EUROPEAN JOURNAL OF CANCER 42 (2006) 2598–2608

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Variation in relative survival of thyroid cancers in Europe: Results from the analysis on 21 countries over the period 1983–1994 (EUROCARE-3 study)

Marc Colonna[a,*], *Enrico Grande*[b,e], *Jón G. Jónasson*[c,d,f], *EUROCARE Working Group*[g]

[a]*Isère Cancer Registry, 23 Chemin des Sources, 38240 Meylan, France*
[b]*Istituto Superiore di Sanità, Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute Reparto Epidemiologia dei Tumori, Viale Regina Elena 299, Rome, Italy*
[c]*Icelandic Cancer Registry, Skogarhlid 8, P.O. Box 5420, 125 Reykjavik, Iceland*
[d]*Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland*

[*] *Corresponding author:* Tel.: +33 4 76 90 76 10; fax: +33 4 76 41 87 00.
E-mail addresses: mcolonna.registre@wanadoo.fr (M. Colonna), e.grande@iss.it (E. Grande), jongj@landspitali.is (J.G. Jónasson).
[e] Tel.: +39 06 49904294; fax: +39 06 49904285.
[f] Tel.: +354 540 1900; fax: +354 540 1910.

[g] EUROCARE Working Group: Austria: W Oberaigner (Tyrol Cancer Registry); Denmark: HH Storm (Danish Cancer Society, Dept. Cancer Prevention & Documentation); Estonia: T Aareleid (Estonian Cancer Registry); Czech Republic: M Jechova, M Rousarova (IHIS and West Bohemia Cancer Registry); Finland: T Hakulinen (Finnish Cancer Registry); France: G Hédelin (Bas-Rhin Cancer Registry), I Tron, E Le Gall (Bretagne Childhood Cancer Registry), G Launoy (Calvados Digestive Cancer Registry), J Macé-Lesec'h (Calvados General Cancer Registry), J Faivre (Côte d'Or Digestive Cancer Registry), G Chaplain (Côte d'Or Gynaecologic Cancer Registry), P-M Carli (Côte d'Or Malignant Haemopathies Registry), A Danzon (Doubs Cancer Registry), B Tretarre (Hérault Cancer Registry), M Colonna (Isère Cancer Registry), B Lacour (Lorraine Childhood Cancer Registry), N Raverdy (Somme Cancer Registry), C Berger, B. Freycon (Rhône-Alpes Childhood Registry), P Grosclaude (Tarn Cancer Registry), J Estève (University of Lyon); Germany: P Kaatsch (German Childhood Cancer Registry), H Ziegler (Saarland Cancer Registry), D Hölzel, G Schubert Fritschle (Munich Cancer Registry); Iceland: L Tryggvadottir (Icelandic Cancer Registry); Italy: F Berrino (Project Leader), C Allemani, P Baili, L Ciccolallo, P Crosignani, G Gatta, A Micheli, M Sant, E Taussig, S Sowe, (Istituto Nazionale per lo Studio e la Cura dei Tumori, Lombardy Cancer Registry), S Ferretti (Ferrara Cancer Registry), E Conti (Latina Cancer Registry), M Vercelli, A Quaglia (Liguria Region Cancer Registry–DOBIG Univ. GE, IST Genova), F Pannelli (Macerata Cancer Registry, Marche Childhood Cancer Registry), M Federico, ME Artioli (Modena Cancer Registry), M Ponz De Leon, P Benatti (Modena Colorectal Cancer Registry), V De Lisi, L Servente (Parma Cancer Registry), R Zanetti, S Patriarca (Piedmont Cancer Registry), C Magnani, G Pastore (Piedmont Childhood Cancer Registry), L Gafà, R Tumino (Ragusa Cancer Registry), F Falcini (Romagna Cancer Registry), M Budroni (Sassari Cancer Registry), E Paci, E Crocetti (Tuscan Cancer Registry), P Zambon, S Guzzinati (Venetian Cancer Registry), R Capocaccia, E Carrani, R De Angelis, P Roazzi, M Santaquilani, A Tavilla, F Valente, A Verdecchia (Istituto Superiore di Sanità, Rome); Malta: M Dalmas (Malta National Cancer Registry); Norway: F Langmark, A Andersen (Cancer Registry of Norway, Institute of Population-based Cancer Research); Poland: J Rachtan (Cracow Cancer Registry), M Bielska–Lasota, Z Wronkowski (Warsaw Cancer Registry); Slovakia: I Pleško, A Obsitníková (National Cancer Registry of Slovakia); Slovenia: V Pompe–Kirn (Cancer Registry of Slovenia); Spain: I Izarzugaza (Basque Country Cancer Registry), C Martinez-Garcia (Granada Cancer Registry), I Garau (Mallorca Cancer Registry), C Navarro, MD Chirlaque (Murcia Cancer Registry), E Ardanaz, C Moreno (Navarra Cancer Registry), J Galceran (Tarragona Cancer Registry), A Torrella (Childhood Tumour Registry of Valencia), R Peris-Bonet (National Childhood Cancer Registry and Instituto Lopez Pinero, Valencia); Sweden: L Barlow, T Möller (Cancer Registry of Sweden); Switzerland: G Jundt (Basel Cancer Registry), JM Lutz, C Bouchardy (Geneva Cancer Registry); The Netherlands: JWW Coebergh (Eindhoven Cancer Registry), A van der Does-van den Berg (Dutch Childhood Oncology Group), O Visser (Amsterdam Cancer Registry); UK - England: S Godward (East Anglian Cancer Registry), MP Coleman (London School of Hygiene and Tropical Medicine), EMI Williams (Merseyside and Cheshire Cancer Registry), D Forman (Northern and Yorkshire Cancer Registry and Information Service), MJ Quinn (Office for National Statistics), M Roche, S Edwards (Oxford Cancer Intelligence Unit), C Stiller (Childhood Cancer Research Group, Oxford), J Verne (South West Cancer Intelligence Services), H Møller, J Bell (Thames Cancer Registry), JL Botha, (Trent Cancer Registry), G Lawrence (West Midlands Cancer Intelligence Unit); UK - Scotland: R Black (Scottish Cancer Intelligence Unit); UK - Wales: JA Steward (Welsh Cancer Intelligence and Surveillance Unit).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.04.026

ARTICLE INFO

Article history:
Received 14 March 2006
Received in revised form
21 April 2006
Accepted 27 April 2006
Available online 18 September 2006

Keywords:
Thyroid cancer
Relative survival
Histology
European countries

ABSTRACT

We described the relative survival of thyroid cancer cases diagnosed in Europe during the period 1990–1994 and analysed time trends in relative survival during the period 1983–1994 using the EUROCARE-3 database. Relative survival of thyroid cancers is one of the highest amongst cancer sites, with age-standardised relative survival rates of 74% in men and 82% in women over the period 1990–1994, with marked differences between countries. The higher relative survival rates are observed in Scandinavian countries and the lower rates are observed in the UK and the countries of Eastern Europe. Relative survival is higher in women than in men, and decreases with age whatever the histological group. There are significant differences in relative survival according to histological type. Relative survival has slightly increased over the period 1983–1994 only when all histological types have been considered together. Time trend was, however, non-existent when the different histological groups were taken into account except during the most recent period of observation. One possible explanation for the differences in relative survival between countries and sex may probably be found in the changes in thyroid classification and diagnosis techniques. When these changes are not homogeneous, the distribution of thyroid cancers by histology and by stage at diagnosis may be very different. The only way to understand these differences is to conduct specific studies including a description of stage at diagnosis, diagnosis procedures used for staging and details of treatment.

