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Invasive extramammary Paget's disease and the risk for secondary tumours in Europe

J.M. van der Zwan [a,*], S. Siesling [a,b], W.A.M. Blokx [c], J.P.E.N. Pierie [d], R. Capocaccia [e,f]

[a] Comprehensive Cancer Centre The Netherlands, Department of Research and Registration, Utrecht, The Netherlands
[b] Health Technology and Services Research, University of Twente, Enschede, The Netherlands
[c] Department of Pathology, University Medical Centre Nijmegen, Nijmegen, The Netherlands
[d] Department of Gastrointestinal & Minimally Invasive Surgery, Medical Centre Leeuwarden, Leeuwarden, The Netherlands
[e] National Cancer Centre for Epidemiology, Health Surveillance and Promotion, Istituto Superiore di Sanita, Rome, Italy

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Abstract

The aim of this study was to determine the incidence and survival of Extramammary Paget's disease (EMPD) and to describe the possible increased risk of tumours after EMPD.

All invasive cases diagnosed between 1990 and 2002 were selected from the RARECARE database. Incidence was expressed in European standardized rates. Relative survival was calculated for the period 1995–1999, with a follow-up until 31st December 2003. Standardized incidence ratios of second primary tumours were calculated to reveal possible increased risk after EMPD.

European age standardized Incidence of EMPD within Europe is 0.6 per 1000,000 person years. Five-year relative survival for invasive EMPD was 91.2% (95%CI; 83.5–95.4), 8.6 percent of the EMPD patients developed other malignancies. The highest increased risk of developing a second primary tumour was found in the first year of follow-up (SIR:2.0 95%CI; 1.3–2.9), living in the South European region (SIR:2.3 95%CI; 1.5–3.5) or being female (SIR:1.5 95%CI; 1.1–1.9). Female genital organs displayed greatest increased risk of developing a second primary tumour after EMPD (SIR:15,1 95%CI; 0.38–84.23).

Due to the increased risk of a second primary tumour after EMPD a thorough search for other tumours during their follow-up is recommended.

Keywords: Epidemiology; Extramammary Paget's; Second cancer risk; Rare tumours; Europe

Introduction

Extramammary Paget's Disease (EMPD) is a rare tumour whose precise incidence is not clear[1] because of the non specific clinical findings of EMPD, which easily lead to wrong diagnoses.[2] EMPD mostly affects individuals between the ages 50 and 80 years and is more frequently diagnosed in women than men.[2]

In 1874, James Paget described Mammary Paget's Disease (MPD) as a chronic disease of the skin of the nipple and areola only.[3] In 1888, during a meeting of the Pathological Society of London, Crocker presented a special case of MPD, which was located on the scrotum and penis in a goldsmith, aged sixty years old.[4] In 1889, Crocker officially described EMPD as a special form of ductal carcinoma involving other parts of the body than the breast, as first described by James Paget.[3] The clinical symptoms, eczema-like lesions, had clinical and histological features similar to those of MPD.[4] Histological EMPD is described as a cutaneous adenocarcinoma with typical Paget cells,[5–7] i.e. large cells with large nuclei and abundant cytoplasm which usually stain pale. It occurs with preference in skin zones rich of apocrine glands, but can occur anywhere on

* Corresponding author. Comprehensive Cancer Centre The Netherlands, Department of Research and Registration Utrecht, PO Box 19079, 3501DB Utrecht, The Netherlands. Tel.: +31 30 233 80 60; fax: +31 30 233 80 79.
E-mail address: j.vanderzwan@iknl.nl (J.M. van der Zwan).
[f] On behalf of the RARECARE Working Group (Members of the RARECARE working group can be seen in Appendix).

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the skin or mucosa. Its most common visible symptom of EMPD is signs of pruritus,[6] and it occurs mainly among the elderly, with a higher risk seen in Caucasian women in their 60s and 70s.[8]

Since a possible association with other malignancies, before or after diagnosis of EMPD, has been described,[7,9] a thorough physical examination with a 5-year follow-up after diagnosis has been recommended for patients being diagnosed with EMPD, to discover other regional rectal, urothelial or vulvar malignancies at time of diagnoses or during follow-up.[7,10] The location of the underlying internal malignancy is often linked to the location of the EMPD: a perianal location may signify a malignancy of the gastrointestinal tract and a penile, scrotal or groin location may be associated with an adenocarcinoma of the genitourinary tract.[5]

As it is a rare cancer, no clear guidelines have been established for diagnosis, treatment and follow-up of patients, presenting a challenge for clinical practice, and research is often confined to case reports or small retrospective studies.

The RARECARE database, a European database that contains data from a large group of European cancer registries (CRs), has been developed to describe the burden of rare cancers and allows comparison of different European regions. Furthermore, it allows comparison between countries with different Gross Domestic Products (GDP) and Total National Expenditure on Health (TNEH), which could influence the survival.

