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Trends in cervical cancer survival in Europe, 1983–1994: A population-based study

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Abstract

Objective. To evaluate trends in survival from cervical cancer in Europe and in European countries participating in the EUROCARE study as a function of age, morphology and stage at diagnosis.

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Methods. Relative survival and relative excess risk of death within 5 years of diagnosis, as a function of age, morphology and stage, among 73,022 women aged 15–99 years diagnosed during 1983–1994 and followed up to 1999 in each of 18 European countries participating in the EUROCARE study, using data from 34 population-based cancer registries.

Results. Overall five-year relative survival was 62%, rising by 2% during the period 1983–1994. The highest survival occurred in Northern and Western Europe and the lowest in Central Europe. Survival falls with age at diagnosis, but mainly for localised disease. Survival is higher for adenocarcinoma in younger women, but higher for squamous cell carcinoma in older women. The proportions of younger women, localised cancer and adenocarcinoma all increased. The main improvements in survival were for women under 65, and for metastatic disease.

Conclusions. Survival in Europe has improved slowly but steadily, but the trend is not geographically uniform. Central European countries and the UK saw little or no improvement, and survival in those countries remains the lowest among participating countries in Europe.

Further reduction of cervical cancer mortality in Europe may be expected from expansion of screening, and improvement in the treatment of older women, and of metastatic disease.

Keywords: Cervical cancer; Survival; Trends; Population-based study; Europe

Introduction

In the last 40 years, there is evidence that cervical cancer incidence and mortality rates have fallen in wealthy countries as a combined result of risk reduction from health education, changes in lifestyle, and the beneficial effects of screening programmes [1]. These factors have led to women being diagnosed at an earlier stage of disease and at a younger age. Given the improvements in cervical cancer management [2], survival would be expected to increase.

Analysis of Europe-wide population-based data from the EUROCARE project has previously shown an increase of about 2% in five-year relative survival of cervical cancer over the period 1978–1989 [3]. The main objective of this paper is to update this analysis for Europe to the end of the 20th century, by including data for women diagnosed during the period 1983–1994 and followed up to the end of 1999. The second objective is to use the available data, expanded with respect to previous studies, to examine the prognostic impact of several key variables collected by cancer registries: the woman's age at diagnosis and country of residence (usually also the country of treatment), the morphological type of the tumour and the stage at diagnosis.

Materials and methods

The analyses included 73,022 women diagnosed with cervical cancer as a first primary malignancy during the period 1983–1994 and registered in one of 34 population-based cancer registries in 18 European countries participating in the EUROCARE study [4–6]. Only cancer registries that could provide data for the entire period were included. Cases were defined by anatomic site code 180 in the ninth revision of the International Classification of Diseases (ICD-9) [7]. Histologically verified and non-verified cases were all considered for analysis, but we excluded *in situ* and benign tumours, cervical cancers diagnosed as the woman's second or subsequent primary malignancy. We also excluded cases registered from a death certificate only (DCO cases) and those discovered only at autopsy, since the date of diagnosis and thus the survival time were unknown. All women were followed up for at least 5 years in the analysis until loss to follow-up, or death by 31 December 1999, whichever occurred first.

For 10 of the 18 participating countries (*Northern Europe*: Denmark, Finland, Iceland, Norway, Sweden; *Western Europe*: Scotland, Wales; *Central Europe*: Estonia, Slovakia, Slovenia), the data analysed came from cancer registries covering the entire national population. For England, participating registries covered 63% of the national population, and data from the other seven countries represented 2–16% of the national population. The incidence periods, rules for data inclusion and characteristics of participating cancer registries are fully described in the first, second and third monographs from the EUROCARE study [4–6].

More than half the patients (56%) were from Western Europe, a quarter (24%) from Northern Europe, 15% from Central Europe and 5% from Southern Europe (Table 1). Overall, about 93% of cervical cancers included in the analyses were microscopically verified. The proportion reached almost 100% in Northern and Western Europe, with the exception of Wales and East Anglia (England), where microscopic confirmation was only reported for about 60% of cases. Morphology was grouped into three categories: squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma (hereinafter, adenocarcinoma), and other and unspecified categories (not analysed as a separate category). Overall, 14% of the cancers were adenocarcinomas, ranging from less than 10% in Germany, Estonia, Poland and Slovakia up to 25% in Northern Europe. The proportion of adenocarcinomas varied up to two-fold within countries such as England (11% to 18%), Switzerland (14% to 20%), Italy (10% to 20%) and Spain (10% to 22%). The overall percentage of DCO and autopsy cases was 1.2%, with the highest value in the Thames (England) cancer registry (7%). Overall, fewer than 0.5% of patients were lost to follow-up, but the figure reached 4% in Krakow (Poland), 5% in Turin (Italy) and 5–9% in Switzerland.

