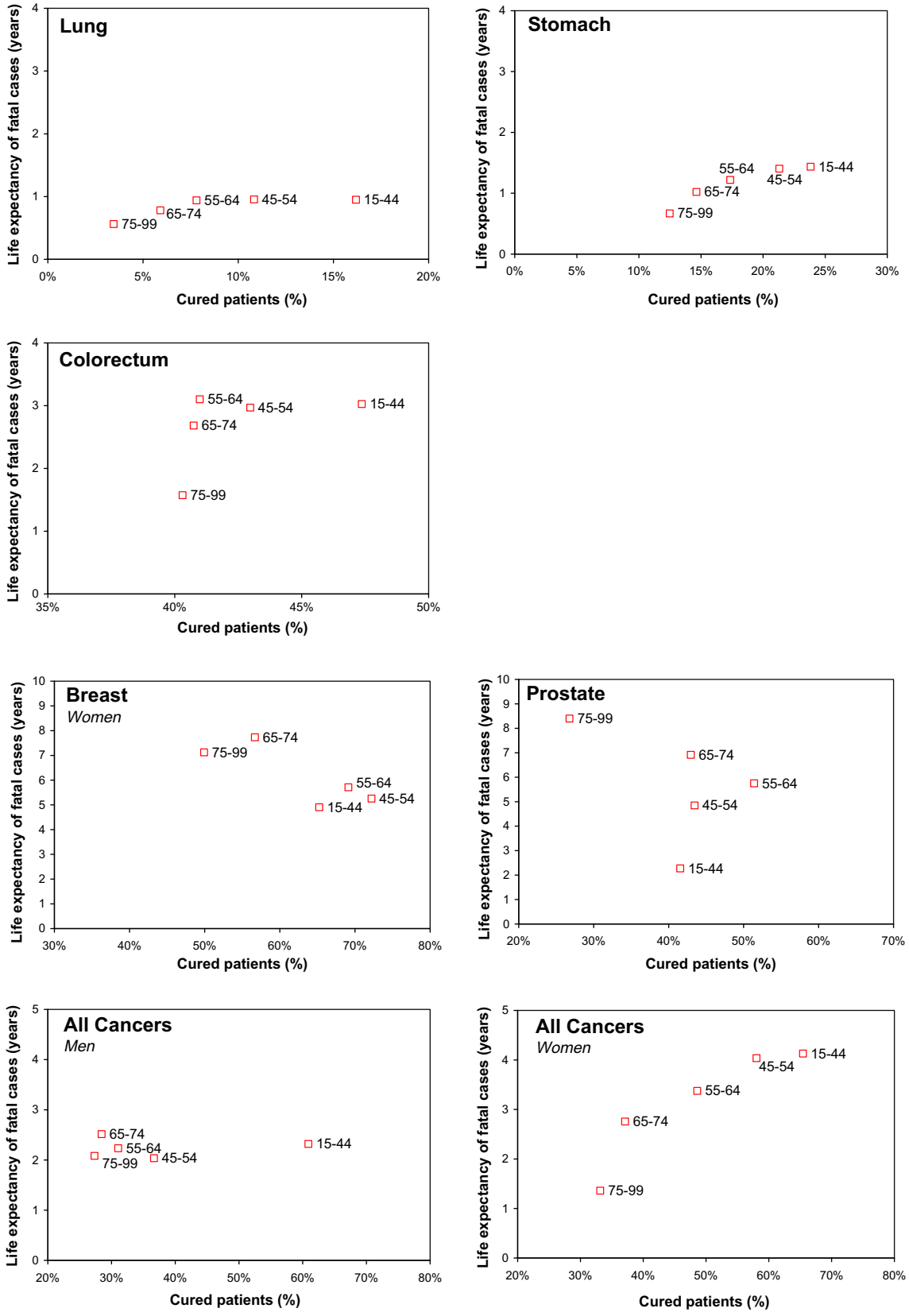

Fig. 3 – Graphs showing, for selected cancer sites, changes in the proportion of cured cases (horizontal axis) and the life expectancy of fatal cases (vertical axis) with age at diagnosis (15–44, 45–54, 55–64, 65–74 and 75–99 years) in adult (15–99 years) European cancer patients (from a pool of 49 European cancer registries) diagnosed from 1988 to 1999.