The aim of this population-based study was to describe the incidence, survival and risk of developing other malignancies in patients with EMPD within Europe based on the RARECARE database.

Patients and methods

Patients

Data on patients diagnosed with invasive EMPD were provided by European population-based CRs which participated in the RARECARE project. Only registries with detailed data on morphology available were included, resulting in 63 population-based CRs from 16 different European countries. Period coverage of the different registries participating in the RARECARE project is described in Table 1. These were divided into four regions following the EUROCARE project[11]; Northern Europe (Sweden, Norway and Iceland), UK and Ireland (United Kingdom, Ireland), Central Europe (Austria, Belgium, France, Germany, the Netherlands, Switzerland) and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain). For this study, Eastern Europe was not considered as a separate region because only three registries with a few cases could be included, even though these registries are included in the EU overall region.

Data on the macro indicators Gross Domestic Product (GDP) and Total National Expenditure on Health (TNEH) per country was provided by the Organisation for Economic Co-operation and Development (OECD).[12] The GDP and TNEH were categorised in three different levels following the RARECARE project.[13]

Between the 1st of January 1990 and the 31st of December 2002 all participating registries had good equal coverage of data for all participating registries and all cases of invasive EMPD diagnosed in this period were included.

EMPD cases were defined by morphological code 8542 in the third edition of the International Classification of Diseases for Oncology (ICD-O-3),[14] consistent in all the 3 revisions. All cases were histologically confirmed, and excluded if registered based on death certificate only. In total 871 patients with invasive EMPD were diagnosed and included in the period 1990–2002 as a primary malignancy.

For the 5-year cohort survival analyses we used the coverage period 1995–1999, conform the RARECARE project, representing the latest data available included in the RARECARE database. Follow-up was complete until 31 December 2003, resulting in a minimum follow-up time of 4 years.

For the patients included in this study we also analysed all subsequent cancers. Malignant tumours simultaneously diagnosed with the EMPD were counted as a second primary tumour with a follow-up time of zero.

Statistical analyses

Crude incidence rates, age standardized incidence rates and relative survival analyses were calculated by using SEER*stat.[15] The European standardized incidence rate was calculated by age standardisation according to the European Standard Population, STATA version 9.[16]

Relative survival for EMPD was estimated according to the Hakulinen method.[17] The effects of age and gender were determined.

The standardized incidence ratio (SIR) was used to assess the possible increased occurrence of cancer in patients with EMPD. This expresses the occurrence of cancer in this patient group relative to what would have been expected in the general population, based on the EU regions according to the participating registries (Table 1), matched by age class and sex. The SIR was calculated for specific cancer sites according to the ICD-O-3[14] to evaluate possible tumour site- specific elevated risks, we did not differentiate for histology. All SIR analyses were conducted using STATA version 9.[16]

Results

Incidence

In the 13-year period, 871 cases of EMPD were registered as primary malignancy (male to female ratio 1:2.8; Table 2). The median age at diagnosis for EMPD for

Table 1
Included participating registries per region, years of data coverage and *N* per region and registry during the period 1990–2002.

Country	Registry	Part period	*N*	Country	Registry	Part period	*N*	Country	Registry	Part period	*N*	Country	Registry	Part period	*N*
Northern EU *N* = 174572328				France	Bas Rhin	1990–1997	7854673	Italy	Alto Adige	1995–2002	3678239		Varese	1990–2002	8850925
Iceland	Iceland	1990–2002	3504591		Doubs	1990–1997	3933278		Biella	1995–2002	1514102		Veneto	1990–2002	23867456
Norway	Norway	1990–2002	56906123		Haut Rhin	1990–1997	5487824		Ferrara	1991–2002	4240039	Malta	Malta	1993–2002	3768270
Sweden	Sweden	1990–2002	114161614		Herault	1995–1997	2583988		Firenze	1990–2002	15070157	Portugal	South Portugal	1998–1999	8803804
UK and Ireland *N* = 467814624					Isere	1990–1997	8375975		Friuli V.G.	1995–2002	9507797	Slovenia	Slovenia	1990–2002	25877585
Ireland	Ireland	1994–2002	33392186		Manche	1994–1997	1921214		Genova	1990–2000	9416933	Spain	Basque Country	1991–1999	18864835
UK England	UK_East Anglia	1990–2002	31447351		Somme	1990–1997	4404764		Macerata	1991–1999	2632596		Girona	1994–2002	4804389
	Yorkshire	1990–2002	62128982		Tarn	1990–1997	2738395		Modena	1990–2002	8031077		Murcia	1995–1998	4374754
	UK_Oxford	1990–2002	34418304	Germany	Saarland	1990–2002	13994615		Napoli	1996–2000	2700828		Navarra	1990–1999	5255593
	UK_South Western	1990–1999	64946933	Netherlands	Amsterdam	1990–2002	35773250		Parma	1990–2002	5137440		Tarragona	1990–1999	5661233
	UK_Trent	1990–2000	52449975		Eindhoven	1990–2001	11425011		Ragusa	1990–2002	3807761	Other registries			
	UK_West Midlands	1990–2002	68557863		North Netherlands	1995–2001	11501474		Reggio Emilia	1996–2002	3153367	Poland	Cracow	1990–2002	9624286
UK N-Ireland	UK_Northern Ireland	1993–2002	16687081	Switzerland	Basel	1990–2001	5209369		Romagna	1990–2002	11762482		Kielce	1995–2002	9890783
UK Scotland	UK_Scotland	1990–2002	66055070		Geneva	1990–2002	5189759		Salerno	1996–2001	6525709		Warsaw	1990–2002	21221388
UK Wales	UK_Wales	1990–2002	37730879		St. Gallen	1990–2002	6602319		Sassari	1992–2002	5160911				
Central EU *N* = 268438850					Ticino	1996–2002	2159114		Torino	1990–2001	11179984				
Austria	Austria	1990–2002	103279823		Valais	1990–1999	2657940		Trento	1995–2000	2761003				
Belgium	Flanders	1997–2001	29667826	Southern EU *N* = 220209762					Umbria	1994–2002	7478732				