1. Introduction

Carcinoma of the thyroid is an uncommon cancer that comprises less than 2% of total cancer cases in developed countries. It consists of several morphologic types with distinct clinical and epidemiological patterns. Papillary carcinoma accounts for 50–60% of all thyroid cancers, follicular cancer for about 15–20%, medullary and anaplastic for approximately 6% each.[1] Different publications have described thyroid cancer time trends, confirming that thyroid cancer incidence has been increasing in many countries over the last 30 years[2–10] while mortality rates have been slowly decreasing, except in some countries.[11] There is a marked female predominance in thyroid cancer incidence of the order of 2–3-fold, but this varies according to morphological type and age.

The reason for the increased incidence is still controversial and is beyond the scope of this paper. However, the changes in diagnostic practices are probably a major factor that could affect the apparent incidence of thyroid cancer.[7,12] It appears that the spread of new diagnostic techniques leads to an increase in the proportion of microcarcinoma.[13] The reduction in tumour size may influence the survival of recently diagnosed thyroid cancers.[14]

The aim of this study is to report relative survival of thyroid cancer patients from the data of EUROCARE-3. Relative survival data is analysed according to age at diagnosis, sex and histologic subtypes. Time trends in relative survival of patients with thyroid cancer are also reported.

2. Materials and methods

The EUROCARE-3 data used to describe the relative survival of thyroid cancers was provided by 47 cancer registries in 21 countries. We have analysed prognosis of thyroid cancer in terms of relative survival, i.e. the ratio between survival of thyroid cancer patients irrespective of cause of death, and corresponding survival of the general cancer-free population matched by age, sex, year of diagnosis, and geographical region. This indicator corrects survival for competing death risk and is an estimate of survival of patients if their cancer were the only cause of death.

The objective of the study over the period 1990–1994 was to estimate relative survival by age, sex and country. The countries where the number of cases were less than 15 (gender or age-specific) were excluded from this analysis. This condition was applied separately for men and women: 14 countries were excluded from the analysis among men and four countries were excluded from the analysis among women. However, the calculation of relative survival rates for Europe as a whole took into account of the observations of the 21 countries. The relative survival rates are presented separately for men and women and for five age groups. We calculated the relative survival according to histology for Europe as a whole considering papillary, follicular, medullary, anaplastic carcinoma and 'other' (unspecified or non-microscopic confirmation histology: 70% of the cases of this group-oncocytic carcinoma: 15% of the cases-other specified histology: 15% of the cases) as available in the EUROCARE database.

In the analysis for the period 1983–1994, relative survival rates are not presented if the number of gender and/or period specific cases was less than 50 for a particular country. The estimation of relative death rates according to the period of diagnosis has been done using the approach used in the EUROCARE-2 study.[15] The relative death rates were obtained by comparison of rates of cancer death between the latest 3-year period of diagnosis and the first period. The relative death rates correspond to the ratio of the logarithm of the relative survival probability of the most recent diagnosis period and the logarithm of the relative survival probability of the first diagnosis period.

The European relative survival rates were calculated as weighted averages, the weights being the numbers of cases of thyroid cancer in the country in 1990–1994. For countries with incomplete coverage of the population, these numbers were estimated using the method described in EUROCARE-3 publication.[16] Country-specific relative survival rates were age-standardised using the age distribution of the EUROCARE thyroid data as a reference.[16]

We performed a multiple regression analysis for the relative survival in the framework of generalised linear models using a Poisson assumption for the observed number of deaths.[17] This analysis took into account follow-up duration, sex, age at diagnosis (15–44, 45–54, 55–64, 65–74, 75+), period of diagnosis (1983–1985, 1986–1988, 1989–1991, 1992–1994), country (16 countries where the the number of period specific cases was higher than 50), and histology (papillary and follicular in a first regression analysis, medullary and anaplastic carcinoma in a second regression analysis), using them as covariates in order to provide a description of their role in relative survival time. The multivariate analysis allowed for statistical hypothesis using the information provided by the overlapping or the lack of overlapping of confidence intervals. When histology were considered, data from Sweden and Finland was excluded from the analysis.

3. Results

3.1. *Description of the data*

There were 13,277 malignant tumours of the thyroid (excluding lymphomas and sarcomas) diagnosed in patients aged at least 15 years during the period 1990–1994 (Table 1). Of these, 92.8% were histologically confirmed, ranging from 78.2% (England) to 100% (Iceland, Netherlands). The proportion of death certificate only (DCO) cases varied from 0 to 5% between the countries but these were excluded from the relative survival analysis. Data covered the entire population for Denmark, Estonia, Finland, Iceland, Norway, Scotland, Sweden, Slovakia, Slovenia and Wales. In the other countries, the coverage varied between 2.8 and 62.6% of the population. The distribution of cases according to sex, age group and histology is reported in Table 2. Cases from Sweden and Finland were excluded from this table because of the absence of distinction between the histological types in the EUROCARE database. The distribution of thyroid cancers by country and histology is reported in Table 1. Thyroid cancer cases in women represented 75% of the cases diagnosed during the period 1990–1994. More than half of the cases were diagnosed before age 55. Papillary cancer was the most frequent histological group being 53% of the cases. Variation in relative survival within Europe was analysed using data from 1990–1994. Trend analyses were performed for the 12-year period 1983–1994. This corresponds to the largest period completely covered by the data of the majority of the participating registries. Although data checks were realised in the EUROCARE-3 database, no specific verifications on the coding and classification according to histology has been done in this study.

3.2. *Relative survival by country*

The age-standardised relative survival rates at 5 years after diagnosis (1990–1994) by country for all histological groups showed substantial variations, ranging from 71% (England and Scotland) to 80% (Finland) in men, and from 66% (Poland) to 89% (Norway) in women.