Information on stage is not routinely collected, however, provided by some registries in a simplified form introduced by American Join Committee on Cancer and recommended by IARC for use in studies based on cancer registries data, but not for adoption in the clinical work [8]. Consequently Stages Ia–Ib according to FIGO classification were included into *localized*, stages IIa–IIIb were classified as *regional* and IVa–IVb as *metastatic* or *distant*. In our study we included data from 16 cancer registries with data on simplified staging from over 40% of patients in Saarland, Slovakia and Krakow to over 95% in Denmark, Estonia and Slovenia.

We analysed the prognosis of cervical cancer in terms of relative survival. This is the ratio between the proportion of patients who survive a given period of time, irrespective of cause of death, and the survival that would have been expected if they experienced only the all-cause mortality observed in the general population, matched by age, sex, calendar period and country or region. The expected survival was obtained from population life tables for women by age, country or region and calendar period [9]. Relative survival is thus corrected for competing (or background) risks of death at each age and time period, and it can be interpreted as an estimate of the patients' survival if their cancer were the only cause of death. Relative survival at 5 years after diagnosis was calculated by the Hakulinen method and expressed as a percentage [10]. Overall survival estimates were derived by pooling the data from all contributing registries. Relative survival varies with age, and the age distribution of cervical cancer patients varies between countries, so to facilitate international comparison, age-standardised relative survival was calculated as a weighted average of the age-specific estimates for women aged 15–44, 45–54, 55–64, 65–74 and 75–99 years at diagnosis. The corresponding age-specific proportions of all cervical cancer patients in the EUROCARE-3 patient population were used as standard weights [6].

Temporal trends of cervical cancer survival were analysed over four consecutive three-year periods of diagnosis: 1983–1985, 1986–1988, 1989–1991 and 1992–1994. The increase (or decrease) in relative survival for women

Table 1
Number and characteristics of cervical cancer patients included in the analyses, with indicators of data quality, by cancer registry: Europe, women aged 15–99 years diagnosed during 1983–1994 and followed up to 1999

Region of Europe	Included in analyses		Adenocarcinoma %	Morphologically verified %	Autopsy or DCO cases %	Lost to follow-up %
Cancer registry	No.	%				
Northern Europe						
Denmark	6015	8.2	16	99.1	0.2	0.1
Finland	1722	2.4	22	99.2	0.2	0.2
Iceland	163	0.2	25	100.0	0.0	0.0
Norway	4038	5.5	15	99.3	0.4	0.6
Sweden	5774	7.9	18	99.8	0.0	0.6
Western Europe						
France						
Bas-Rhin	744	1.0	12	99.7	0.0	2.6
Calvados	572	0.8	11	100.0	0.0	0.0
Germany						
Saarland	1075	1.5	9	98.0	1.4	0.0
Netherlands						
Eindhoven	443	0.6	17	99.8	0.0	0.0
Switzerland						
Basel	196	0.3	20	100.0	0.0	5.1
Geneva	220	0.3	14	99.1	0.9	8.6
UK—England						
East Anglia	1748	2.4	18	57.7	0.1	1.1
Merseyside	2811	3.8	13	92.5	1.6	0.0
Oxford	1812	2.5	16	92.1	0.0	0.0
South West	5501	7.5	15	86.1	3.0	0.0
Thames	4723	6.5	15	86.4	7.1	0.3
Trent	4304	5.9	15	90.6	0.2	0.0
West Midlands	4952	6.8	13	92.6	0.9	0.2
Yorkshire	4014	5.5	11	96.2	0.4	0.0
UK—Scotland	4967	6.8	14	92.7	0.7	0.6
UK—Wales	2963	4.1	12	63.6	0.0	0.0
Southern Europe						
Italy						
Latina	229	0.3	12	94.8	0.4	0.4
Parma	272	0.4	16	99.3	0.4	0.0
Ragusa	211	0.3	20	97.6	0.0	0.0
Turin	664	0.9	11	92.9	0.6	4.5
Tuscany	624	0.9	12	94.4	0.5	1.6
Varese	451	0.6	10	98.9	0.0	1.1
Spain						
Mallorca	338	0.5	10	98.5	0.9	0.0
Navarra	153	0.2	22	98.0	2.0	0.0
Tarragona	328	0.4	16	98.5	0.3	0.0
Central Europe						
Estonia	1930	2.6	5	99.9	0.1	1.4
Poland						
Krakow	1223	1.7	4	89.5	2.4	3.7
Slovakia	5894	8.1	9	96.9	2.2	0.0
Slovenia	1948	2.7	13	98.7	0.2	0.8
All registries	73,022	100.0	14	92.5	1.2	0.4

diagnosed during 1992–1994 compared with those diagnosed during 1983–1985 (baseline) was estimated as a relative excess risk (RER) of death within 5 years of diagnosis. The RER for a given country, taken as the ratio of the logarithms of the two relative survival estimates [9] expresses the excess hazard of death (i.e. the hazard over and above the relevant background mortality) within 5 years of diagnosis, for women diagnosed in 1992–1994 compared with those diagnosed in 1983–1985. An RER lower than unity represents a gain in survival over this period. The significance of any change was evaluated at the 5% level.

