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Multiple tumours in survival estimates

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ABSTRACT

In international comparisons of cancer registry based survival it is common practice to restrict the analysis to first primary tumours and exclude multiple cancers. The probability of correctly detecting subsequent cancers depends on the registry's running time, which results in different proportions of excluded patients and may lead to biased comparisons. We evaluated the impact on the age-standardised relative survival estimates of also including multiple primary tumours.

Data from 2,919,023 malignant cancers from 69 European cancer registries participating in the EUROCARE-4 collaborative study were used. A total of 183,683 multiple primary tumours were found, with an overall proportion of 6.3% over all the considered cancers, ranging from 0.4% (Naples, Italy) to 12.9% (Iceland). The proportion of multiple tumours varied greatly by type of tumour, being higher for those with high incidence and long survival (breast, prostate and colon-rectum). Five-year relative survival was lower when including patients with multiple cancers. For all cancers combined the average difference was –0.4 percentage points in women and –0.7 percentage points in men, and was greater for older registries. Inclusion of multiple tumours led to lower survival in 44 out of 45 cancer sites analysed, with the greatest differences found for larynx (–1.9%), oropharynx (–1.5%), and penis (–1.3%).

Including multiple primary tumours in survival estimates for international comparison is advisable because it reduces the bias due to different observation periods, age, registration quality and completeness of registration. The general effect of inclusion is to reduce survival estimates by a variable amount depending on the proportion of multiple primaries and cancer site.

1. Introduction

The occurrence of subsequent cancer in long-surviving patients has become more frequent as the chances of surviving the first cancer have substantially improved over the past decades.[1] Cancer registries record these events on a population basis, enhancing opportunities for a better understanding of the epidemiology of multiple primary tumours.

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However, when studying these cases, several aspects have to be considered starting with the very clinical problem of differential diagnosis with distant metastases, recurrences and the onset of a truly new lesion. Classifications may also vary leading to substantial differences in rates of reported multiple primaries. For example, Surveillance Epidemiology and End Results (SEER) rules[2] differ substantially from those adopted by the European registries, who generally follow the rules issued by the International Agency for Research on Cancer (IARC).[3] The time of occurrence is often difficult to ascertain with precision, leading, for example, to the convenient definition of synchronous cancers when diagnosed at the same time, but not really knowing when they started. Usually, synchronous tumours are excluded from survival analyses in the belief that they rather represent prevalent silent tumours coming to evidence during diagnostic procedures.

The limited observation time of population-based cancer registration causes another problem in detecting multiple tumours: as cancer can occur over the entire lifespan, only very few cancer registries have a sufficient period of observation covering such a long time. Thus, subjects classified with only one cancer during observation time might have had other malignancies that the local cancer registry was unable to report. Some cancer registries try to minimise this bias relying on lists of prevalent cases. However, comparability and quality of such lists vary and there is no guarantee that all previous cancers were detected.

Consequently, the effect of multiple tumours on patients' survival has been neglected in population-based survival analyses. In international comparisons, such as the EUROCARE study, patients with multiple primary tumours were analysed for their first tumour occurrence only.[4,5] However, this approach can be viewed as somewhat 'artificial' as clinicians in their practice treat all patients and not just first primary cancers. In addition, since the probability of correctly identifying a primary tumour as being subsequent strongly depends on the observation time length, we inevitably include unrecognised multiple cancers when analysing cases from the most recently established cancer registries. Since the prognosis of patients with a previous cancer can differ from the prognosis of patients with only one cancer, different inclusion/exclusion criteria may bias survival comparison between registries with different observation periods. A previous study addressed this issue using the data from the Finnish Cancer Registry, which analyses the effect of multiple tumours exclusion strategies across different calendar periods.[6] Since the Finnish Cancer Registry has a long registration period, starting from 1953, the scrutiny of their data allows the evaluation of both the proportion of cancer patients with known previous diagnosis since the start of cancer registration and the impact of excluding or including such patients on survival estimates. These analyses illustrated (mostly small) differences in survival estimates according to different inclusion/exclusion strategies. However, these results are not easily applied to other cancer registries with different observation periods, data collection procedures, levels of data quality and completeness. In this study we specifically explored the impact of excluding patients with multiple tumours in the very large European database provided by the EUROCARE-4 study.[1]

2. Patients and methods

We analysed data on 2,919,023 cancers diagnosed during the period 1995–1999 in 22 European countries. Diagnostic information on these cancers and patients' demographic and follow-up data were provided by 82 cancer registries participating in the EUROCARE-4 study according to a standardised protocol.[7] Data were then centrally checked for their quality and completeness as described elsewhere.[1,8] Patients notified by death certificate or by autopsy only were excluded. We also excluded non-melanoma skin cancers and cases from those cancer registries (13 in total) that included only selected cancer sites ('specialised' cancer registries), as the second and later tumour ascertainments could be incomplete.

The European cancer registries included in the present study follow IACR rules[3] for the definition of multiple cancer sites. These rules differ substantially from those issued by SEER.[2] For example, contralateral malignant lesions of the breast are considered as subsequent primary tumours according to SEER rules, but not according to IARC rules. Similarly, subsequent melanomas are counted as multiple primaries by SEER, but not by IARC. However, it cannot be excluded that in some areas, especially those with screening programmes, those rules were relaxed, resulting in different proportions of multiple tumours. Tumour sequence numbers were requested in the study protocol in order to distinguish between first and subsequent tumours. Along with the *original* sequence number provided by the registries, a *recoded* sequence number was derived, by using a unique methodology, to obtain a more standardised definition. The recoded sequence number was assigned on the basis of the patient's identity code, date of diagnosis (month/year), behaviour, cancer site and morphology. As index date, we used the date of diagnosis indicated by the cancer registries. In general, European cancer registries follow the rules of the European Network of Cancer Registries (ENCR: www.encr.com.fr) for the date of diagnosis which gives priority to the date when a biopsy is performed. In the case of synchronous diagnosis of two or more primary malignant cancers, the most lethal cancer was considered as the first occurring cancer. The cancer lethality was based on the overall 5-year relative survival from the EUROCARE-3 study.[9] The recoding procedure treated benign and malignant tumours separately in order to enable different types of analysis.

The recoded sequence number could not be assigned for nine registries providing the tumour's, rather than patient's, identification code (Amsterdam, Malta, Norway, Portugal, East Anglia, Mersey, Northern Ireland, Scotland and Warsaw) and we could only rely on the original sequence number. The *original* sequence number was also used for three North European registries (Iceland, Finland and Sweden) where the proportion of multiple tumours obtained from the recoding was far below the original one, due to diagnoses prior to 1978 that were not in the study database and which could not be accounted for in the recoded sequence numbering. Finally, identification of multiple cancers with a unified procedure was possible for 57 cancer registries out of a total of 69 registries available for the present analysis.

For a selected set of 45 cancer sites and for all cancers we calculated the observed survival probabilities up to 5 years

Table 1 – Percentage distribution of cases by sequence number, country and registry: age 15–99, period of diagnosis 1995–1999.