Table 1 – Data description for adult patients (15+ years of age), 1990–1994 (EUROCARE-3)

Country	% coverage	% DCO[a]	% Microscopically confirmed	Number of cases by histological group					
				Papillary	Follicular	Medullary	Anaplastic	Other	All
Denmark	100.0	0.2	97.6	268	105	33	34	49	489
Finland	100.0	0.1	99.3	998	0	44	0	289	1331
Iceland	100.0	0.0	100.0	63	16	0	4	2	85
Norway	100.0	0.6	98.6	568	111	27	6	75	787
Sweden	100.0	0.0	99.9	0	0	62	163	1090	1315
England	62.6	2.5	78.2	1281	557	125	172	852	2987
Scotland	100.0	0.2	93.7	255	113	30	24	70	492
Wales	100.0	0.0	79.9	100	44	24	18	66	252
Austria	8.0	0.8	98.0	141	70	5	10	22	248
France	5.7	0.0	99.4	205	55	21	13	27	321
Germany	2.8	5.0	94.3	107	46	20	18	70	261
Netherlands	23.7	0.0	100.0	185	81	13	24	31	334
Switzerland	11.9	1.3	98.7	48	12	2	6	7	75
Italy	15.3	1.1	94.1	1385	268	107	85	372	2217
Malta	100.0	0.0	100.0	22	2	1	1	1	27
Spain	14.5	2.3	97.4	344	107	26	33	62	572
Czech	8.3	0.0	95.5	36	12	1	10	29	88
Estonia	100.0	0.6	99.4	72	40	12	14	37	175
Poland	6.2	2.7	86.8	121	68	19	40	91	339
Slovakia	100.0	4.6	92.4	295	113	23	57	116	604
Slovenia	100.0	0.7	98.6	160	42	13	35	28	278
EUROPE	**24.9**	**1.3**	**92.8**	**6654**	**1862**	**608**	**767**	**3386**	**13277**

a DCO: Death certificate only.

Table 2 – Distribution of cases by histology, sex and age (1990–1994)

Sex		15–44		45–54		55–64		65–74		75–99		TOTAL	
		Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%	Number of cases	%
Men	Papillary	583	68	227	52	209	43	177	34	80	26	1276	49
	Follicular	104	12	76	17	93	19	112	22	51	16	436	17
	Medullary	77	9	52	12	29	6	37	7	16	5	211	8
	Anaplastic	7	1	16	4	48	10	51	10	29	9	151	6
	Other	82	10	69	16	109	22	141	27	135	43	536	21
	All	853	100	440	100	488	100	518	100	311	100	2610	100
Women	Papillary	2109	71	908	66	615	51	452	38	296	23	4380	55
	Follicular	504	17	238	17	250	21	226	19	208	16	1426	18
	Medullary	86	3	62	4	60	5	44	4	39	3	291	4
	Anaplastic	11	0	21	2	74	6	147	12	200	16	453	6
	Other	252	9	157	11	212	18	332	28	518	41	1471	18
	All	2962	100	1386	100	1211	100	1201	100	1261	100	8021	100

3.3. *Relative survival according to histology, age and sex*

We present relative survival data for Europe as a whole (Table 3). Overall, between 1990 and 1994, the age-standardised 5-year relative survival rates were 73% for males and 81% for females. The relative survival rate was always higher among women than among men, whatever the histological group, and the age group, except in the 65–74 age group for the follicular cancers. The relative survival decreased with age, whatever the histological group. The highest discrepancies between age groups were observed in the anaplastic carcinoma. Relative survival was better for papillary cancers and worst for anaplastic cancers. The 5-year relative survival, for papillary cancers, was higher than 90% in women up to the 55–64 age group, and in men up to the 45–54 age group. The relative survival was lower than 30% in men and lower than 40% in women for anaplastic cancers whatever the age group.

3.4. *Relative survival by country and period*

We have reported the age-standardised relative survival rates by period in Figs. 1 and 2. The relative survival rates were always higher in women than in men. The age-standardised relative survival rate was higher than 80% in men only in Denmark over the period 1992–1994. During this same period, the relative survival was higher than 80% for women except in England, Scotland, Estonia, Slovakia and Slovenia. The relative survival had improved during the 12 years covered by the period, with relative survival increasing from 67% to 73% in men, and from 75% to 82% in women, for Europe as a whole (Table 4). It corresponds to relative all-age death rates respectively of 0.73 and 0.74 (Fig. 3) among men and women. The main changes in death rates have occurred between the periods 1986–1988 and 1989–1991 in men and between the periods 1989–1991 and 1992–1994 in women. This difference between men and women is probably amplified by the lower number of cases among men.

There were marked differences in time trends according to sex and country. In men, relative survival remained lower than in Europe as a whole over the period 1983–1994 for England, Scotland, Italy and Slovakia. Relative survival was very low in men in Denmark during the period 1983–1985 but markedly improved to become the highest during the period 1992–1994. Relative survival remained unchanged in Finland, Scotland and Italy. It decreased in Norway, but remains the highest in the whole of Europe, except for the period 1992–1994. It increased in Denmark, Sweden and England where relative survival was lower than in Europe as a whole. Relative survival increased between the period 1989–1991 and 1992–1994 in Slovakia.

In women, relative survival remained lower than in Europe as a whole over the period 1983–1994 in Denmark, UK, Germany and in the three countries of Eastern Europe. Relative survival remained unchanged in Sweden. It increased in Denmark, Finland, Norway, England, Scotland, France, Italy, Slovakia and Slovenia. In Wales and Germany, relative survival decreased between the 1983–1985 and 1989–1991 periods but has increased since the 1989–1991 period. In Estonia, relative survival has increased between the 1983–1985 and 1986–1988 periods and has decreased between the 1986–1988 and 1992–1994 periods.

3.5. *Relative survival by histology, sex and period*

When we consider time trends in relative survival by histological category, relative survival rates remain largely unchanged over the period 1983–1994 (Table 4). There was a sudden change in relative survival between 1989–1991 and 1992–1994 in men with follicular cancers. We must notice that confidence intervals were overlapped between these two periods. We have reported results concerning differentiated carcinoma (papillary and follicular cancers), that present a slight increase in relative survival rates. The relative survival in the category 'other' improved in women over the whole period 1983–1994.