Results

Relative survival and main prognostic factors

Relative survival at 5 years drops markedly with age at diagnosis in most countries, the European pooled estimate falling from 78% in women aged 15–44 years to just 33% in

women aged 75–99 years at diagnosis (Table 2). The decline with age is much less marked in the Netherlands, where survival is high in the oldest age groups, but also in Estonia, because survival is low (60% or less) even in young and middle-aged women.

Age-standardised relative survival at 5 years ranged from about 70% in several Northern and Western European countries (Iceland, Norway, Sweden, France, the Netherlands) to 50–60% in Central Europe (Estonia, Poland, Slovakia, Slovenia) (Table 3). Survival in the UK (England, Scotland, Wales) was intermediate at about 60%. The European average age-standardised five-year relative survival for women diagnosed during the period 1983–1994 was 62% (crude rate 64%).

Survival was similar for squamous cell carcinoma and adenocarcinoma in the European pool as a whole (64% and 63%, respectively), but both varied widely between countries (Table 3). In most countries, women with adenocarcinoma had somewhat poorer prognosis than those with squamous cell carcinoma, but none of the differences was statistically significant. The decline in relative survival with age was significantly more marked for adenocarcinoma than for squamous cell carcinoma (Fig. 1). Survival was significantly higher for adenocarcinoma in women under 55 years of age at diagnosis, but significantly higher for squamous carcinoma in women aged 65 and over.

Age-standardised five-year survival was examined by stage at diagnosis for 16 of the 34 registries, which provided information on stage for at least 40% of patients (Table 4). Survival in the European pool as a whole varied from 80% for women with localised cancer to 47% for those with regional cancer and 21% for women with metastatic disease at diagnosis.

Five-year survival for localised disease was in the range 78–88% in most countries, with relatively little variability. Survival was clearly below the European average only in Thames (England) and Basel (Switzerland), at around 72%, and it was low in Krakow (Poland). For women diagnosed at the regional stage, geographic variability in survival was more marked, ranging from 58% to 59% in Norway, Geneva (Switzerland) and Tuscany (Italy) down to about 30% in Basel (Switzerland) and West Midlands (UK), and even 19% in Slovakia. Survival for metastatic cancers is difficult to interpret because the proportion of metastatic cancers was generally low and, in many countries, comparable with that of cases with no data on stage. Nevertheless, the highest survival estimates for metastatic disease were observed in Northern and some Western European countries.

Average annual incidence rates of cervical cancer in the participating countries, age-standardised to the European population [11], varied three-fold and more, from 6 per 100,000 per year in Finland to 23 or more in Estonia, Krakow (Poland), and Slovakia, but also Denmark (Table 4).

The proportion of cancers that were localised at diagnosis also varied three-fold, from 23% to 75%, but with the exception of Estonia and Slovenia, localised cancers were more frequent than those diagnosed at the regional stage. In Northern Europe,

Table 2
Five-year relative survival (%) from cervical cancer by country and age at diagnosis: Europe, women diagnosed aged 15–99 years during 1983–1994 and followed up to 1999

	Age at diagnosis (years)					All ages (15–99)
	15–44	45–54	55–64	65–74	75–99	
Northern Europe						
Denmark	83	68	58	55	29	66
Finland	80	66	61	48	37	59
Iceland	87	76	74	67	34	80
Norway	82	70	64	55	39	69
Sweden	85	74	60	52	41	69
Western Europe						
France	81	70	67	60	38	68
Germany	76	57	65	60	38	64
Netherlands	79	65	68	64	56	72
Switzerland	78	70	64	51	39	64
UK						
England	78	65	58	47	31	64
Scotland	76	64	53	42	23	61
Wales	74	61	54	44	42	60
Southern Europe						
Italy	75	68	68	51	30	61
Spain	79	72	68	47	47	67
Central Europe						
Estonia	60	57	58	56	29	56
Poland	65	55	44	37	20	52
Slovakia	71	66	55	44	28	63
Slovenia	76	61	53	48	27	62
All registries	78	66	58	49	33	64