Country	Registry	Starting year of registration	First year available in EUROCARE Database	One primary only (a)	1st of 2 or more primaries (b)	2nd (c)	3rd (d)	4th + (e)	Total				
									First (f = a + b)		Multiple (g = c + d + e)		All (f + g)
									n	%	*n*	%	*n*
Austria	Austria	1983		91.5	3.5	4.8	0.2	0.0	164,348	95.0	8702	5.0	173,050
	Tyrol	1988		91.3	2.7	5.7	0.2	0.0	12,889	94.0	818	6.0	13,707
Belgium	Flanders	1997		94.5	3.5	2.0	0.0	0.0	79,765	98.0	1641	2.0	81,406
Czech Republic	West Bohemia	1988		90.4	4.5	4.8	0.3	0.0	18,757	94.9	1011	5.1	19,768
England	East Anglia[a]	1961	1978	90.7	3.6	5.7	0.0	0.0	56,747	94.3	3425	5.7	60,172
	Mersey[a]	1959	1978	91.9	3.1	4.9	0.0	0.0	54,192	95.1	2804	4.9	56,996
	North Western	1995		95.2	2.4	2.4	0.1	0.0	95,426	97.6	2388	2.4	97,814
	Northern&Yorkshire	1978		90.3	4.0	5.4	0.3	0.0	105,539	94.3	6353	5.7	111,892
	Oxford	1963	1978	92.8	4.4	2.7	0.1	0.0	50,476	97.2	1436	2.8	51,912
	South Western	1960	1978	89.5	2.9	7.2	0.4	0.0	154,039	92.4	12,725	7.6	166,764
	Thames	1985		93.3	2.0	4.5	0.2	0.0	278,028	95.3	13,582	4.7	291,610
	Trent	1966	1979	91.0	2.5	6.1	0.3	0.0	101,509	93.6	6972	6.4	108,481
	West Midlands	1960	1978	89.7	3.9	6.1	0.3	0.0	109,318	93.6	7488	6.4	116,806
Finland	Finland[a]	1953	1978	81.5	5.9	12.5	0.0	0.0	89,624	87.5	12,859	12.5	102,483
France	Bas Rhin	1975	1989	90.0	2.9	6.5	0.5	0.1	12,121	92.9	923	7.1	13,044
	Doubs	1978	1989	91.5	2.3	5.8	0.4	0.0	5348	93.8	353	6.2	5701
	Haut Rhin	1988	1989	90.5	2.8	6.3	0.3	0.1	8389	93.3	599	6.7	8988
	Herault	1987	1995	95.9	2.0	2.0	0.0	0.0	10,210	97.9	215	2.1	10,425
	Isere	1979	1989	92.1	2.2	5.5	0.2	0.0	11,680	94.2	713	5.8	12,393
	Manche	1994		94.4	2.5	3.1	0.0	0.0	6033	96.9	192	3.1	6225
	Somme	1982	1989	92.9	2.2	4.7	0.2	0.0	6124	95.1	316	4.9	6440
	Tarn	1982	1989	91.2	2.4	5.9	0.4	0.0	4601	93.7	311	6.3	4912
Germany	Saarland	1968	1978	89.0	4.3	6.3	0.3	0.0	26,236	93.3	1887	6.7	28,123
Iceland	Iceland[a]	1955	1978	80.5	6.5	12.9	0.0	0.0	4494	87.1	668	12.9	5162
Ireland	Ireland	1994		93.2	3.9	2.8	0.1	0.0	61,388	97.1	1836	2.9	63,224
Italy	Alto Adige	1995		90.7	5.5	3.6	0.2	0.0	10,404	96.2	412	3.8	10,816
	Biella	1995		91.4	5.3	3.1	0.1	0.0	6001	96.7	202	3.3	6203
	Ferrara	1991		90.7	4.7	4.4	0.1	0.0	11,020	95.4	526	4.6	11,546
	Firenze	1985		90.4	3.7	5.7	0.2	0.0	33,224	94.0	2108	6.0	35,332
	Friuli V.G.	1995		89.9	6.3	3.6	0.1	0.0	38,601	96.2	1513	3.8	40,114
	Genova	1986		90.2	3.6	5.9	0.2	0.0	29,761	93.8	1955	6.2	31,716
	Macerata	1991		92.2	2.8	4.8	0.2	0.0	8076	95.1	420	4.9	8496
	Modena	1988		91.5	4.1	4.2	0.1	0.0	16,771	95.6	769	4.4	17,540
	Napoli	1996		99.0	0.6	0.4	0.0	0.0	5824	99.6	26	0.4	5850
	Parma	1978		88.9	4.2	6.6	0.3	0.0	12,316	93.2	902	6.8	13,218
	Ragusa	1981		92.2	3.2	4.5	0.1	0.0	4890	95.4	236	4.6	5126

	Reggio Emilia	1996		94.2	4.2	1.6	0.0	0.0	9786	98.4	158	1.6	9944
	Romagna	1986		88.1	5.3	6.2	0.4	0.0	29,183	93.4	2062	6.6	31,245
	Salerno	1996		98.2	1.1	0.7	0.0	0.0	15,413	99.3	108	0.7	15,521
	Sassari	1992		93.0	3.6	3.2	0.1	0.0	8598	96.7	297	3.3	8895
	Torino	1985		90.3	3.8	5.7	0.2	0.0	24,628	94.0	1,560	6.0	26,188
	Trento	1995		93.1	3.6	3.1	0.1	0.0	11,847	96.7	399	3.3	12,246
	Umbria	1994		90.9	5.2	3.8	0.1	0.0	23,345	96.1	945	3.9	24,290
	Varese	1980		88.5	3.2	7.9	0.5	0.0	19,687	91.6	1794	8.4	21,481
	Veneto	1987		88.6	4.2	6.8	0.4	0.0	54,684	92.8	4226	7.2	58,910
Malta	Malta[a]	1993		97.2	1.4	1.4	0.0	0.0	5871	98.6	82	1.4	5953
Netherlands	Amsterdam[a]	1988		83.6	6.6	9.8	0.0	0.0	50,219	90.2	5443	9.8	55,662
	Eindhoven	1958	1978	85.3	5.2	8.7	0.8	0.1	17,761	90.4	1879	9.6	19,640
	North Netherlands	1995		90.9	5.2	3.7	0.2	0.0	38,949	96.1	1591	3.9	40,540
Northern Ireland	Northern Ireland[a]	1993		94.1	2.4	3.4	0.0	0.0	30,308	96.6	1081	3.4	31,389
Norway	Norway[a]	1952	1978	81.9	6.3	11.8	0.0	0.0	85,547	88.2	11,460	11.8	97,007
Poland	Cracow	1965	1978	92.4	1.4	2.1	2.0	2.1	12,854	93.8	850	6.2	13,704
	Kielce	1995		98.2	1.2	0.7	0.0	0.0	16,959	99.3	116	0.7	17,075
	Warsaw[a]	1989		92.3	3.4	4.3	0.0	0.0	28,767	95.7	1295	4.3	30,062
Portugal	South Portugal[a]	1998		97.5	0.0	2.5	0.0	0.0	31,569	97.5	822	2.5	32,391
Scotland	Scotland[a]	1958	1978	87.0	4.3	8.7	0.0	0.0	118,397	91.3	11,258	8.7	129,655
Slovenia	Slovenia	1956	1978	93.2	3.8	2.9	0.1	0.0	33,154	97.0	1030	3.0	34,184
Spain	Basque Country	1986		92.1	2.4	5.2	0.3	0.0	41,907	94.5	2440	5.5	44,347
	Girona	1994		93.4	3.8	2.7	0.0	0.0	11,482	97.2	326	2.8	11,808
	Murcia	1995		95.6	2.2	2.2	0.0	0.0	13,514	97.8	306	2.2	13,820
	Navarra	1973	1985	91.0	2.7	5.8	0.4	0.1	11,109	93.7	742	6.3	11,851
	Tarragona	1985		92.4	2.2	5.1	0.2	0.0	11,602	94.7	653	5.3	12,255
Sweden	Sweden[a]	1958	1978	82.9	5.7	11.3	0.0	0.0	173,008	88.7	22,149	11.3	195,157
Switzerland	Basel	1981		81.9	6.6	10.4	0.9	0.1	8583	88.5	1114	11.5	9697
	Geneva	1970	1980	82.6	6.9	9.5	0.9	0.1	8399	89.5	987	10.5	9386
	St. Gallen	1980	1988	86.0	6.1	7.4	0.6	0.0	8836	92.0	765	8.0	9601
	Ticino	1996		92.9	4.7	2.4	0.1	0.0	5736	97.6	142	2.4	5878
	Valais	1989		89.3	3.7	6.6	0.5	0.0	4055	92.9	309	7.1	4364
Wales	Wales	1978		86.5	5.1	7.8	0.6	0.0	65,414	91.6	6008	8.4	71,422
Total	European Pool	–		90.0	3.7	6.1	0.2	0.0	2,735,340	93.7	183,683	6.3	2,919,023

Starting year of registration and first year of diagnosis available in the EUROCARE-4 database (only if different from the starting year of registration) are displayed.
a The original sequence number provided by CRs was used to identify multiple tumours.