3.6. *Multivariate analysis*

We have performed two multivariate analysis in order to take into account of the fact that well differentiated cancers (papillary and follicular) are frequent and contribute, proportionately, to few deaths and that medullary and anaplastic

Table 3 – Five-years relative survival by histology, sex and age-group (1990–1994)

Sex	Histology	15–44		45–54		55–64		65–74		75–99		TOTAL		ASRS[a]	
		RSR	95% CI	RSR	95% CI	RSR	95% CI	RSR	95% CI	RSR	95% CI	RSR	95% CI	RSR	95% CI
Men	Papillary	0.98	(0.96–1.01)	0.94	(0.87–1.02)	0.79	(0.66–0.94)	0.75	(0.59–0.96)	0.61	(0.32 – 1.14)	0.91	(0.86–0.95)	0.85	(0.79–0.92)
	Follicular	0.96	(0.87–1.05)	0.90	(0.74–1.08)	0.77	(0.59–1.01)	0.76	(0.56–1.03)	0.65	(0.30–1.39)	0.84	(0.75–0.95)	0.84	(0.75–0.94)
	Medullary	0.82	(0.66–1.03)	0.49	(0.28–0.88)	0.56	(0.27–1.17)	0.46	(0.20–1.09)	0.32	(0.03–2.99)	0.62	(0.47–0.77)	0.59	(0.45–0.77)
	Anaplastic	0.29	(0.03–3.20)	0.00	(0.00–0.00)	0.07	(0.01–0.67)	0.00	(0.00–0.00)	0.00	(0.00–0.00)	0.04	(0.01–0.24)	0.11	(0.01–1.09)
	Other	0.85	(0.71–1.03)	0.57	(0.37–0.89)	0.43	(0.26–0.71)	0.29	(0.15–0.56)	0.20	(0.07–0.58)	0.47	(0.37–0.59)	0.55	(0.47–0.65)
	All	0.95	(0.92–0.98)	0.79	(0.71–0.88)	0.63	(0.53 – 0.74)	0.54	(0.44–0.66)	0.40	(0.26–0.63)	0.75	(0.70–0.79)	0.73	(0.69–0.77)
Women	Papillary	1.00	(1.00–1.00)	0.99	(0.97–1.01)	0.96	(0.91–1.00)	0.87	(0.78–0.96)	0.70	(0.54 – 0.90)	0.96	(0.95–0.98)	0.93	(0.90–0.96)
	Follicular	0.99	(0.96–1.01)	0.94	(0.88–1.01)	0.82	(0.71–0.93)	0.73	(0.60–0.89)	0.69	(0.51–0.94)	0.99	(0.83–0.92)	0.87	(0.83–0.92)
	Medullary	0.92	(0.81–1.05)	0.85	(0.68–1.07)	0.77	(0.57–1.05)	0.73	(0.47–1.14)	0.48	(0.18–1.27)	0.81	(0.71–0.93)	0.79	(0.69–0.91)
	Anaplastic	0.36	(0.07–1.81)	0.24	(0.05–1.17)	0.13	(0.04–0.46)	0.05	(0.01–0.24)	0.07	(0.02–0.29)	0.10	(0.05–0.19)	0.21	(0.07–0.61)
	Other	0.98	(0.93–1.02)	0.85	(0.73–0.98)	0.62	(0.49–0.78)	0.41	(0.30–0.56)	0.24	(0.15–0.38)	0.58	(0.51–0.64)	0.70	(0.66–0.74)
	All	0.99	(0.98–1.00)	0.95	(0.92–0.98)	0.81	(0.76 – 0.86)	0.62	(0.55–0.68)	0.43	(0.35–0.52)	0.84	(0.82–0.86)	0.81	(0.79–0.83)

Finland and Sweden have been excluded from the calculation.

a ASRS: age-standardised relative survival using the age distribution of the EUROCARE thyroid data as a reference.

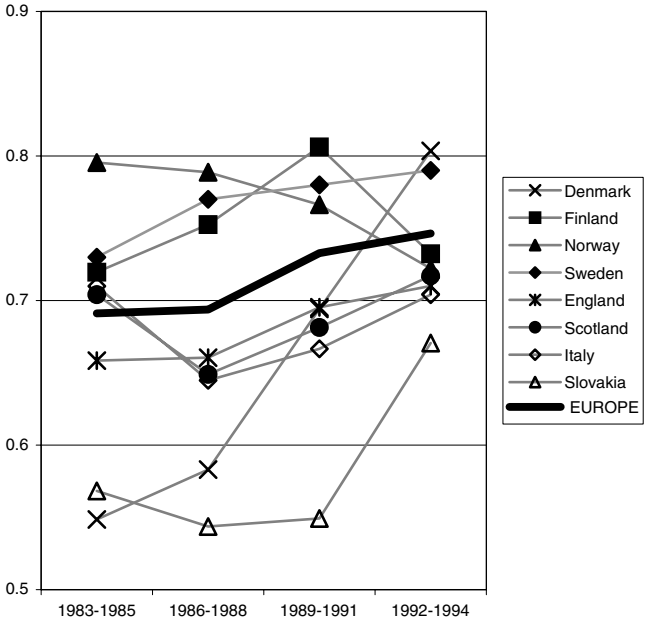

Fig. 1 – Age-standardised relative survival by country and period (all histology, men), using the age distribution of the EUROCARE thyroid data as a reference.

cancers are uncommon but often fatal. The multivariate analysis took account of follow up duration, age, sex, country, period and histology. The corresponding variables have been included in a forward way. Data from Sweden and Finland was not taken into account because of the lack of information about the patients' histological group. The results of the multivariate analysis are reported in Table 5a (well differentiated cancers) and 5b (medullary and anaplastic cancers).

Results concerning well differentiated cancers showed that the effects of sex and age were statistically significant whatever the other variables in the models. Period effect was statistically significant with a higher survival during the last period (1992–1994). The effect of histology was strong and statistically significant when the models were adjusted for the follow up duration, sex, age and period. This result was observed when the country effect was included or not. The country effect, with Denmark as reference, showed the lowest relative survival in Poland and Slovakia and the highest relative survival in Norway and Iceland when histology was included. The country effect was statistically significant. The ranking of countries was quite similar whether histology was included or not.