high fatal case survival time (4.3 years), but only an average value for the proportion was cured (37%). The proportion of women cured of all cancers combined in the European pool was higher than for men (see Fig. 2 and Table 2), and both the proportion cured and the fatal case survival time varied less than in men. The proportion of women cured ranged from 38% in Poland to 59% in Finland, and the life expectancy for fatal patients was similar in all countries (in the range 1.5–3 years).

For men, all cancers combined survival differences by age were mainly due to a marked variation in the proportion cured. For the youngest patients (15–44 years) this was about 61%, while for all other ages was in the range of about 27–37%. For all ages, fatal case survival was about 2–2.5 years. For women, all cancer survival decreased conspicuously with age in terms of both proportion cured and time to fatal case death: in the oldest age class 33% were cured and fatal case survival was about a year, for the youngest women, 65% were cured and fatal case survival was about 4 years. The period effect for all cancers combined was similar in all age groups, both for men and women, with β estimates varying from –0.03 to –0.04. The exception was that the oldest patients were less advantaged by diagnosis in the most recent periods (β estimates were –0.02 in men aged 75–99 and –0.02 and –0.01 for women aged 65–74 and 75–99, respectively). The period effect varied in the range 0.01–0.05 (absolute values) between. Low β values were estimated for Denmark and France in men (–0.02) and for Wales in men (–0.02) and women (–0.01) with the highest values (–0.05) in the Czech Republic in men, and Poland in men and women.

4. Discussion

We applied cure models to the cancer incidence and follow-up data provided by EUROCARE-4 cancer registries, with the aim of providing additional insights into the survival of European cancer patients diagnosed from 1988 to 1999.[14,15] Cure models allow survival information on groups of patients with sufficiently long follow-up to be split into two estimates: the proportion of cured and the mean life expectancy of the remaining fatal cases. The two categories are derived by the analysis of relative survival rates. Patients with the same survival as the general population of the same sex and age are cured of their cancer; those whose survival probability is below that of the general population are fatal cases. A major objective of cancer treatment is to avoid premature death, and the proportion of cured patients is a direct estimate of the extent to which this objective is achieved. Another aim of treatment is to prolong the lives of those whose cancers cannot be cured, and the mean life expectancy of fatal cases is an indicator of extent to which this is achieved. The third objective of cancer treatment, emphasised much more today than in the past, is to improve the quality of life of cancer patients. Good quality of life is clearly important for the