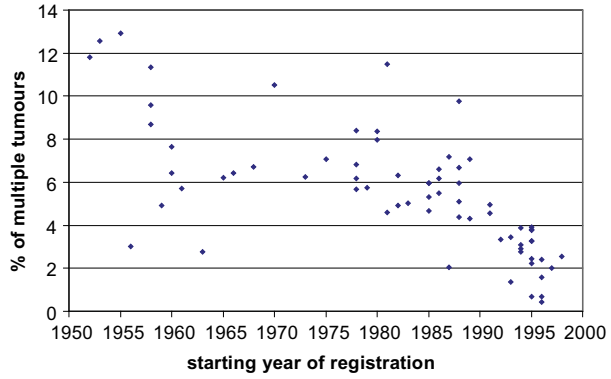

Fig. 1 – Proportion of multiple tumours by starting year of registration: EUROCARE-4 Cancer Registries.

after diagnosis and their ratio to the expected survival probabilities, according to the Hakulinen method to derive relative survival.[10] Expected numbers of deaths were derived from all cause mortality figures of the general population covered by each cancer registry, specific by age, sex and calendar period. To reduce confounding, due to possible differences in age distribution of cases relative survival, which quantifies the probability of surviving the cancer of interest rather than the total survival probability, we then standardised by age according to the International Cancer Survival Standard (ICSS) populations.[11] We restricted the analysis to patients from 15 to 99 years of age. Standardisation by geographical area was also applied to derive overall survival estimates (European average), by following the same procedure as described in.[8] According to the UN classification, five different European areas were identified (UK and Ireland, Northern, Central, Eastern and Southern Europe) and weighted on the basis of population size.

We then compared different strategies of analysis: (1) first or single tumour: survival indicators were calculated considering the first occurring tumour only, as usually done in common practice; (2) subsequent cancer inclusion: survival indicators were calculated for all tumours whatever their order. The analyses were conducted using the SEER*Stat Software (ver. 6.4.4).[12]

3. Results

Our study dataset included information on a total of 183,683 multiple primary tumours (Table 1) corresponding to a proportion of 6.3% of all tumours incidents in the resident population of most of the Western European and two Eastern European countries during the period 1995–1999. The proportion of multiple tumours ranged from 0.4% for the Naples registry (Italy), started in 1996, to 12.9% for the Icelandic registry, started in 1955. For cancer registries operating for less than 10 years, there was a strong relationship between the registry's running time and the proportion of multiple primary tumours. For 'older' registries, no such association was seen (Fig. 1).

The quality of case ascertainment was measured by the percentage of microscopic verification and its completeness by the percentage of cases identified with death certificate only (DCO). A high percentage of DCO can affect both the possibility of correctly detecting subsequent tumours and survival estimates. Completeness of case ascertainment varied greatly across registries; however, it was suboptimal (% of DCO higher than 10%) only for a few registries for first cancers (the Austria, Thames and Wales registries). Both quality and completeness were better for subsequent tumours for the majority of registries (Table 2). Also, the percentage of patients lost to follow-up can affect the possibility of detecting subsequent tumours. Among the registries considered in the present study, the overall percentage of cases lost to follow-up is rather low (0.3%). Few registries (Haut-Rhin, Herault, Somme, Salerno and Geneva) showed a percentage of loss to follow-up after diagnosis of first cancer between 5% and 8% (Table 2). The registry of Kielce (Poland) showed a high percentage of 26.7% cases lost to follow-up for the multiple tumours that could have affected the survival estimates. In particular, long-term survival is rather sensitive to the proportion of patients that are actually not under follow-up, without the registry knowing that they have been lost to follow-up. This proportion can vary across registries according to the different sources of information that registries can consult and access.

The practice of autopsy can also influence the proportion of multiple primaries that are found. We observed low percentages of cases detected at autopsy, with the exception of the registries of West Bohemia (Czech Republic), Friuli Venezia Giulia (Italy) and Basel (Switzerland) where the percentages of cases detected at autopsy were 11.7%, 12.0% and 16.8% respectively. However, the percentages of cases detected at autopsy in the same registries were not remarkably high in the case of first tumours, suggesting that autopsies were more likely to be performed in patients with more than one tumour (Table 2).

In Table 3 we show the distribution, in percentages, of subsequent tumours by site and registry. Colon and rectum, lung, breast and prostate were the most frequent cancer sites of multiple tumour occurrence: this was usually higher for tumours that exhibited a higher incidence (lung), and also for those with a longer survival (breast, prostate and colon-rectum).

The effect of multiple tumour inclusion in survival analysis is presented in Table 4, by sex and registry for all cancers combined. With very few exceptions, survival calculated by including first primary tumours only is higher than that from all tumours (first and subsequent). However, since the percentage of all multiple tumours was relatively small, the discrepancies are small. For all cancers as a whole, we observed an average difference in age-adjusted 5-year relative survival of –0.4 percentage points in women and –0.7 in men when including patients with multiple cancers. The difference was greater for older registries, i.e. with more than 10 years of running time. They showed an average difference (weighted by their standard error) of –0.3 percentage points of survival in women and –1.0 in men compared to a difference of –0.3 and –0.6 respectively in younger registries. This effect is clearly due to the variable proportion of second and subsequent cancers, as shown in Fig. 2, where the same registry and sex specific survival differences are plotted against

Table 2 – Quality indicators for first and multiple tumours by registry: all cancer sites, age 15–99, period of diagnosis 1995–1999.

Country/registry		First				Multiple			
		% Microscopic. verified	% DCO	% Lost to follow-up	% Autopsy	% Microscopic. verified	% DCO	% Lost to follow-up	% Autopsy
Austria	Austria	83.1	11.0	0.0	0.0	95.2	0.0	0.0	0.0
	Tyrol	91.0	3.6	0.0	0.1	96.2	0.0	0.0	0.0
Belgium	Flanders	86.7	0.0	0.0	0.2	96.1	0.0	0.0	0.4
Czech Republic	West Bohemia	84.7	3.7	0.5	6.0	89.8	1.0	0.3	11.7
England	East Anglia[a]	81.8	0.7	0.2	1.1	83.4	0.3	0.1	1.7
	Mersey[a]	77.8	5.5	0.0	0.0	79.6	6.3	0.0	0.0
	North Western	78.2	1.5	0.0	0.0	79.2	3.3	0.0	0.0
	Northern&Yorkshire	82.5	1.8	0.0	0.3	83.9	1.7	0.0	0.2
	Oxford	86.9	1.0	0.0	0.4	91.4	1.0	0.0	0.6
	South Western	70.9	7.8	0.0	0.1	61.4	9.2	0.0	0.1
	Thames	71.7	14.1	0.1	0.6	65.9	20.3	0.1	0.6
	Trent	73.9	7.1	0.0	0.0	71.8	11.2	0.0	0.0
	West Midlands	80.4	5.6	0.1	1.1	78.9	6.6	0.1	1.5
Finland	Finland[a]	93.1	2.6	0.1	1.8	91.9	0.1	0.0	3.3
France	Bas Rhin	95.8	0.0	3.1	0.0	95.6	0.0	0.5	0.0
	Doubs	95.6	0.0	1.3	0.0	98.3	0.0	0.6	0.0
	Haut Rhin	96.3	0.0	5.8	0.0	97.7	0.0	2.3	0.0
	Herault	NA	NA	6.6	NA	NA	NA	2.8	NA
	Isere	94.1	0.0	4.8	0.0	94.1	0.0	1.1	0.0
	Manche	96.5	0.0	0.6	0.0	94.8	0.0	0.0	0.0
	Somme	94.0	0.0	7.9	0.0	97.5	0.0	2.5	0.0
	Tarn	93.8	0.0	2.2	0.0	93.6	0.0	0.0	0.0
Germany	Saarland	89.5	5.9	0.0	0.0	93.2	0.2	0.0	0.0
Iceland	Iceland[a]	95.8	0.2	0.0	1.1	95.8	0.0	0.0	4.5
Ireland	Ireland	83.0	3.1	0.0	0.4	84.3	7.2	0.0	0.9
Italy	Alto Adige	87.9	0.8	0.0	0.0	92.0	0.0	0.0	0.0
	Biella	83.8	1.6	0.1	0.5	89.6	1.0	0.0	1.0
	Ferrara	85.3	1.8	1.0	0.0	89.5	0.2	0.4	0.0
	Firenze	77.8	1.4	0.1	0.1	88.3	0.0	0.1	0.0
	Friuli V.G.	88.5	1.0	0.8	2.4	92.9	0.1	0.5	12.0
	Genova	79.2	2.2	0.0	0.0	79.9	1.7	0.0	0.0
	Macerata	84.8	1.6	0.0	0.0	87.4	1.2	0.0	0.0
	Modena	85.3	0.8	1.3	0.0	94.4	0.0	0.7	0.0
	Napoli	72.1	4.6	3.2	0.0	100.0	0.0	0.0	0.0
	Parma	83.7	1.6	0.6	0.0	86.1	0.3	0.2	0.1
	Ragusa	74.8	2.0	0.0	0.8	78.8	1.7	0.0	0.8
	Reggio Emilia	84.8	0.4	0.1	0.0	92.4	0.0	0.0	0.0
	Romagna	85.7	3.4	0.2	0.0	84.9	3.0	0.0	0.0
	Salerno	75.0	2.8	6.7	0.0	90.7	0.0	6.5	0.0