Table 3
Age-standardised five-year relative survival (%) from cervical cancer, with standard error (S.E.), by country and morphology: Europe, women diagnosed aged 15–99 years during 1983–1994 and followed up to 1999

	All cases [a]		Squamous cell		Adenocarcinoma	
	%	S.E.	%	S.E.	%	S.E.
Northern Europe						
Denmark	65	1.3	65	1.4	64	3.2
Finland	64	2.5	65	3.0	64	4.9
Iceland	73	8.5	79	8.8	57	20.4
Norway	68	1.6	69	1.7	67	4.2
Sweden	68	1.3	69	1.4	67	2.8
Western Europe						
France	68	2.7	68	3.0	65	7.5
Germany	63	3.2	67	4.2	50	10.5
Netherlands	70	5.1	72	5.9	67	13.5
Switzerland	65	4.9	65	5.4	69	11.7
UK						
England	62	0.6	64	0.7	63	1.5
Scotland	58	1.4	58	1.7	62	3.8
Wales	60	1.9	59	2.8	65	5.3
Southern Europe						
Italy	63	2.1	63	2.4	66	5.5
Spain	67	3.6	67	4.1	64	9.2
Central Europe						
Estonia	55	2.6	56	2.9	45	13.9
Poland	50	3.1	53	3.7	47	15.4
Slovakia	58	1.5	59	1.7	57	4.4
Slovenia	59	2.4	60	2.9	52	5.9
All registries	62	0.4	64	0.4	63	1.0

[a] 73,022 cases, of which 53,941 squamous cell carcinomas and 10,013 adenocarcinomas.

up to 30% of cancers were metastatic at diagnosis, but in a number of countries, stage at diagnosis was unavailable for up to 50% of all cancers, and more precise comparisons of stage distribution are impossible.

Five-year relative survival for women with localised disease depends strongly on age at diagnosis (Fig. 2), but for regional and metastatic disease, age at diagnosis has no discernible effect on survival for women under 75 years of age. The impact of age on overall survival from cervical cancer up to age 75 (Table 2) is thus due almost entirely to the effect of age on survival from localised disease.

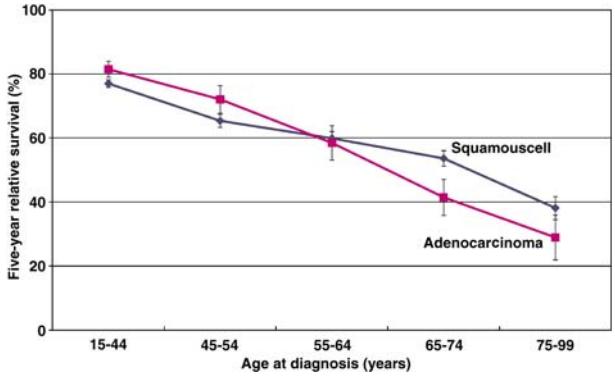

Fig. 1. Five-year relative survival (%) from cervical cancer, with 95% confidence intervals, by morphology and age at diagnosis: Europe, women diagnosed aged 15–99 during 1983–1994 and followed up to 1999.

Trends in prognostic factors and in survival

The proportion of women aged 15–54 years at diagnosis rose slightly from 51% in 1983–1985 to 56% in 1992–1994 (Table 5). The proportion of localised cancers rose by about 4% over the same period, from 42% to 46%, whereas the proportion of regional and metastatic cancers decreased. The 5% proportionate increase in adenocarcinoma, from 11% to 16%, was matched by a decline in the proportion of cases with other or unspecified morphology.

Age-standardised five-year relative survival in the pooled European data rose by 2% from 1983–1985 to 1992–1994, corresponding to a 7% reduction in the excess risk of death within 5 years (RER 0.93), but this small trend was not statistically significant ($p=0.19$) (Table 6). The trend differed widely between countries. The excess risk of death within 5 years fell by over 30% in Spain (RER 0.68; $p=0.08$) and 20% in Italy (RER 0.78, $p=0.05$). The excess risk fell by 10–20% in most other countries, but none of the changes was individually significant. The excess risk of death rose by 10–15% in France, Switzerland, Wales and Estonia, but only in Wales did the increase reach borderline statistical significance (RER 1.14, $p=0.05$), corresponding to a fall in five-year relative survival

Table 4
Five-year relative survival (%) from cervical cancer by stage of disease, with stage distribution (%) and age-standardised incidence per 100,000: Europe, selected cancer registries[a], women diagnosed aged 15–99 years during 1983–1994 and followed up to 1999