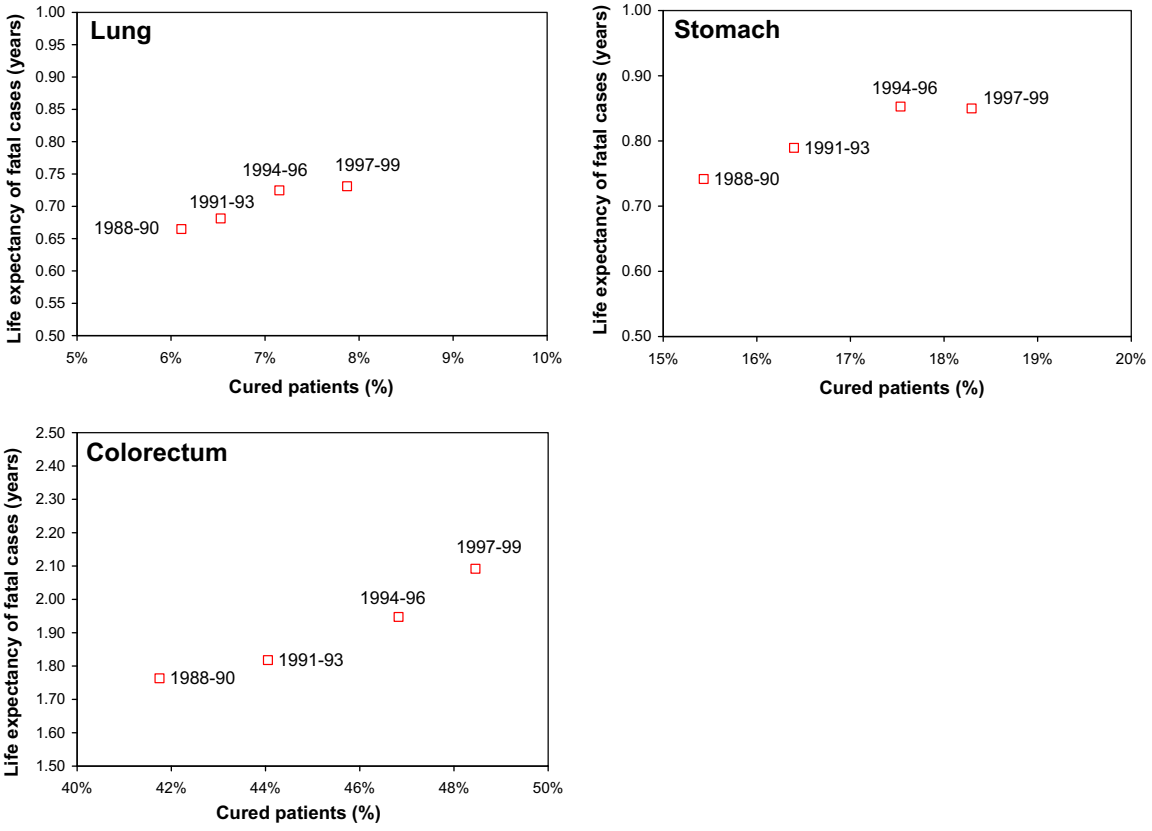

Fig. 4 – Graphs showing, for selected cancer sites, changes in the proportion of cured cases (horizontal axis) and the life expectancy of fatal cases (vertical axis) with diagnosis period (1988–1990, 1991–1993, 1994–1996 and 1997–1999) in adult (15–99 years) European cancer patients (pool of 49 European cancer registries) diagnosed from 1988 to 1999.

terminally ill; but is also relevant to cured patients who may suffer major physical or psychological effects arising from the disease or its treatment, even though treatment has prolonged life expectancy to that of the general population. However, quality of life is beyond the remit of the EUROCARE project, and cannot be investigated using the information currently collected by the cancer registries.

Lead time bias (early diagnosis without postponement of death), over-diagnosis (diagnosis of cancers that will not become symptomatic in the patient's lifetime), erroneous diagnoses and incomplete follow-up (particularly failure to record deaths) complicate the interpretation of population-based cancer survival data. Lead time bias increases the survival time of fatal cases, but cannot affect the proportion of cured cases. By contrast, over-diagnosis, erroneous diagnoses and incomplete follow-up mainly affect the estimates of the proportion cured. Lead time bias and over-diagnosis arise as a result of screening, early diagnosis or use of imaging modalities that incidentally detect cancer when investigating other conditions. It has been estimated that 5–15% of screening-detected breast cancers will not become symptomatic in the lifetime of the patient;[16,17] a figure of 30–45% had been estimated for prostate cancers detected by PSA testing.[18] Erroneous diagnosis is a potential problem only for cancers not biopsied or not treated surgically.[19] Of our selected cancers, this mainly affects lung cancers, a relatively low proportion (75%) of which were verified microscopically.[8,20–22] The effect of erroneous diagnosis on survival estimates can be important for rapidly fatal diseases like lung cancer.