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Table 2 – *continued*

Country/registry		First				Multiple			
		% Microscopic. verified	% DCO	% Lost to follow-up	% Autopsy	% Microscopic. verified	% DCO	% Lost to follow-up	% Autopsy
	Sassari	79.6	4.0	0.0	0.4	84.2	2.0	0.0	0.3
	Torino	84.3	2.8	0.3	0.1	88.8	0.1	0.0	0.1
	Trento	81.9	2.6	0.6	0.0	88.7	0.3	0.3	0.0
	Umbria	81.7	0.9	0.6	0.0	83.2	0.0	0.2	0.0
	Varese	87.6	1.3	0.6	0.0	88.8	0.8	0.3	0.0
	Veneto	85.0	1.9	0.3	0.2	87.0	0.9	0.2	0.1
Malta	Malta[a]	87.8	1.7	0.0	0.2	89.0	2.4	0.0	0.0
Netherlands	Amsterdam[a]	95.8	0.0	0.2	0.4	93.3	0.0	0.0	2.1
	Eindhoven	95.9	0.0	0.2	0.0	95.4	0.0	0.5	0.0
	North Netherlands	94.6	0.0	0.0	1.0	94.7	0.0	0.0	2.5
Northern Ireland	Northern Ireland[a]	78.4	1.8	0.0	0.6	83.6	0.6	0.1	0.6
Norway	Norway[a]	91.2	1.3	0.3	0.4	91.5	2.6	0.1	1.1
Poland	Cracow	72.9	1.8	2.1	0.1	87.1	0.0	0.8	0.0
	Kielce	77.1	0.0	0.1	0.0	94.0	0.0	26.7	0.0
	Warsaw[a]	76.1	5.4	0.0	0.1	87.3	1.8	0.1	0.1
Portugal	South Portugal[a]	93.8	0.0	0.0	0.0	96.0	0.0	0.0	0.0
Scotland	Scotland[a]	81.9	1.5	0.0	0.2	83.7	1.6	0.0	0.5
Slovenia	Slovenia	89.5	2.7	0.1	1.2	95.0	0.0	0.2	1.0
Spain	Basque Country	86.1	4.5	0.2	0.0	89.1	0.6	0.5	0.0
	Girona	86.9	3.8	0.1	0.1	93.9	0.0	0.6	0.3
	Murcia	87.7	3.6	1.2	0.1	92.5	1.3	0.3	0.3
	Navarra	88.2	2.9	0.9	0.6	89.6	1.5	0.3	2.6
	Tarragona	86.3	4.8	0.2	0.0	85.6	6.7	0.2	0.0
Sweden	Sweden[a]	97.8	0.0	0.2	2.4	98.0	0.0	0.1	4.2
Switzerland	Basel	98.8	0.0	1.4	3.2	98.4	0.0	0.8	16.8
	Geneva	92.3	0.6	5.0	1.0	89.6	0.4	3.1	4.6
	St. Gallen	91.5	0.8	0.9	1.1	90.3	0.5	0.7	3.7
	Ticino	91.1	3.7	1.8	0.3	95.8	0.7	2.1	0.7
	Valais	90.7	1.6	1.9	0.4	93.5	0.6	0.6	1.3
Wales	Wales	NA	13.7	0.0	0.0	NA	20.5	0.0	0.0
Total	European Pool	82.0	4.5	0.3	0.5	83.8	4.2	0.2	1.4

a Original sequence number.

Table 3 – Proportion of second and subsequent tumours by registry and cancer site: age 15–99, period of diagnosis 1995–1999.