	Five-year relative survival (%)				Proportion of all cases (%)				Incidence rate per 10^5
	Local	Regional	Metastatic	All[b]	Local	Regional	Metastatic	N/A	
Northern Europe									
Denmark	83	51	25	65	53	23	19	4	23
Finland	84	52	27	64	46	6	31	16	6
Norway	85	58	22	68	38	18	16	28	20
Western Europe									
Germany									
Saarland	84	45	16	63	26	10	4	59	18
Switzerland									
Basel	72	30	0	59	75	11	6	8	8
Geneva	83	59	23	71	46	40	8	5	10
UK									
East Anglia	88	55	23	63	52	16	14	17	17
Thames	71	48	16	59	46	31	5	17	13
West Midlands	83	33	13	63	54	24	4	18	19
Yorkshire	79	52	26	63	24	17	12	47	22
Southern Europe									
Italy									
Tuscany	78	59	19	63	27	26	1	46	10
Varese	78	48	3	67	43	22	7	29	10
Central Europe									
Estonia	85	50	11	55	23	61	13	2	23
Poland									
Krakow	57	38	15	50	37	11	4	48	33
Slovakia	78	19	12	58	47	2	2	49	25
Slovenia	82	43	12	59	44	50	6	1	20
All registries	80	47	21	62	43	21	10	25	18

N/A—not available.
[a] Restricted to cancer registries with data on stage available for at least 40% if women with cervical cancer.
[b] All women with known stage of disease at diagnosis.

from 62% to 58%. In the Netherlands, Sweden and Poland, survival did not change.

In women aged 15–44 at diagnosis, who comprised 37% of all cases, the 3% improvement in five-year survival from 76% to 79% corresponded to a borderline significant 14% reduction in the excess risk of death within 5 years of diagnosis (RER 0.86, $p=0.05$) (Table 6). The risk also fell 10–20% in women aged 45–64, but these gains were not significant. The 6% increase in the excess risk of death within 5 years for women aged 65 years and older did not reach statistical significance.

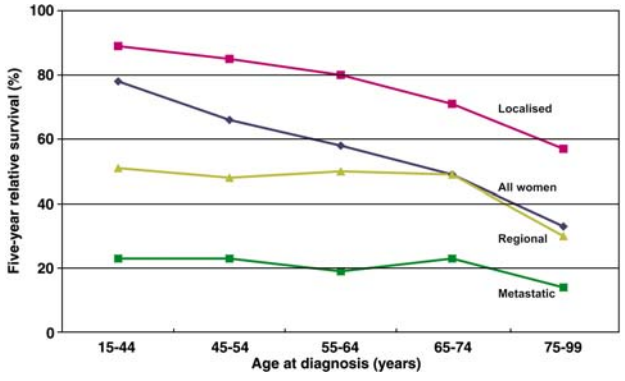

Fig. 2. Five-year relative survival (%) from cervical cancer, with 95% confidence intervals, by stage and age at diagnosis: Europe, women diagnosed aged 15–99 during 1983–1994 and followed up to 1999.

Trends in survival were similar for squamous cell carcinoma and adenocarcinoma (Table 6). Overall (all ages) trends were not marked for local or regional disease, but for metastatic disease the 6% reduction in the risk of death within 5 years was significant (RER 0.94, $p=0.04$). When trends are examined by age group and stage at diagnosis, survival for both local and regional stage of disease is seen to increase slightly but steadily for women aged 15–44 years (Fig. 3). Trends were stable for women aged 45–74, but five-year survival has fallen substantially for women aged 75 and over at diagnosis. By contrast, for women with metastatic disease, five-year survival has generally increased with time.

Discussion

This study presents data on cervical cancer survival derived from 18 countries participating in the EUROCARE-3 study.

Table 5
Trends in the distribution of women with cervical cancer by age group, morphology and stage of disease: Europe, women diagnosed aged 15–99 years during 1983–1994 and followed up to 1999

	Calendar period of diagnosis								All periods (1983–1994)	
	1983–1985		1986–1988		1989–1991		1992–1994			
	No.	%	No.	%	No.	%	No.	%	No.	%
Age group (years)										
15–44	6609	35	7181	37	6926	38	6481	39	27,197	37
45–54	2963	16	3124	16	3073	17	2867	17	12,027	16
55–64	3860	21	3550	18	3001	16	2351	15	12,762	18
65–74	3248	17	3259	17	3063	17	2673	16	12,243	17
75–99	2087	11	2288	12	2276	12	2142	13	8793	12
All ages (15–99)	18,767	100	19,402	100	18,339	100	16,514	100	73,022	100
Stage at diagnosis										
Local	4388	42	4470	42	4463	44	4367	46	17,688	43
Regional	2339	22	2337	22	2204	22	1808	19	8688	21
Metastatic	1236	12	1064	10	985	10	890	9	4175	10
Other	2458	24	2724	26	2523	24	2517	26	10,222	26
All with known stage	10,421	100	10,595	100	10,175	100	9582	100	40,773	100
Morphology										
Squamous cell	13,733	73	14,477	75	13,584	74	12,147	74	53,941	74
Adenocarcinoma	2094	11	2409	12	2723	15	2787	16	10,013	14
Other	2940	16	2516	13	2032	11	1580	10	9068	12