The results concerning medullary and anaplastic cancers showed that the effects of age were statistically significant whatever the other variables in the models. Sex effect was statistically significant when histology was included in the model. No period effect was demonstrated. The effect of histology was strong and statistically significant when the models were adjusted for the follow up duration, sex, age and period. This result was observed when the country effect was included or not. When histology was not included in the model, the country effects, with Denmark as reference, showed the lowest relative survival in Poland, Slovakia and Slovenia and the highest relative survival in Norway. The

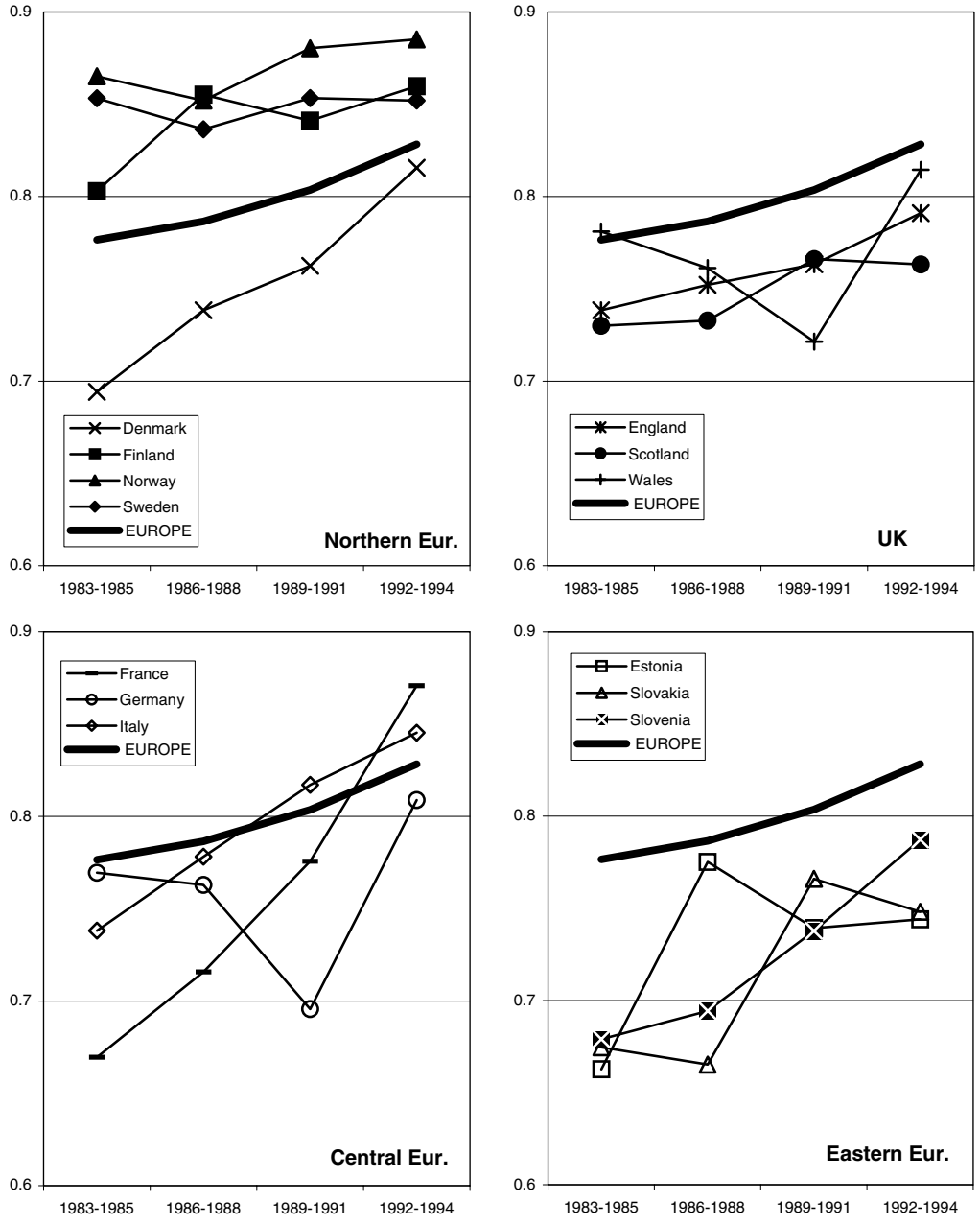

Fig. 2 – Age-standardised relative survival by country and period (all histology, women), using the age distribution of the EUROCARE thyroid data as a reference.

ranking of countries was different when histology was included. In that case, no negative association was observed and a better relative survival was observed for England, Italy, Netherland, Scotland and Spain.

4. Discussion

The analysis of the EUROCARE-3 data has demonstrated that relative survival rates for thyroid cancers are higher than for most other cancer sites. There are differences in relative survival according to age and between countries when considering age-standardised relative survival separately for each sex, whatever the studied period. A higher relative survival rate was observed in Scandinavian countries, and a lower rate in the UK and the countries of Eastern Europe. When considering thyroid cancers as a whole, the relative survival rate has increased slightly over the period 1985–1994, with marked differences between countries. The increase in relative survival rate is predominantly in women. The information provided by the analysis of the relative survival rates in the different histological categories showed the absence of a marked improvement in relative survival over the period 1983–1994. These results were confirmed by the multivariate analysis that only showed an increase in survival for the period 1992–1994 in differentiated cancers.

The influence of sex, age, period and histology on relative survival we have presented in our study is similar to the

Table 4 – Five-years relative survival by histology, sex and period (Sweden and Finland excluded)

Sex	Histology	1983–1985		1986–1988		1989–1991		1992–1994	
		ASRS[a]	95% CI	ASRS	95% CI	ASRS	95% CI	ASRS	95% CI
Men	Papillary	0.83	(0.71–0.98)	0.83	(0.72–0.96)	0.86	(0.76–0.96)	0.85	(0.74–0.96)
	Follicullar	0.78	(0.66–0.93)	0.79	(0.68–0.92)	0.77	(0.64–0.92)	0.86	(0.74–1.01)
	Differentiated carcinoma	0.81	(0.73–0.91)	0.82	(0.74–0.90)	0.83	(0.75–0.91)	0.86	(0.78–0.95)
	Medullary	0.62	(0.41–0.93)	0.51	(0.31–0.81)	0.54	(0.36–0.82)	0.62	(0.43–0.90)
	Anaplastic	0.06	(0.01–0.33)	0.04	(0.01–0.29)	0.18	(0.03–1.14)	0.01	(0.00–0.48)
	Other	0.51	(0.38–0.67)	0.48	(0.36–0.63)	0.57	(0.44–0.73)	0.54	(0.42–0.69)
	All	0.67	(0.61–0.73)	0.67	(0.61–0.73)	0.71	(0.65–0.77)	0.73	(0.67–0.79)
Women	Papillary	0.90	(0.84–0.96)	0.90	(0.85–0.96)	0.92	(0.88–0.97)	0.91	(0.87–0.95)
	Follicullar	0.87	(0.80–0.94)	0.86	(0.80–0.93)	0.84	(0.77–0.91)	0.88	(0.82–0.94)
	Differentiated carcinoma	0.89	(0.84–0.93)	0.89	(0.85–0.93)	0.90	(0.86–0.94)	0.90	(0.87–0.94)
	Medullary	0.72	(0.56–0.92)	0.70	(0.56–0.88)	0.76	(0.61–0.96)	0.81	(0.67–0.96)
	Anaplastic	0.18	(0.03–1.15)	0.26	(0.08–0.85)	0.32	(0.11–0.87)	0.20	(0.04–1.10)
	Other	0.62	(0.55–0.69)	0.64	(0.58–0.70)	0.67	(0.60–0.73)	0.73	(0.67–0.79)
	All	0.75	(0.71–0.77)	0.77	(0.74–0.79)	0.79	(0.76–0.82)	0.82	(0.79–0.84)

a ASRS: age-standardised relative survival using the age distribution of the EUROCARE thyroid data as a reference.