Country	Registry	Colon-rectum	Lung	Breast f	Prostate	Stomach	Kidney	Non hodgkin	Leuk-aemia	Corpus uteri	Pancreas	Skin melanoma	Head and neck	Ovary	Oeso-phagus	Brain	Hodgkin disease	Other
Austria	Austria	14.9	10.9	9.2	14.4	4.7	5.8	3.1	2.3	3.9	2.5	3.1	2.4	2.3	1.0	0.7	0.2	18.6
	Tyrol	12.5	14.5	8.6	13.4	6.1	6.2	2.1	2.1	4.5	1.8	2.1	2.2	2.8	1.5	0.5	0.1	18.9
Belgium	Flanders	14.0	13.5	16.1	14.7	2.3	5.8	2.9	2.1	2.6	0.6	1.5	4.8	1.0	1.5	0.4	0.4	16.0
Czech Republic	West Bohemia	21.0	13.1	13.1	5.1	2.9	9.3	1.9	3.5	4.0	2.0	2.7	1.5	2.4	1.3	0.3	0.1	16.1
England	East Anglia[a]	15.7	13.3	16.5	9.0	3.4	3.5	3.1	2.9	3.3	2.5	2.7	1.2	2.4	3.2	0.7	0.2	16.4
	Mersey[a]	14.1	19.6	12.0	8.0	4.5	2.6	3.4	2.6	2.2	2.4	2.4	2.2	2.4	3.0	0.7	0.1	17.8
	North Western	17.8	13.3	12.2	11.0	3.3	4.6	3.1	3.5	2.8	2.1	1.5	2.0	2.2	2.0	0.5	0.3	17.8
	Northern& Yorkshire	16.2	16.0	12.8	7.8	3.7	3.7	2.5	5.3	3.4	2.2	2.1	1.3	2.3	2.3	0.8	0.3	17.5
	Oxford	19.8	8.8	18.8	12.4	2.5	3.4	3.3	4.0	2.3	1.5	2.9	0.9	2.0	1.7	0.6	0.1	14.9
	South Western	12.4	12.2	13.0	9.9	3.1	3.0	4.6	3.5	2.6	2.6	2.7	1.4	2.5	2.6	1.1	0.3	22.7
	Thames	14.5	16.6	7.1	10.2	3.8	3.4	4.1	3.8	4.1	2.7	1.9	1.8	3.0	3.0	1.0	0.3	18.8
	Trent	14.1	16.3	13.0	7.7	4.9	3.2	3.7	3.2	2.8	2.5	1.3	1.6	2.2	2.6	1.2	0.2	19.6
	West Midlands	13.8	15.5	12.5	9.4	4.2	3.5	3.2	4.0	3.7	2.4	1.8	1.4	2.4	2.7	0.7	0.1	18.6
Finland	Finland[a]	11.7	10.5	14.3	13.4	4.5	4.4	4.1	2.6	2.9	3.5	3.1	1.0	1.9	1.1	1.0	0.3	19.8
France	Bas Rhin	12.0	18.6	3.8	8.5	1.4	5.6	2.8	2.0	2.7	2.4	1.8	14.6	1.3	4.4	0.7	0.3	17.0
	Doubs	12.7	15.6	6.2	9.1	4.2	2.5	3.1	5.1	0.8	1.7	0.8	15.9	0.6	2.5	0.3	0.0	18.7
	Haut Rhin	14.2	10.9	4.8	7.7	5.3	4.5	3.0	5.3	4.2	2.2	1.0	10.7	1.3	4.0	0.3	0.3	20.2
	Herault	13.0	9.3	5.6	20.9	2.8	4.7	4.2	3.7	2.3	0.9	0.9	9.3	1.4	2.3	0.0	0.0	18.6
	Isere	16.8	13.9	5.6	11.1	2.7	2.7	2.8	2.8	2.9	2.4	2.0	9.0	1.1	2.9	1.1	0.1	20.1
	Manche	12.0	13.5	3.6	13.5	3.1	7.3	1.0	1.0	1.6	0.5	1.0	15.1	2.1	5.2	1.6	0.0	17.7
	Somme	14.9	13.0	3.8	11.4	3.8	3.5	2.5	1.6	3.2	0.3	0.6	13.3	1.9	6.0	0.0	0.0	20.3
	Tarn	17.0	7.4	6.4	13.5	3.9	4.2	2.9	4.2	2.3	2.3	1.3	6.8	2.3	2.3	0.3	0.6	22.5
Germany	Saarland	17.9	13.9	7.8	12.6	4.8	4.2	3.7	3.7	3.8	1.6	1.4	3.6	1.9	1.9	0.7	0.3	16.3
Iceland	Iceland[a]	14.2	15.1	10.3	10.3	5.5	5.8	3.0	3.0	2.5	3.4	1.8	1.8	2.2	1.6	0.6	0.1	18.4
Ireland	Ireland	21.2	9.9	10.4	12.1	3.8	3.9	2.6	3.4	3.3	2.1	3.5	1.7	2.3	1.7	0.8	0.2	17.2
Italy	Alto Adige	13.1	6.8	5.1	16.7	6.6	4.1	2.2	2.2	1.7	2.4	0.5	6.6	1.2	3.2	1.5	0.5	25.7
	Biella	13.9	10.4	6.4	13.4	5.0	5.4	5.0	3.5	4.0	2.5	1.5	6.9	0.5	2.0	0.0	1.5	18.3
	Ferrara	17.1	16.0	7.8	6.1	4.4	7.2	5.7	2.9	1.5	1.5	1.1	1.9	1.3	1.0	1.1	0.0	23.4
	Firenze	17.0	15.6	6.1	9.2	8.9	3.8	4.2	2.3	3.7	2.4	2.1	1.6	1.7	0.6	0.7	0.4	19.5
	Friuli V.G.	14.7	13.7	5.0	15.1	4.1	6.9	3.6	2.8	2.8	3.0	1.3	4.6	1.1	2.0	0.5	0.2	18.6
	Genova	15.7	15.3	5.9	10.5	3.9	4.2	3.0	2.7	2.4	2.5	1.7	3.3	1.8	1.1	0.9	0.3	24.7
	Macerata	16.4	9.3	5.2	15.0	9.0	4.8	3.8	2.6	1.9	3.3	1.0	1.0	2.4	0.2	0.5	0.2	23.3
	Modena	13.9	13.5	9.5	8.5	7.0	4.3	3.4	3.3	3.5	1.2	1.7	0.4	2.2	0.7	0.5	0.3	26.3
	Napoli	3.8	7.7	11.5	7.7	3.8	11.5	11.5	3.8	3.8	0.0	3.8	0.0	0.0	0.0	0.0	0.0	30.8
	Parma	12.4	16.0	7.2	8.8	7.5	3.3	4.0	2.4	3.5	4.8	1.3	2.1	1.9	2.1	1.0	0.0	21.6
	Ragusa	15.3	14.0	5.9	6.4	8.9	2.5	0.8	1.7	7.6	3.0	1.7	1.7	5.1	0.8	2.1	0.0	22.5
	Reggio Emilia	12.7	9.5	11.4	15.8	5.1	6.3	2.5	3.8	2.5	2.5	2.5	1.3	0.6	1.3	0.0	0.0	22.2
	Romagna	14.1	15.1	5.7	11.7	9.3	5.0	3.8	4.0	1.9	4.2	1.7	1.3	1.4	0.4	1.3	0.2	18.9
	Salerno	9.3	13.0	8.3	13.0	2.8	6.5	5.6	0.9	4.6	0.9	2.8	1.9	2.8	0.9	0.0	0.9	25.9
	Sassari	11.4	10.8	5.1	9.1	3.0	5.4	3.4	5.7	4.4	1.3	0.7	4.0	1.3	3.0	0.0	0.7	30.6

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Table 3 – *continued*

Country	Registry	Colon-rectum	Lung	Breast f	Prostate	Stomach	Kidney	Non hodgkin	Leuk-aemia	Corpus uteri	Pancreas	Skin melanoma	Head and neck	Ovary	Oeso-phagus	Brain	Hodgkin disease	Other
	Torino	13.4	17.2	7.0	10.3	4.6	3.8	3.8	2.9	4.2	2.8	2.9	2.5	1.9	1.8	0.9	0.2	19.8
	Trento	12.3	12.5	4.5	8.3	6.8	6.3	3.5	1.0	2.5	2.3	1.0	4.8	1.8	4.0	0.8	0.3	27.6
	Umbria	14.1	12.9	5.5	11.4	7.0	5.1	3.9	3.9	2.5	2.3	0.6	1.4	2.3	0.6	1.2	0.5	24.7
	Varese	12.9	15.1	7.7	11.3	6.6	3.7	3.5	2.5	2.4	3.1	1.2	3.8	2.0	1.9	1.1	0.3	21.1
	Veneto	11.4	17.9	5.9	11.5	5.2	4.9	3.6	2.6	2.0	3.5	1.7	4.1	1.4	2.3	0.6	0.1	21.3
Malta	Malta[a]	11.0	11.0	11.0	9.8	6.1	3.7	4.9	7.3	2.4	0.0	1.2	1.2	1.2	1.2	1.2	0.0	26.8
Netherlands	Amsterdam[a]	14.6	17.7	8.1	9.9	3.9	3.8	3.2	2.3	2.7	2.9	2.4	3.2	2.4	2.7	0.9	0.2	19.3
	Eindhoven	16.1	20.4	15.9	6.8	3.5	4.2	2.0	2.0	3.1	1.6	2.7	3.5	1.5	1.8	0.5	0.2	14.3
	North Netherlands	18.4	15.1	15.3	10.1	3.3	4.5	2.9	2.6	2.6	1.6	2.0	3.5	1.4	1.3	0.6	0.1	14.8
Northern Ireland	Northern Ireland[a]	18.3	12.5	4.5	6.9	4.0	5.5	4.6	2.2	2.1	2.1	1.5	4.4	5.0	3.0	0.6	0.5	22.3
Norway	Norway[a]	22.3	9.5	13.8	10.6	3.8	3.9	2.7	2.1	2.2	2.8	4.7	1.7	2.1	1.1	1.1	0.2	15.5
Poland	Cracow	9.1	20.4	20.2	4.2	6.1	1.4	1.8	0.2	4.1	1.1	2.5	1.1	6.6	1.3	0.4	1.1	18.6
	Kielce	16.4	7.8	6.9	8.6	6.0	6.9	6.0	2.6	4.3	2.6	1.7	3.4	0.9	0.0	1.7	0.9	23.3
	Warsaw[a]	12.7	15.7	15.3	5.9	3.7	5.0	2.6	2.2	5.1	1.6	1.7	1.9	4.3	0.9	1.0	0.2	20.1
Portugal	South Portugal[a]	15.7	8.4	11.6	12.0	5.2	3.0	4.1	3.0	3.8	1.3	2.8	2.9	2.9	2.3	0.2	0.6	20.0
Scotland	Scotland[a]	15.4	18.9	12.7	6.6	3.6	3.5	2.9	2.7	2.3	2.4	2.5	2.8	2.3	3.0	0.7	0.3	17.4
Slovenia	Slovenia	14.9	16.8	6.0	6.4	5.1	3.6	3.2	2.9	5.2	1.7	2.0	9.7	2.0	1.5	0.3	0.3	18.3
Spain	Basque Country	14.0	16.8	4.4	9.4	5.2	4.4	2.3	2.6	2.7	1.4	1.3	5.9	1.6	3.1	0.9	0.1	23.9
	Girona	15.3	13.2	4.6	18.1	4.9	3.7	3.4	1.5	4.6	0.9	2.1	2.5	0.6	2.5	0.0	0.6	21.5
	Murcia	16.7	12.1	4.6	13.7	6.2	3.9	2.0	2.3	2.3	0.3	1.0	3.9	2.0	1.6	0.3	0.3	26.8
	Navarra	13.2	13.7	3.4	10.6	5.7	5.5	3.5	3.2	3.6	2.8	0.9	3.1	2.2	1.9	1.8	0.5	24.3
	Tarragona	12.3	15.3	5.1	10.1	5.1	4.9	3.8	2.3	4.0	1.5	1.5	4.0	1.4	1.2	0.8	0.3	26.5
Sweden	Sweden[a]	16.4	7.2	16.7	10.6	3.1	4.3	3.2	2.7	2.6	2.5	4.1	1.4	2.1	1.0	0.7	0.2	21.1
Switzerland	Basel	16.8	12.2	15.6	14.1	2.6	4.3	3.9	2.6	2.2	2.5	3.5	3.3	1.1	1.5	0.5	0.4	12.8
	Geneva	13.2	13.0	12.4	9.7	1.9	3.5	2.9	4.3	2.5	2.6	4.3	8.3	0.9	2.3	1.2	0.4	16.5
	St. Gallen	12.5	10.1	11.0	9.9	3.4	5.4	3.8	4.4	2.9	3.5	4.6	2.7	7.5	1.4	0.7	0.5	15.7
	Ticino	12.7	12.0	7.7	12.0	3.5	4.2	4.9	3.5	1.4	0.7	2.1	3.5	2.1	2.1	0.7	0.0	26.8
	Valais	12.0	12.3	18.8	10.4	3.9	2.9	2.3	1.6	2.6	1.6	5.5	6.5	1.6	2.3	0.6	0.0	15.2
Wales	Wales	12.9	13.7	7.0	9.9	4.6	2.9	4.1	4.1	2.9	3.0	2.1	2.7	2.7	2.6	0.8	0.2	23.8
Totals	European Pool	15.1	13.4	11.5	10.3	4.1	4.0	3.4	3.0	3.0	2.6	2.6	2.4	2.2	2.0	0.8	0.2	19.4