Most of the 34 participating cancer registries provided data of good quality, and the few registries with lower indices of data quality are not expected to affect significantly the findings on international differences or trends in five-year survival [12]. Information on prevention, screening and treatment is not generally available to population-based cancer registries, so only indirect inferences can be made about international differences in the efficacy of prevention or the standard of treatment.

The trend in five-year relative survival reported here for cervical cancer is stable: a closely similar estimate for the reduction in the risk of death (RER 0.91) was obtained from the EUROCARE-2 study [3] for the overlapping period 1978–1989. The trend is associated with an increasing prevalence of favourable prognostic factors: young age and early stage of disease.

Clinical and population studies have shown that the main factors affecting cervical cancer survival are the stage of disease at diagnosis, the woman's age and the tumour morphology, along with the availability of effective prevention and the standard of cancer treatment [2,13–18]. The last two factors are connected with the woman's place of residence.

The 2% increase in five-year survival over 12 years is smaller than the increases in survival for breast and other gynaecological cancers. The largest available clinical series of cervical cancer patients also reported a larger improvement in five-year survival, from 60% for women diagnosed during 1982–1986 to 72% for 1993–1995 [2], even though a similar proportion of women were diagnosed in stage I in FIGO and in this study (*circ* 43%). The comparison is weakened, however, because cancer registry data are population-based (unselected), whereas even large clinical series are subject to selection bias that can invalidate comparisons with population-based data. Trends in the crude survival rates used in FIGO also partly reflect declining trends in background mortality, whereas these are appropriately compensated in the relative survival trends reported here. Clinical case series such as the FIGO data usually have good information on stage, whereas registry data often include only simplified staging data, and in this study, data on stage were unavailable for many patients. Finally, the EUROCARE study included a number of countries in which survival was lower and trends less marked than those included in the FIGO study.

Survival increased slightly more than average in Italy, Spain, Iceland and Scotland. In other Northern and Western European countries, survival increased less, or did not change, or even fell, but survival in those countries was already high in the mid-1980s. Little or no improvement was observed in Estonia and Poland, where survival remains around 50%, well below the European average of 63%. The lack of any marked improvement in the four participating countries from Central Europe means that the European range in survival for cervical cancer remains as wide as ever [3], although the range is even wider for some other malignancies [12].

Age at diagnosis remains an important prognostic factor for both the main morphological types of cervical cancer, squamous cell carcinoma and adenocarcinoma. A similar pattern was observed in the EUROCARE-2 study and in some other population studies, as well as the FIGO survey [2,3,14,17].

The negative association between survival and age was particularly strong in the four Central European countries (Estonia, Slovakia, Slovenia, Poland), as well as Denmark and Scotland, where five-year survival for women aged 75–99 was below 30%. In sharp contrast, survival for women aged 75–99

Table 6
Trends in five-year relative survival (%) for cervical cancer by period of diagnosis, Europe, women diagnosed aged 15–99 during 1983–1994 and followed up to 1999: country, age group, morphology and stage at diagnosis

	No. of women	Five-year relative survival (%)				Trend [a]	
		1983–1985	1986–1988	1989–1991	1992–1994	RER	*p*
Northern Europe							
Denmark	6015	62	66	67	66	0.87	0.17
Finland	1722	65	60	62	69	0.86	0.57
Iceland	163	69	75	67	75	0.78	0.61
Norway	4038	67	65	66	71	0.86	0.38
Sweden	5774	68	67	71	68	1.00	0.60
Western Europe							
France	1316	70	64	71	67	1.12	0.91
Germany	1075	63	63	61	66	0.90	0.59
Netherlands	443	66	69	72	66	1.00	0.86
Switzerland	416	66	62	70	61	1.19	0.79
UK							
England	29,865	59	61	65	62	0.91	0.29
Scotland	4967	54	58	61	60	0.83	0.11
Wales	2963	62	59	59	58	1.14	0.05
Southern Europe							
Italy	2451	60	62	63	67	0.78	0.05
Spain	819	59	59	70	70	0.68	0.08
Central Europe							
Estonia	1930	51	58	59	49	1.06	0.89
Poland	1223	49	52	48	49	1.00	0.63
Slovakia	5894	56	60	57	58	0.94	0.96
Slovenia	1948	56	61	60	59	0.91	0.51
All registries	73,022	61	62	64	63	0.93	0.19
Age group (year) [b]							
15–44	27,197	76	77	79	79	0.86	0.05
45–54	12,027	61	65	69	68	0.78	0.09
55–64	12,762	56	58	61	59	0.91	0.20
65–74	12,243	50	48	50	48	1.06	0.75
75–99	8793	33	34	35	31	1.06	0.65
All ages (15–99)	73,022	62	64	66	65	0.90	0.11
Morphology [c]							
Squamous cell	53,941	61	63	65	65	0.87	0.12
Adenocarcinoma	10,013	61	63	65	63	0.93	0.21
Stage at diagnosis [c]							
Local	17,688	81	80	80	79	1.12	0.10
Regional	8688	47	48	48	46	1.03	0.75
Metastatic	4175	20	21	22	22	0.94	0.04
All stages available	40,773	60	62	63	63	0.90	0.16