Previous studies[23–25] have noted that breast and prostate cancer patients continue to have a higher mortality than the general population for many years after diagnosis. Our data also show excess mortality for these cancer sites, and the relative survival curves for these cancers (Fig. 1) did not flatten out within the observation period. We observed similar behaviour for all cancers combined, mainly because breast and prostate cancers constitute a large proportion of the total cases. Estimation of the proportion cured and the fatal case survival time by cure models is therefore less certain for these cancers than for sites such as colon and stomach, in which the proportion cured is indicated clearly by the flattening of the relative survival curve (Fig. 1).

For European pool of lung, stomach, colon and rectum and all cancers combined, both the proportion of patients cured and the mean survival time of fatal cases declined as age increased. For lung cancer, younger patients had appreciable proportions of cured cases: 16.2% (95% CI 15.9–16.5) for the 15–44 year age class and 10.8% (95% CI 10.6–11.1) for the 45–54 year age class. Closely similar findings were obtained when the analysis was restricted to microscopically verified cases (results not shown). Since there is no reason to suppose that follow-up failure selectively affects younger patients, it is unlikely that these age-related differences in the proportion of cured are due to the major bias.

For colon and rectum cancer, age-related differences in fatal case survival time were marked, while the proportion cured was similar for all age classes except for the youngest, as reported previously.[1,5]

For breast and prostate cancers, the survival time of fatal cases increased with advancing age. For breast cancer, this effect cannot be explained by lead time bias, since age classes 45–54 and 55–64 years had low fatal case survival times (closely similar to the youngest age class) and women of these age classes are the main target of screening. Biological factors are therefore likely to be the main reasons for low fatal case survival times in younger women (<65 years) with breast cancer. In fact, there is considerable evidence that breast cancers tend to be more aggressive in younger, particularly per-menopausal women.[26,27]

Over-diagnosis is likely to have contributed to the high proportions of cured breast cancer cases in the 45–54 and 55–64 year age classes, since as noted, women of this age are the main target of screening, and also because countries that have implemented screening generally had higher proportions of cured patients than those who did not.

With regard to prostate cancer, routine PSA testing started around the middle of the 1990s, and has since spread to most European countries.[28–31] PSA testing can detect prostate cancer at a very early stage, and a large proportion of such cases would not have become symptomatic in the patient's lifetime or symptoms would not have manifested until many years after high PSA was first detected.[19,32]

For lung, stomach and colon and rectum cancers, the proportion cured and the survival time of fatal cases increased from the first to the most recent diagnosis period. While the improvements in fatal case survival may be due to the increasingly wider use of imaging techniques and to earlier diagnoses, none of the sources of bias considered previously can plausibly explain the increasing proportion of patients cured of these cancers. An effect of erroneous diagnosis can be excluded because most stomach and colon and rectum cancers cases were verified microscopically, and the results did not change when non-microscopically verified lung cancers were removed from the analysis (data not shown). Some over-diagnosis of lung cancers may occur in screening trials for early diagnosis,[33] but this cannot have had a Europe-wide impact. Finally, there is no reason to suppose a generalised worsening of follow-up quality over the study period. We conclude that the increases in proportions cured for lung, stomach and colon and rectum cancers are in large part real. Improvements in diagnostic and surgical techniques, the introduction of adjuvant chemotherapy and radiotherapy and spreading practice of treating metastases[14,15] are all consistent with this conclusion. For lung, stomach and colon and rectum cancers, our estimates of the proportions cured varied markedly (two to threefold) between countries. As noted above, we performed a separate analysis restricted to microscopically verified lung cancer cases (results not shown), and found only a slight generalised improvement in the proportion cured, thereby excluding a major effect of erroneous diagnoses on between-country differences in proportion of cured. However, because lung cancer is rapidly fatal, we cannot exclude that the ranking of countries in terms of proportion cured could be affected by the variations of follow-up completeness. It is noteworthy that we found very little between-country variation in average time to death for fatal cases of stomach and lung cancers, suggesting that quality of care has little influence on the survival of these fatal cases.