a Original sequence number.

Table 4 – Age-adjusted 5-year relative survival (RS) by registry for all malignant cancer sites – first only versus first and multiples figures (including SE): age 15–99, period of diagnosis 1995–1999.

Registry		Women					Men				
		First		First & multiples		Abs. diff.	First		First & multiples		Abs. diff.
		RS	S.E.	RS	S.E.	RS	RS	S.E.	RS	S.E.	RS
Austria	Austria	58.7	0.2	58.2	0.2	–0.5	53.6	0.2	53.1	0.2	–0.5
	Tyrol	60.7	0.8	60.2	0.7	–0.5	61.5	0.8	60.7	0.8	–0.8
Belgium	Flanders	58.8	0.3	58.6	0.3	–0.2	49.3	0.3	48.9	0.3	–0.4
Czech Republic	West Bohemia	49.2	0.7	48.7	0.7	–0.5	36.3	0.7	36.1	0.7	–0.2
England	East Anglia[a]	47.5	0.4	47.5	0.4	0.0	37.9	0.4	37.6	0.4	–0.3
	Mersey[a]	46.7	0.4	46.2	0.3	–0.4	39.4	0.4	39.0	0.4	–0.4
	North Western	45.6	0.3	45.5	0.3	–0.1	36.8	0.3	36.5	0.2	–0.2
	Northern&Yorkshire	47.8	0.3	47.5	0.3	–0.2	38.3	0.2	38.0	0.2	–0.4
	Oxford	51.4	0.4	51.3	0.4	–0.1	44.1	0.4	43.9	0.4	–0.2
	South Western	55.0	0.2	54.0	0.2	–1.0	46.2	0.2	45.3	0.2	–0.9
	Thames	52.6	0.2	52.1	0.2	–0.5	42.9	0.2	42.4	0.2	–0.5
	Trent	47.6	0.3	47.3	0.3	–0.3	37.9	0.3	37.5	0.3	–0.4
	West Midlands	50.9	0.3	50.5	0.2	–0.4	41.6	0.3	41.0	0.2	–0.5
Finland	Finland[a]	59.2	0.3	58.9	0.3	–0.3	51.4	0.3	50.9	0.3	–0.6
France	Bas Rhin	60.8	0.8	60.2	0.8	–0.6	49.5	0.8	47.2	0.8	–2.2
	Doubs	59.9	1.2	59.3	1.1	–0.6	44.7	1.1	43.5	1.1	–1.2
	Haut Rhin	57.9	1.0	57.0	0.9	–0.9	45.4	1.0	43.2	0.9	–2.2
	Herault	64.4	0.9	64.2	0.9	–0.2	48.5	0.8	48.1	0.8	–0.4
	Isere	62.7	0.8	62.1	0.8	–0.7	47.5	0.8	46.3	0.8	–1.2
	Manche	57.9	1.1	57.5	1.1	–0.4	42.6	1.1	41.6	1.0	–1.0
	Somme	55.9	1.2	55.6	1.1	–0.3	37.4	1.0	36.4	1.0	–1.0
	Tarn	59.9	1.3	59.6	1.2	–0.3	48.1	1.2	47.0	1.2	–1.1
Germany	Saarland	57.1	0.6	56.4	0.5	–0.7	47.6	0.6	46.6	0.6	–1.0
Iceland	Iceland[a]	56.1	1.3	54.9	1.2	–1.2	55.7	1.3	54.2	1.2	–1.6
Ireland	Ireland	48.7	0.3	48.5	0.3	–0.1	41.9	0.4	41.6	0.4	–0.2
Italy	Alto Adige	59.7	0.8	59.2	0.8	–0.5	50.7	0.8	49.9	0.8	–0.7
	Biella	57.2	1.1	56.7	1.0	–0.5	43.9	1.1	43.5	1.1	–0.4
	Ferrara	61.0	0.8	60.1	0.8	–0.9	43.3	0.8	42.8	0.8	–0.6
	Firenze	58.7	0.4	58.2	0.4	–0.5	46.4	0.4	45.9	0.4	–0.5
	Friuli V.G.	55.7	0.4	55.3	0.4	–0.4	45.6	0.4	44.9	0.4	–0.7
	Genova	56.3	0.5	55.7	0.5	–0.6	44.7	0.5	43.9	0.5	–0.8
	Macerata	56.5	0.9	56.1	0.9	–0.4	50.0	0.9	49.2	0.9	–0.8
	Modena	60.4	0.6	60.3	0.6	–0.2	47.9	0.6	47.5	0.6	–0.4
	Napoli	49.9	1.3	49.8	1.3	–0.2	33.4	1.1	33.4	1.1	0.0
	Parma	57.7	0.7	56.9	0.7	–0.8	44.4	0.8	43.4	0.7	–1.0
	Ragusa	54.1	1.2	53.8	1.2	–0.3	38.6	1.1	38.5	1.1	–0.1
	Reggio Emilia	61.4	0.8	61.3	0.8	–0.1	47.9	0.9	47.8	0.8	–0.1
	Romagna	61.0	0.5	60.2	0.5	–0.7	49.8	0.5	48.8	0.5	–1.0
	Salerno	49.0	0.7	49.1	0.7	0.0	37.6	0.6	37.4	0.6	–0.1
	Sassari	56.0	0.9	55.8	0.9	–0.2	37.1	0.9	36.6	0.8	–0.5
	Torino	57.9	0.5	57.3	0.5	–0.6	46.7	0.6	45.8	0.5	–0.9
	Trento	58.7	0.8	58.3	0.7	–0.3	44.9	0.8	43.9	0.8	–1.0
	Umbria	58.5	0.5	57.8	0.5	–0.6	50.1	0.5	49.5	0.5	–0.6
	Varese	58.6	0.6	57.9	0.6	–0.7	46.4	0.6	45.5	0.6	–0.9
	Veneto	58.6	0.3	58.0	0.3	–0.7	47.5	0.4	46.4	0.3	–1.1
Malta	Malta[a]	55.8	1.1	55.6	1.1	–0.3	40.5	1.1	40.3	1.1	–0.2
Netherland	Amsterdam[a]	56.0	0.4	54.9	0.4	–1.1	46.1	0.4	44.8	0.4	–1.3
	Eindhoven	58.6	0.7	58.1	0.6	–0.5	45.7	0.7	44.3	0.6	–1.4
	North Netherlands	56.2	0.4	56.0	0.4	–0.2	43.9	0.4	43.3	0.4	–0.6
Northern Ireland	Northern Ireland[a]	49.5	0.5	49.2	0.5	–0.3	38.5	0.5	38.1	0.5	–0.4
Norway	Norway[a]	56.9	0.3	56.5	0.3	–0.4	49.9	0.3	48.9	0.3	–1.0