[a] Relative excess risk (RER) of death within 5 years of diagnosis for women diagnosed during 1992–1994, compared with those diagnosed during 1983–1985 (see text).
[b] Apart from survival by age group, all relative survival estimates are age-standardised (see text).
[c] Women with specific morphology or known stage at diagnosis.

in the Netherlands was 56%. This finding is distressing, because it suggests different standards of treatments for elderly women in different countries. In less wealthy countries, the low survival in the oldest women may also reflect hard economic conditions for elderly people [18].

The overall difference in prognosis between women with squamous cell carcinoma and those with adenocarcinoma is negligible, but younger women with adenocarcinoma had a better prognosis, whilst the reverse was true for older women. The impact of morphology on the outcome of cervical cancer is controversial [14,16], but numerous studies indicate an adverse effect of adenocarcinoma, either as an independent risk factor, or in relation to a less favourable stage distribution or the type of treatment [2,13,15,17,19]. In a population-based study of 1386 women in Poland, adenocarcinoma was associated with a significantly higher risk of death, after adjustment for stage, age and place of residence [20]. In a sub-set analysis restricted to women in this cohort who were treated with curative intent, the

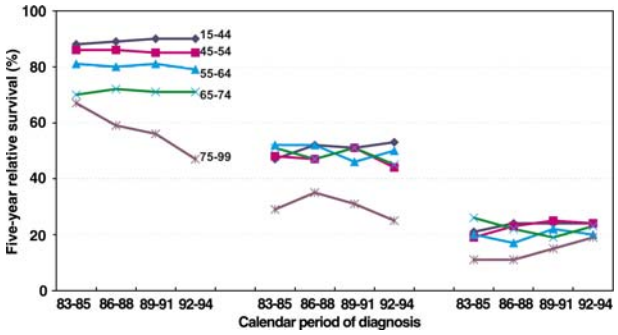

Fig. 3. Time trends in five-year relative survival (%) from cervical cancer by stage of disease and age group: Europe, women diagnosed aged 15–99 during 1983–1994 and followed up to 1999.

significance of adenocarcinoma disappeared. These results suggest that factors influencing the aim of treatment (curative, palliative, symptomatic) may explain the poorer prognosis of women with adenocarcinoma [21]. Since adenocarcinoma of the cervix is a rare disease, more studies are needed of the factors that underpin the choice of treatment, in order to confirm and explain the different prognosis associated with the two morphological groups.

Stage of disease at diagnosis is the main prognostic factor for cancer. The analysis of stage in population-based studies of cancer survival is made difficult by the lack of standardised clinical data on stage in all clinical records, and by the need to collect additional information on diagnostic procedures in order to adjust for diagnostic intensity in stage-specific analyses. In this study, we used a simplified stage classification with an unknown degree of standardisation among different populations. Stage-specific survival estimates from different registries should therefore be compared with great caution. We can nevertheless consider stage as a ranking variable: women recorded as having local stage generally have less advanced disease than those with regional stage, who are in turn less advanced than metastatic cases. Despite these limitations, survival variability between registries did not decrease when stage distribution was taken into account. This suggests that other factors influencing the treatment offered to women with cervical cancer may also affect prognosis.

Recent progress in diagnostic and therapeutic regimes has led to wider adoption of adjuvant or neo-adjuvant chemotherapy and chemo-radiation therapy in more advanced disease, while treatment modalities for early disease have not changed greatly [2]. According to the FIGO survey, there is little change in survival at early stages, while survival for women with stage II–IV disease has risen by about 10%. These impressive improvements in metastatic disease are consistent with the EUROCARE data we report here.