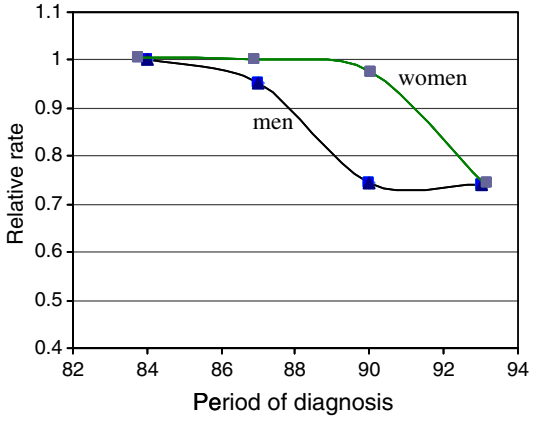

Fig. 3 – Country weighted European mean 5-year relative death rate by sex (all-age).

results concerning data from Southeastern Netherlands over the period 1960–1992.[18] The distribution of relative survival rates according to sex, age and country are similar to those previously published using the EUROCARE-2 study which drew attention to the favourable outcome of thyroid cancers.[19] However, no relative survival results according to histology were reported in that previous study. As noticed by Teppo and colleagues,[19] there are no simple ways to assess the role of the different causes of variations on relative survival. However, the effect of age on relative survival has been corrected for when comparing inter-country age-standardised relative survival.

The estimations of relative survival of thyroid cancers classified as 'other' have to be considered with caution. More than half of the cancers included in this category belong to the categories uncertain or unspecified carcinoma. The proportion of 'other' among thyroid cancers is different according to countries with a highest proportion of other carcinomas in Sweden (80%) and a lowest proportion in Iceland (2%). It is not astonishing that the highest relative survival rates were observed in Sweden for this category because it has corresponded to mis-classified cases.

Differences in relative survival by age and by country could be attributable to the distribution of histological type within these factors. The distribution of cases according to histology is very dependant on age group. Concerning the country factor, we notice that the proportion of papillary cancers in men is high in Norway (high relative survival) and low in England and Scotland (low relative survival). This proportion, for women, is high in Norway (high relative survival) and low in Poland (low relative survival). This correlation between relative survival rate and the proportion of papillary cancers seems to be, *a priori*, a satisfactory argument to explain, at least partly, the discrepancies in relative survival between countries. However, we have to take into account the differences in classification practices that may exist between cancer registries, and, consequently, between countries. Practices may differ due to changes that occurred in the World Health Organization (WHO) histological classification[20] of thyroid tumours in 1974 and in 1988. With this last change, diagnosis of the papillary sub-types has been favoured to the detriment of the follicular one. According to this new classification, a recent study conducted by the Geneva Cancer Registry has shown that 25% of the cases diagnosed as follicular cancers during the period 1990–1998 should be reclassified as papillary cancer.[20] This is, perhaps, the reason why we observed only a slight difference in relative survival between papillary and follicular cancers. The correlation between the proportion of papillary cancers and relative survival rates could be checked using the ratio papillary/follicular cancers. This ratio for men is high in Norway (10.0), low in Scotland (2.0) and England (2.2) and for women, high in Norway (4.5) and low in Poland (1.9). However, we observed a low ratio in Austria (2.1) where the relative survival is high (86%) in women, and a fairly high ratio (3.8) in Slovenia where the relative survival rate (76%) is low in women. The proportion of papillary cancers in Austria and Slovenia was similar (about 57% of the cases). The proportion of papillary cancers and the ratio papillary/follicular cancers appear to be complementary and

Table 5a – Regression analysis on differentiated thyroid cancer survival: results (exponential form)

Variables	Parameters	MODELS											
		FU, SEX, AGE			FU, SEX, AGE, PERIOD			FU, SEX, AGE, PERIOD, COUNTRY			FU, SEX, AGE, PERIOD, COUNTRY, HISTOLOGY			FU, SEX, AGE, PERIOD, HISTOLOGY		
		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
FU[a]	1 year	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	2 year	0.28	0.23	0.35	0.28	0.23	0.35	0.28	0.23	0.35	0.28	0.23	0.35	0.28	0.22	0.34
	3 year	0.18	0.14	0.25	0.18	0.14	0.25	0.20	0.15	0.26	0.20	0.15	0.26	0.19	0.14	0.25
	4 year	0.17	0.12	0.23	0.17	0.12	0.23	0.16	0.11	0.23	0.16	0.12	0.23	0.17	0.12	0.23
	5 year	0.21	0.16	0.29	0.21	0.16	0.29	0.22	0.17	0.30	0.23	0.17	0.30	0.22	0.17	0.29
SEX	Female	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	Male	1.83	1.58	2.11	1.82	1.58	2.10	1.89	1.63	2.18	1.87	1.62	2.16	1.79	1.55	2.07
AGE	15–44	0.07	0.05	0.10	0.07	0.05	0.10	0.07	0.05	0.10	0.08	0.05	0.11	0.08	0.05	0.11
	45–54	0.36	0.27	0.48	0.37	0.28	0.49	0.36	0.27	0.48	0.37	0.28	0.49	0.38	0.29	0.50
	55–64	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	65–74	1.98	1.63	2.40	2.00	1.64	2.42	2.03	1.68	2.47	1.98	1.63	2.40	1.92	1.58	2.33
	75–99	4.07	3.35	4.94	4.09	3.37	4.97	4.28	3.52	5.20	4.12	3.38	5.00	3.86	3.17	4.69
PERIOD	1983–85				1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	1986–88				0.99	0.81	1.20	1.01	0.83	1.23	1.01	0.83	1.23	0.99	0.81	1.20
	1989–91				0.89	0.73	1.09	0.90	0.74	1.10	0.93	0.76	1.13	0.93	0.76	1.13
	1992–94				0.78	0.64	0.96	0.75	0.61	0.92	0.77	0.63	0.94	0.80	0.65	0.98
COUNTRY	Denmark							1.00	(reference)		1.00	(reference)				
	England							0.84	0.64	1.09	0.82	0.63	1.06			
	Estonia							0.91	0.54	1.52	0.94	0.56	1.57			
	France							1.10	0.72	1.67	1.11	0.73	1.69			
	Germany							1.23	0.78	1.94	1.19	0.75	1.88			
	Iceland							0.30	0.11	0.83	0.29	0.10	0.85			
	Italy							0.68	0.48	0.96	0.73	0.51	1.03			
	Netherland							0.63	0.28	1.43	0.64	0.29	1.42			
	Norway							0.51	0.37	0.71	0.55	0.39	0.76			
	Poland							1.77	1.00	3.14	1.73	0.98	3.07			
	Scotland							1.08	0.77	1.50	1.05	0.75	1.46			
	Slovakia							1.77	1.29	2.41	1.74	1.28	2.38			
	Slovenia							0.99	0.62	1.57	1.02	0.65	1.62			
	Spain							0.83	0.51	1.35	0.82	0.50	1.33			
	Switzerland							0.65	0.27	1.56	0.70	0.30	1.65			
	Wales							0.61	0.36	1.04	0.57	0.33	0.99			
HISTOLOGY	Papillary										1.00	(reference)		1.00	(reference)	
	follicular										1.41	1.22	1.63	1.51	1.31	1.74
	Deviance/df	1.82			1.82			1.80			1.80			1.81		
	df	4993			4990			4975			4974			4989		
	Log-likelihood	−5758.90			−5755.10			−5709.80			−5699.10			−5739.40		