For stomach and colon and rectum cancers, the between-country differences are too large to be attributable to over-diagnosis or diagnostic errors, which are features of intense screening and low microscopic verification rates, respectively; furthermore, differences in completeness of follow-up are likely to contribute at most only a few percentage points to the survival differences.[21–23] We conclude that we are dealing with the real differences in the proportion of cured, probably due to between-country variation in the efficacy of the treatments applied, or the stage at diagnosis.

With regard to breast cancer, between-country variation in the proportion of women cured was generally in the contained range of 63–73%, although Poland, the Czech Republic and Slovenia had a low proportion of cured (55%, with large confidence intervals, Table 2b). The gap between these last three countries and most of the rest of the Europe cannot be explained entirely in terms of over-diagnosis. If we assume the high figure of 15% over-diagnoses[17,18] among western European women (irrespective of age and country), the 65% proportion of cured will reduce to (65–15)/(100–15) = 59%, when cases that would never have progressed to symptomatic disease are removed. The true correction is likely to be much less, suggesting that in round figures 10% more western European breast cancer patients were cured (lives saved) than in the eastern European countries we studied. Part at least of this difference has been attributed to the introduction of breast cancer screening from the mid-1990s in several western European countries[34,35]. If this is true the implication is that the early diagnosis saves the lives of women with breast cancer by rendering their disease more curable.

For all cancers combined, estimates of the proportion cured and the fatal case survival time are influenced by between-country variation in the distribution of cases by cancer site. To help interpret between-country differences in these estimates, we present, in Table 3, the distribution of cases between the major sites considered in this study and all other sites, for each country and for men and women separately. Prostate cancers formed high percentages (33–27%) of the male total in Sweden, Finland, Iceland, Norway and Switzerland, and low percentages (11–12%) of the total in the Czech Republic, Poland and Slovenia. Furthermore, prostate cancers had high proportions of cured (as well as long fatal case survival time) in the former countries, while the Czech Republic, Poland and Slovenia had high proportions of poor prognosis lung cancers (and to some extent stomach cancers). Similarly, for women the case-mix was favourable (i.e. with high proportions of relatively good prognosis breast cancers, and generally low proportions of lung and stomach cancers) in Finland, France, the Netherlands and Switzerland particularly in comparison to the Czech Republic, Poland and Switzerland. It is evident, therefore, that the countries with generally high proportions of cured and long fatal case survival time for all cancers combined were characterised by a generally favourable case mix. Nevertheless, the proportion of all cancers combined that is cured is a useful general indicator of cancer control in a country as it reflects progress in diagnosis and treatment, as well as success in cancer prevention of the most fatal cancers.

Table 3 – Case mixes by country (as percentages of total cancers in each country) and by sex, of colon and rectum, lung, prostate, stomach, breast (women) and all other cancer sites in European adult (15–99 years) cancer patients diagnosed in the period 1997–1999.

Country	Men					Women				
	Colon and rectum	Lung	Prostate	Stomach	Other sites	Breast	Colon and rectum	Lung	Stomach	Other sites
Czech Republic	20	22	11	5	43	22	15	5	3	55
Denmark	16	19	17	3	45	30	15	12	2	41
Finland	10	15	31	4	40	33	11	5	3	48
France	14	15	19	4	48	34	15	4	3	45
Iceland	11	13	29	6	41	30	10	11	3	46
Italy	14	18	16	6	45	31	14	5	5	45
Netherlands	14	20	20	4	42	35	13	8	2	42
Norway	15	13	29	4	39	27	17	7	3	46
Poland	12	24	11	6	48	25	11	9	3	52
Scotland	15	22	16	5	43	27	12	14	3	43
Slovenia	15	21	12	8	44	27	12	5	5	50
Spain	14	16	16	6	49	31	14	3	5	48
Sweden	13	8	33	3	42	31	13	5	2	48
Switzerland	12	14	27	3	43	34	12	6	2	45
England	14	17	19	5	45	32	12	10	2	44

Conflict of interest statement

None declared.

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