The analysis of survival by stage was restricted to the sub-set of registries in which stage was known for at least 40% of cases, and among them, to the sub-set of women for whom information on stage was actually available. This double selection could give biased results if those women had different survival from the rest of the European pool. To test this point, we calculated survival with three different criteria. Overall five-year survival for the 16 selected registries was 64.0%; further restricting the analysis to cases with stage available gave 65.3%: both values are very close to the overall survival for the pooled European data (64.1%). The maximum difference was found for one-year survival: 84.0% in the selected registries, 85.6% for women with information on stage in those registries, and 83.6% for the European pool. We conclude that the sub-set of women for whom stage data were available has slightly higher short-term survival than all women in the study, but this very small difference is unlikely to affect the results of our analyses.

Europe does not have a uniform health policy on cervical cancer prevention or treatment [22]. Mass screening programmes designed to detect cervical cancers before they become invasive are still not available in all countries. The first screening programmes in Europe were organised in the 1960s in Finland, Iceland, Denmark, Sweden, Luxembourg and the Czech Republic, initially on a regional scale, and later expanded to national coverage. In the 1970s, screening was developed in Saarland (Germany) and in the 1980s in the Netherlands, UK and Tuscany (Italy). The population coverage of screening programmes has grown more rapidly since the 1990s.

Cervical screening varies widely between countries. It is variously either population-wide (mass screening) or opportunistic, with national or regional coverage, aimed at different target age ranges and with different recommended screening intervals. The recommended number of lifetime smears ranges from 7 in Finland to more than 60 in Saarland (Germany) and Luxembourg, and the efficacy and cost-effectiveness of these screening programmes also varies widely [22–24]. Based on experience from British Columbia (Canada), Finland and other Nordic countries, the World Health Organisation (WHO) recommends cervical screening programmes with national coverage, a standardised structure, adherence to quality assurance standards and at least 75–80% coverage of the target population [25]. To ensure cost-effectiveness, the recommended total number of smears in a woman's lifetime should be no more than is required by the actual risk estimated from the natural history of disease.

The screening programme introduced in Finland in the 1960s was more effective in preventing slow-growing tumours than faster-growing and more aggressive malignancies, because these tumours spend longer in the pre-invasive phase [26]. Cervical screening enables detection and ablation of pre-invasive malignancy, and it is therefore a tool for *primary* prevention, actually reducing the incidence of invasive disease. In unscreened women, clinical diagnosis at the localised stage is also more likely for slower-growing tumours than for rapidly growing tumours. Thus, the decline in incidence of invasive cervical cancer after the introduction of screening was also associated with an increase in the proportion of tumours that were non-localised at diagnosis. This shift in the stage distribution of invasive malignancy helps to explain the decline in relative survival among cases of invasive cervical cancer diagnosed after the introduction of screening. When the programme has stabilised, relative survival continues to improve once again, but this time mainly as a result of progress

in the treatment of more advanced disease. This phenomenon, first described by Saxën and Hakama [26], probably explains our findings in Finland: low incidence of invasive disease, a high proportion of metastatic cancer and only a slight improvement in survival. It may also explain the lack of any marked improvement in survival from cervical cancer in other countries where mass screening has been successfully implemented, e.g. Sweden and the Netherlands.

In most European countries where early detection operates efficiently, the proportion of adenocarcinoma is high, up to 25% in Iceland [13,15,27,28]. Conversely, in Estonia, Slovakia, Slovenia and Poland, where survival from cervical cancer was below the European average [3], the proportion of adenocarcinoma was less than half of that in other countries. Therefore, the adverse prognosis of adenocarcinoma cannot explain the low survival rates in Central European countries, and the main explanation is likely to be the lack of effective early detection programmes [20,29]. Cervical cancer mortality in those countries remains high.

Conclusion

This large population-based study of cervical cancer survival in Europe, based on the EUROCARE-3 study, confirms a slow but steady improvement of about 2% in five-year survival over the 12 years up to 1994. The increase occurred for both squamous cell and adenocarcinoma. It was more marked in younger women, and in the more advanced stages of disease. Improvement was not uniform across countries, and little improvement occurred in Central European countries, which remain, with the UK, at the lowest levels in Europe. Prognosis is better for younger women, particularly those diagnosed at an early stage. International variation in survival for women aged 75 and over was particularly marked, with the highest survival in the Netherlands. Five-year survival was higher for adenocarcinoma in younger women and for squamous cell carcinoma in older women.

Screening continues to play an important role in cervical cancer control. The potential for further improvement in outcome for early stage invasive cervical cancer seems limited. Further progress may arise from better results in the treatment of advanced cancer and, as suggested by the example of the Netherlands and the FIGO surveillance, from making treatment of curative intent available to older women. If those encouraging trends could be made accessible to many more women with cervical cancer in Europe, age would become much less important as a prognostic factor, and cervical cancer mortality among European women would be further reduced.

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