(continued on next page)

Table 4 – *continued*

Registry		Women					Men				
		First		First & multiples		Abs. diff.	First		First & multiples		Abs. diff.
		RS	S.E.	RS	S.E.	RS	RS	S.E.	RS	S.E.	RS
Poland	Cracow	40.5	0.7	40.3	0.7	–0.3	25.9	0.7	25.7	0.7	–0.2
	Kielce	50.7	0.7	50.7	0.7	0.0	39.9	0.7	39.8	0.7	–0.1
	Warsaw[a]	45.6	0.5	45.8	0.5	0.2	34.4	0.6	34.4	0.5	0.0
Portugal	South Portugal[a]	55.9	0.5	55.9	0.5	0.0	48.5	0.5	48.4	0.5	–0.1
Scotland	Scotland[a]	46.7	0.2	46.4	0.2	–0.3	38.7	0.2	38.1	0.2	–0.6
Slovenia	Slovenia	49.6	0.5	49.3	0.5	–0.3	33.4	0.5	32.9	0.5	–0.5
Spain	Basque Country	56.4	0.5	56.0	0.4	–0.4	43.0	0.4	42.1	0.4	–0.9
	Girona	57.7	0.9	57.6	0.9	–0.1	45.2	0.8	44.5	0.7	–0.7
	Murcia	56.2	0.8	55.9	0.8	–0.3	43.8	0.7	43.4	0.7	–0.4
	Navarra	55.0	0.8	54.8	0.8	–0.2	44.3	0.7	43.1	0.7	–1.2
	Tarragona	56.2	0.8	55.8	0.8	–0.5	47.2	0.7	46.0	0.7	–1.2
Sweden	Sweden[a]	60.0	0.2	59.6	0.2	–0.4	55.6	0.2	54.6	0.2	–1.1
Switzerland	Basel	60.0	0.9	59.9	0.9	–0.1	53.9	1.0	52.4	0.9	–1.4
	Geneva	62.7	0.9	61.8	0.9	–0.9	52.6	0.9	50.9	0.9	–1.7
	St. Gallen	56.5	0.9	56.1	0.9	–0.4	51.3	0.9	50.2	0.8	–1.1
	Ticino	58.2	1.1	58.0	1.1	–0.2	46.2	1.1	46.0	1.1	–0.2
	Valais	56.6	1.4	56.1	1.3	–0.6	46.4	1.3	45.0	1.2	–1.4
Wales	Wales	52.2	0.3	51.3	0.3	–0.9	43.9	0.4	43.0	0.3	–0.9

a Original sequence number.

the corresponding proportions of multiple tumours. The plot clearly shows that the decrease in survival due to the inclusion of multiple tumours directly depends on their proportion. The two regression lines give an expected survival difference of –0.5 percentage points for every 3 percentage points of multiple tumours in men and for every 7 percentage points in women.

Differences according to cancer site are presented in Table 5 in terms of area and age-adjusted European 5-year relative survival estimates with and without multiple tumours. These differences, were almost null for highly lethal cancers (lung, pleura, pancreas, liver, biliary tract, brain) and generally increased with prognosis, but did not exceed –1.9 percentage points (larynx cancer). Table 5 also reports in the last three columns the interquartile range of the distribution of survival differences across registries. For this last analysis, unadjusted survival rates for ages 15–99 have been considered instead of age-adjusted rates. The inclusion of multiple tumours produced a not negligible range of variation on registry-specific unadjusted survival rates, especially for the rarest tumours.

In the case of less common cancers, the increase in number of cases included can also lead to a substantial improvement in the precision of survival estimates (data not presented), for example, with a 13% decrease of standard errors for thyroid cancer in Haut-Rhin (France).

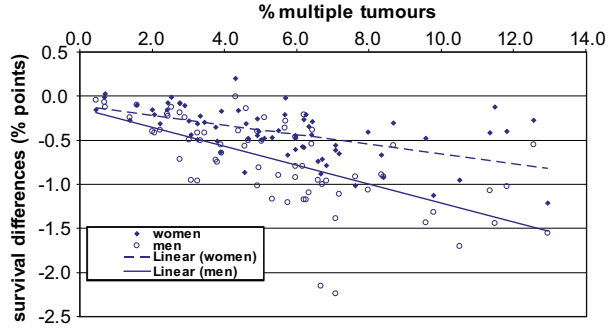

Fig. 2 – Differences in age-standardised 5-year survival (first and multiples tumours – first only) by percentage of multiple tumours among the EUROCARE-4 cancer registries (dotted line = linear trend women, continuous line = linear trend men).

4. Discussion

The present study addresses for the first time the issue of evaluating the influence of different inclusion criteria of multiple cancers in survival analysis on a large number of population-based cancer registries. A systematic decrease in the age-standardised relative survival was found when all the tumours were included in the analysis, with respect to the usual practice of considering only first primaries. The survival difference was usually between zero and –1 percentage points in the European estimates, but never exceeded –1.9 percentage points (larynx cancer), and was larger in the older registries. We also found a variable percentage of multiple cancers, ranging from about 13% in the oldest registries to less than 1% in the most recent registries.

The main collaborative studies comparing survival between different population-based cancer registries have always adopted the policy of excluding subsequent cancers from analyses.[4,5,7] The rationale for this policy was to remove

Table 5 – Area and age-adjusted 5-year relative survival (RS) with standard errors (S.E.) by cancer site. Overall absolute difference (in percentage points) between first and multiple RS (b) and first only RS (a) values (absolute differences by registry in crude 5-year relative survival with and without subsequent tumours: interquartile range; age 15–99, period of diagnosis 1995–1999).