a FU: follow up duration.

Table 5b – Regression analysis on medullary and anaplastic thyroid cancer survival: results (exponential form)

Variables	Parameters	MODELS															
		FU, SEX, AGE			FU, SEX, AGE, PERIOD			FU, SEX, AGE, PERIOD, COUNTRY			FU, SEX, AGE, PERIOD, COUNTRY, HISTOLOGY			FU, SEX, AGE, PERIOD, HISTOLOGY		
		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
FU[a]	1 year	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	2 year	0.19	0.16	0.23	0.19	0.16	0.23	0.19	0.16	0.24	0.26	0.21	0.31	0.25	0.21	0.31
	3 year	0.10	0.07	0.13	0.10	0.07	0.13	0.10	0.07	0.13	0.13	0.09	0.18	0.13	0.09	0.18
	4 year	0.07	0.05	0.11	0.07	0.05	0.11	0.08	0.05	0.11	0.10	0.07	0.15	0.10	0.07	0.15
	5 year	0.06	0.04	0.10	0.06	0.04	0.10	0.06	0.04	0.10	0.08	0.05	0.13	0.08	0.05	0.13
SEX	Female	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	Male	1.06	0.95	1.20	1.06	0.94	1.19	1.06	0.94	1.19	1.33	1.18	1.51	1.32	1.17	1.49
AGE	15–44	0.16	0.12	0.21	0.16	0.12	0.21	0.17	0.12	0.22	0.38	0.28	0.51	0.37	0.28	0.50
	45–54	0.50	0.41	0.63	0.51	0.41	0.63	0.51	0.41	0.64	0.77	0.62	0.96	0.75	0.61	0.94
	55–64	1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	65–74	1.59	1.36	1.85	1.59	1.36	1.85	1.65	1.42	1.93	1.50	1.28	1.75	1.49	1.28	1.74
	75–99	2.34	2.01	2.72	2.33	2.00	2.71	2.37	2.03	2.77	1.76	1.50	2.06	1.73	1.48	2.02
PERIOD	1983–85				1.00	(reference)		1.00	(reference)		1.00	(reference)		1.00	(reference)	
	1986–88				1.05	0.91	1.22	1.03	0.89	1.20	1.15	0.99	1.34	1.16	1.00	1.34
	1989–91				0.95	0.82	1.11	0.95	0.81	1.11	1.11	0.95	1.30	1.10	0.94	1.28
	1992–94				0.88	0.75	1.02	0.87	0.74	1.01	1.02	0.87	1.20	1.02	0.87	1.19
COUNTRY	Denmark							1.00	(reference)		1.00	(reference)				
	England							0.99	0.81	1.20	0.80	0.66	0.97			
	Estonia							0.93	0.65	1.34	0.94	0.65	1.35			
	France							0.92	0.64	1.33	0.95	0.66	1.37			
	Germany							1.00	0.66	1.52	0.78	0.51	1.19			
	Iceland							0.91	0.46	1.79	0.68	0.35	1.34			
	Italy							0.86	0.67	1.12	0.69	0.53	0.90			
	Netherland							0.68	0.35	1.32	0.41	0.21	0.80			
	Norway							0.45	0.30	0.68	0.98	0.65	1.49			
	Poland							1.87	1.20	2.93	1.00	0.64	1.57			
	Scotland							0.90	0.69	1.18	0.70	0.54	0.92			
	Slovakia							1.36	1.05	1.75	0.93	0.72	1.20			
	Slovenia							1.34	1.03	1.76	0.89	0.68	1.17			
	Spain							0.66	0.43	1.01	0.55	0.36	0.85			
	Switzerland							1.24	0.75	2.06	0.89	0.53	1.48			
	Wales							0.92	0.67	1.25	0.76	0.55	1.03			
HISTOLOGY	Medullary										1.00	(reference)		1.00	(reference)	
	anaplastic										6.54	5.54	7.74	6.37	5.42	7.48
	Deviance/df	1.42			1.42			1.40			1.09				1.10	
	df	2178			2175			2160			2159				2174	
	Log-likelihood	−2316.60			−2313.70			−2283.40			−1945.50				−1958.90	

a FU: follow up duration.

could explain the differences in relative survival between countries.

It may be noticed that the age-standardised relative survival rates are unusually high for anaplastic cancers, particularly among women. This result is related to the method of standardisation which is based on an estimation of relative survival starting from a very low number of cases diagnosed for the younger age groups. The relative survival of patients over 55 is, as must be expected, particularly low. Thus the size of the confidence intervals for relative survival estimated per period reveals the instability of the anaplastic cancer relative survival rates.

Another explanation of the differences in relative survival between countries may be the spread of new and more sophisticated diagnostic techniques such as ultrasonography and fine needle aspiration biopsy, which have altered the management of thyroid diseases.[13] A recent study in Marne-Ardennes Cancer Registry (France) demonstrated that the cancer stages changed over time with a dramatic increase of the proportion of microcarcinomas ($\leqslant$1 cm) between the period 1983 to 1987 and 1998 to 2001.[12] A same hypothesis about the role of the improvement in diagnosis method has been reported in a Swedish cohort study of differentiated thyroid cancer.[10] Stage at diagnosis is considered as an important prognostic factor in thyroid cancers.[20] The effect of tumour size has been recently studied in a cohort of 86 follicular cancers that confirms the importance of this information as prognostic factor.[21] There is no reason to think that the new management of thyroid cancers is spatially uniform in Europe. For instance, a recent study showed that diagnostic practice is certainly not uniform even within France.[6]

The higher relative survival rate observed in women may be explained by the greater proportion of papillary cancers. It may also be attributable to the effect of new diagnostic practice since women are the major consumers of health-care and because the prevalence of benign thyroid conditions is greater in women.[6]

The decrease in relative survival rates with age is partially due to the decrease in the proportion of good prognosis thyroid cancers (papillary cancers) with age. A strong age effect remains in both multivariate analyses, and is not substantially affected by inclusion of morphological type. The decrease in relative survival with age is possibly the consequence of the management of thyroid disease that may differ according to age that is a prognostic factor in thyroid cancer.[22]

The multivariate analysis confirms the detailed results. Even if the adjustment for histology produces interesting results, we must remember that the use of histology over the period 1983–1994 probably introduces errors as mentioned by Teppo and colleagues.[19] When we have considered differentiated cancers, the results show clearly that the differences in relative survival that we observed within Europe can only partly be explained by the factors considered. Consequently the explanations we gave above are certainly incomplete. This is confirmed by the fact that differences in relative survival rates for thyroid cancers are similar to those found for many other cancers. In the EUROCARE-2 study,[15] the relative survival estimated for 45 cancer sites is, most of the time, worst in the countries of Eastern Europe, and better in the occidental part of Europe. The analysis of more fatal thyroid cancers (medullary and anaplastic cancers) leads to weaker differences in relative survival between countries. The reason is probably that these cancers are less concerned by the improvement in diagnosis methods.

We found relatively little change in survival over time, but we observed differences in survival by histology, age, sex and country in the analysis of relative survival of thyroid cancers. The country effect on relative survival concerns essentially the differentiated cancer. This effect was not totally explained by the available covariates. This could probably be explained by stage at time of diagnosis but this information was not available. The only way to understand these differences, especially in differentiated cancers, is to conduct specific studies (high resolutions studies) including a description of stage at diagnosis, diagnosis procedures used for staging and details of treatment.[23–25]

Conflict of interest statement

None declared.

REFERENCES

1. Parkin DM, Whelan S, Ferlay J, et al. *Cancer Incidence in Five Continents, Vol VIII*. International Agency for Research on Cancer, IARC Scientific Publications n° 155, Lyon 2003.
2. Pettersson B, Adami H, Wilander E, Coleman M. Trends in thyroid cancer incidence in Sweden, 1958-1981, by histopathologic type. *Int J Cancer* 1991;**48**:28–33.
3. Akslen L, Haldorsen T, Thorensen S, Glattre E. Incidence pattern of thyroid cancer in Norway: influence of birth cohort and time period. *Int J Cancer* 1993;**53**:183–7.
4. Dos Santos I, Swerdlow A. Thyroid cancer epidemiology in England and Wales: time trends and geographical distribution. *Br J Cancer* 1993;**67**:330–40.
5. Zheng T, Holford T, Chen Y, et al. Time trend and age-period-cohort effect on incidence of thyroid cancer in Connecticut, 1935–1992. *Int J Cancer* 1996;**67**:504–9.
6. Colonna M, Grosclaude P, Remontet L, et al. Incidence of thyroid cancer in adult recorded by French cancer registries (1978–1997). *Eur J Cancer* 2002;**38**:1762–8.
7. Hodgson N, Button J, Solorzano C. Thyroid cancer: Is the incidence still increasing? *Ann Surg Oncol* 2004;**11**:1093–7.
8. Cancer Statistics Review 1975–2002. Available at http://seer.cancer.gov/csr/1975_2002/results_merged/sect_26_thyroid.pdf.
9. Burgess JR. Temporal trends for thyroid carcinoma in Australia: An increasing incidence of papillary thyroid carcinoma (1982–1997). *Thyroid* 2004;**12**:141–9.
10. Lundgren CI, Hall P, Ekbom A, Frisell J, Zedenius J, Dickman PW. Incidence and survival of Swedish patients with differentiated thyroid cancer. *Int J Cancer* 2003;**106**:569–73.
11. Plesko I, Macfarlane G, Obsitnikova A, et al. Thyroid cancer in Slovakia, 1968–1990 : incidence, mortality and histological types. *European Journal of Cancer Prevention* 1994;**3**:345–9.
12. Leenhardt L, Grosclaude P, Chérié-Challine L. Increased incidence of thyroid carcinoma in France: a true epidemic of thyroid nodule management effects? Report from the French thyroid cancer committee. *Thyroid* 2004;**14**:1056–60.

13. Leenhardt L, Bernier MO, Boin-Pineau MH, et al. Advances in diagnosis practices affect thyroid cancer incidence in France. *Eur J Endocrinol* 2004;**150**:133–9.
14. Levi F, Randimbison L, Te VC, La Vecchia C. Thyroid cancer in Vaud, Switzerland: An update. *Thyroid* 2002;**12**:163–8.
15. Berrino F, Capocaccia R, Estève J, et al. (eds.) : Survival of cancer patients in Europe : the EUROCARE 2 study. IARC Scientific Publications No. 151. Lyon, France: International Agnecy for Research on Cancer 1999.
16. Capocaccia R, Gatta G, Roazzi P, et al. The Eurocare 3 database: methodology of data collection, standardisation, quality control and statistical analysis. *Ann Oncol* 2005;**14**:v14–27.
17. Dickman P, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004;**23**:41–64.
18. Kuijpens JL, Hansen B, Hamming JF, et al. Trends in treatment and long-term survival of thyroid cancer in Southeastern Netherlands, 1960–1992. *Eur J Cancer* 1998;**34**:1235–41.
19. Teppo L, Hakulinen Tthe Eurocare Working Group. Variation in survival of adult patients with thyroid cancer in Europe. *Eur J Cancer* 1998;**34**:2248–52.
20. Verkooijen H, Fioretta G, Pache JC, et al. Diagnosis changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. *Cancer Causes Control* 2003;**14**:13–7.
21. Guilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma. *Cancer* 1997;**19**:564–73.
22. D'Avenzo A, Ituarte P, Treseler P, et al. Prognostic scoring systems in patients with follicular thyroid cancer: a comparison of different staging systems in predicting the patient outcome. *Thyroid* 2004;**14**:453–8.
23. Berrino F. The Eurocare 3 study : strengths, limitations and perspectives of population-based, comparative survival studies. *Ann Oncol* 2005;**14**:v9–v13.
24. Lundgren CI, Hall P, Dickman, Zedenius J. Clinically significant prognostic factors for differentiated thyroid carcinoma: A population-based, nested case-control study. *Cancer* 2006;**106**:524–31.
25. Kuijpens JL et al. Comorbidity in newly daignosid thyroid cancer patients : a population-based study on prevalence and the impact on treatment and survival. *Clin Endocrinol* 2006;**64**:450–5.