Cancer site	First		First & multiples		Absolute difference RS(b) – RS(a)	Absolute differences by registry		
	RS (a)	S.E.	RS (b)	S.E.		Interquartile range		
						25%	50%	75%
Lip	94.5	0.9	93.3	0.8	–1.23	–3.13	–1.40	0.00
Tongue	44.3	0.9	42.9	0.8	–1.42	–2.48	–1.50	–0.18
Salivary glands	59.1	1.2	58.4	1.1	–0.75	–2.80	–1.30	0.00
Oral cavity	46.8	0.8	45.8	0.8	–1.06	–2.50	–1.30	–0.70
Nasopharynx	50.3	1.3	49.7	1.3	–0.60	–1.38	0.00	0.00
Oropharynx	37.1	0.9	35.5	0.9	–1.52	–2.30	–1.30	0.00
Hypopharynx	24.6	1.0	24.1	1.0	–0.47	–1.30	–0.30	0.00
Head and neck	40.0	0.4	39.0	0.4	–1.08	–1.90	–1.10	–0.40
Oesophagus	11.7	0.3	11.4	0.3	–0.34	–0.60	–0.30	–0.10
Stomach	25.0	0.2	24.7	0.2	–0.29	–0.70	–0.40	–0.10
Small intestine	42.1	1.0	41.7	1.0	–0.42	–2.80	–0.70	0.40
Colon and rectum	54.4	0.1	53.9	0.1	–0.55	–1.00	–0.60	–0.40
Colon	54.8	0.2	54.3	0.2	–0.52	–1.10	–0.70	–0.30
Rectum	53.7	0.2	53.1	0.2	–0.60	–1.10	–0.60	–0.30
Liver, primary	9.1	0.3	9.2	0.3	0.08	–0.20	–0.10	0.10
Biliary tract	14.9	0.4	14.8	0.4	–0.05	–0.40	–0.10	0.10
Pancreas	5.9	0.2	5.8	0.2	–0.06	–0.20	–0.10	0.00
Nasal cavities	45.8	1.3	44.6	1.2	–1.19	–2.13	–0.85	0.00
Larynx	63.6	0.6	61.7	0.5	–1.90	–2.80	–1.90	–0.80
Lung,bronchus,trachea	12.5	0.1	12.4	0.1	–0.03	–0.20	0.00	0.10
Pleura	7.5	0.5	7.4	0.5	–0.07	–0.20	0.00	0.00
Bone	50.8	1.6	50.4	1.5	–0.42	–1.40	0.00	0.00
Soft tissue	59.2	0.6	58.2	0.6	–1.00	–2.13	–1.10	0.00
Skin melanoma	82.6	0.3	81.8	0.3	–0.80	–1.20	–0.90	–0.40
Breast	79.4	0.2	78.9	0.1	–0.49	–0.70	–0.50	–0.30
Cervix	62.8	0.4	62.5	0.4	–0.30	–0.90	–0.30	0.00
Corpus uteri	76.5	0.3	75.6	0.3	–0.95	–1.60	–0.90	–0.50
Ovary	36.9	0.3	36.6	0.3	–0.34	–0.90	–0.50	0.00
Vagina and vulva	59.8	0.7	59.2	0.7	–0.64	–1.50	–0.40	0.00
Prostate	76.8	0.2	75.8	0.2	–1.04	–1.60	–1.20	–0.80
Testis	90.2	0.9	89.9	0.9	–0.30	–0.13	0.00	0.00
Penis	73.8	1.5	72.5	1.4	–1.30	–2.50	–1.00	0.00
Kidney	58.2	0.3	57.6	0.3	–0.59	–1.20	–0.70	–0.30
Melanoma of choroid	68.2	2.1	67.8	2.0	–0.42	–1.30	0.00	0.00
Brain	20.3	0.3	20.3	0.3	0.00	–0.40	–0.20	0.00
Thyroid	82.8	0.4	82.2	0.4	–0.60	–1.30	–0.80	–0.40
Hodgkin disease	80.2	0.5	79.9	0.5	–0.30	–1.10	–0.30	0.00
Non hodgkin lymphoma	51.8	0.3	51.2	0.3	–0.63	–1.40	–0.80	–0.50
Multiple mieloma	35.9	0.4	35.6	0.4	–0.29	–0.90	–0.40	0.00
All leukaemias	42.6	0.3	41.4	0.3	–1.16	–1.90	–1.10	–0.60
Acute lymph. Leukaemia	30.9	1.1	30.7	1.1	–0.20	–1.40	–0.80	0.00
Chronic lymph. Leukaemia	68.8	0.6	67.7	0.6	–1.16	–2.20	–1.40	–0.70
Acute myeloid leukaemia	14.3	0.4	13.8	0.4	–0.45	–1.50	–0.70	–0.20
Chronic myeloid leukaemia	35.7	0.8	34.9	0.8	–0.84	–1.90	–1.10	0.00
All sites, men	45.5	0.1	44.8	0.1	–0.68	–1.20	–0.70	–0.40
All sites, women	55.4	0.1	55.0	0.1	–0.39	–0.80	–0.50	–0.38
All sites	50.5	0.1	50.0	0.1	–0.56	–1.10	–0.70	–0.48

additional sources of variation given by the supposed influence of a second cancer on the patient prognosis. Such exclusion criteria, should, in theory, lead to a more homogeneous and therefore comparable groups of subjects. However, this should be a minor concern compared to the impact of other major sources of variation. For example, other diseases, even more lethal, can be present. Relative survival was devised to control, at least in part, the effect of other diseases on survival. However, people who died because of cancers (single or multiple) are included in the estimation of expected survival, i.e. the denominator of relative survival. Therefore, the exclusion of patients with more than one cancer in observed survival, the numerator of relative survival, may actually bias estimates. Furthermore, when comparing statistics

between registries, or between different periods for the same registry, excluding patients with multiple cancers leads to further spurious comparisons due to the fact that the probability of correctly identifying a tumour following another prevalent tumour directly depends on the completeness of prevalent case collection. In other words, it is dictated by the number of years of registration. Since patients with multiple cancers usually have a poorer prognosis, a recently set cancer registry will show poorer survival estimates because of its inability to identify prevalent cases.

We observed that the older European registries have a proportion of recognised multiple cancers of about 10–13% of all registered tumours, while those with 10 years or less of observation showed a lower proportion of multiple primary tumours depending on the lengths of their activities. Another study on North American registries showed that the cumulative incidence increases at a slower rate after 15 years for most of the cancer sites.[13] Although this is in some way expected, since the risk of a subsequent cancer is higher during the first years following a first primary, and few patients survive for more than 15–20 years, given also their high mean age at the disease's onset, the amount of bias can cause a decrease in survival as high as 2% (larynx cancer).

The previous study on the Finnish Cancer Registry data[6] also showed how the bias was related to the increasing proportion of multiple cancers diagnosed in various 5-year periods since the beginning in 1953 to the last presented data in 1997. For example, 5-year relative survival from leukaemia in 1953–1957 showed no changes including multiple cancers, while it decreased by 2.9% for the last 5-year period in 1993–1997. The authors also investigated the same effect according to age. As expected, since the probability of detecting a subsequent tumour increases with age, excluding multiple tumours led to wider differences in older age classes with a bias that can be as high as 3.5% of the age-standardised 5-year relative survival for patients of 75 years of age or more with leukaemia.[6]

Focussing on the differences across European registries using age-standardised relative survival, along with the variation of the proportion of multiple cancers, we observed a non-negligible bias when analysing first tumours only, with estimates as high as 2–3% of survival, in particular for older registries and for cancer sites with good prognosis (60% of age-standardised 5-year relative survivals or higher).

In addition to the registry observation period and patients' age, other factors can also influence the probability of correctly identifying subsequent tumours, and therefore affect survival estimates. First of all, changes in the sources of clinical documentation and the availability of automated data collection in these years had surely changed the way cancer registries identify patients and detail the tumour's clinical features, so heavily influencing both completeness and quality of collected data.[14,15] Indirectly, the percentage of microscopic confirmation and cases notified by DCO is related to the quality and completeness of data and the registries' ability in detecting subsequent primaries.

Furthermore, criteria for the definition of multiple tumours may not be homogeneous across registries. One might argue that all European cancer registries comply with the rules issued by the IARC,[3] and not with the rules by the SEER programme,[2] which differ substantially. However, some local situations and opportunities, such as those represented by the presence of a screening programme, can lead to a different attitude towards multiple tumours: consequently, implicit rules can become a registry's common practice.[16] The effect of potential heterogeneity in coding practice, completeness and quality of registration of multiple cancers can also explain part of the variability in the proportion of multiple cancers observed even among registries with longer running time, as shown in Fig. 1.

Excluding multiple tumours can therefore lead to a non-negligible bias, as shown in our study. Although based on a very large sample, these results can only be interpreted as an empirical investigation of the potential bias of different exclusion criteria on survival estimates. The present study design could, however, not identify which factors are the most influential, apart from the obvious effect of the registry's running time, since the way registries operate varies significantly.

In conclusion, including multiple primary tumours in survival estimates for international comparison is advisable for several reasons. It reduces the bias due to observation periods, age, quality and completeness, leading to a different probability of identifying multiple tumours. Even if the bias is small, including more patients is, nevertheless, still beneficial as it improves the accuracy of estimates. Finally, as previously suggested by Brenner and Hakulinen,[6] it is also more appropriate from a theoretical point of view, since it reconciles the basis for the numerator and denominator in the calculation of expected survival for relative survival estimates.

Conflict of interest statement

None declared.

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