Table 2
Invasive EMPD overall primary tumours.

		Male	Female
Age (yrs)	Range	16–95	36–96
	Median	74	74
Age group	0–64	43	166
	65+	188	474
Localisation	Rectum	0	1
	Anus and Anal Canal	19	21
	Extragenital skin	108	70
	Eyelid	0	1
	Other unspec part of face	0	4
	Skin of trunk	84	55
	Skin of upper limp and shoulder	3	2
	Skin of lower limp and hip	8	3
	Overlapping lesion of skin	3	1
	Skin not otherwise specified	10	4
	Breast	0	8
	Penis	27	0
	Vulva	0	533
	Vagina	0	0
	Female gen tract[a]	0	3
	Other ill defined sites[b]	0	3
	Male genitals (no penis)[c]	72	0
	Pelvis	3	0
	Unknown	2	1

[a] Cases counted in: Female genital tract NOS {857}.
[b] Cases counted in: Thorax, Pelvis {857}.
[c] Cases counted in: Scrotum, Other specified parts of male genital organs, Male genital organs NOS {857}.

females ($n = 640$) was 74 years (range 36–96 years) which is similar to the median age for males ($n = 231$) (range 16–95 years).

The most frequent parts of the body in which EMPD occurred were the anus and anal canal ($n = 40$), extragenital skin ($n = 178$), vulva($n = 533$) and other and unspecified male genital organs ($n = 72$) (Table 2) For females, invasive EMPD 15% of the primary tumours is not located on a gender related site while this is 55% in males.

The mean RARECARE population consisted of 90,163,609 people over the 13 years selected (male to female ratio 1:1).[13] This yields, for the overall EU region, a crude incidence rate of 0.7 per 1000,000 person years and a ESR of 0.6 per 1000,000 person years (Table 3). In females, the EMPD in the Overall EU region have a crude incidence rate of 0.7 per 1000,000 person years. For males there is a large difference in European Standardized Rate (ESR) between Northern EU (0.7 per 1000,000 person years) and other regions. A less obvious but somewhat higher ESR was seen in the UK and Ireland region (0.9 per 1000.000 person years) in females. For the female ESR in EMPD as well in both sexes combined, the relatively low rate in the Central EU is worthy of note.

Survival

Five-year relative survival for patients with EMPD diagnosed in 1995–1999 was higher in females than males (Table 4), and was almost similar for patients aged older than 65 years (91.9%; 95%CI 80.5–96.8) and for those between 25 and 64 years of age (89.5%; 95%CI 80.1–94.6). There is a slight difference between the different EU regions, with the UK and Northern Ireland having the highest 5-year survival for EMPD.

Although patients included in the high GDP and high TNEH both have a markedly lower 5-year relative survival rate than the patients included in the middle and low groups of GDP and TNEH, none of these differences were statistically significant.

Table 3
Count and rate per 1000,000 person years for EMPD per EU region for the period 1990–2002.

Region 1990–2002	Male	Female	Male and female
	(*n*/ESR)	(*n*/ESR)	Crude/ESR
Northern EU	79/0.73	103/0.68	1.04/0.70
UK and Ireland	77/0.30	293/0.86	0.79/0.60
Central EU	35/0.26	109/0.57	0.54/0.43
Southern EU	38/0.28	130/0.78	0.76/0.55
Overall EU	231/0.35	640/0.73	0.74/0.56

Northern EU: Sweden, Norway and Iceland ($N = 174572328$*).
UK and Ireland: United Kingdom, Ireland ($N = 467814624$*).
Central EU: Austria, Belgium, France, Germany, Netherlands, Switzerland ($N = 268438850$*).
Southern EU: Italy, Malta, Portugal, Slovenia, Spain ($N = 220209762$*).
Overall EU: Northern EU, UK and Ireland, Central EU, Southern EU, Poland ($N = 1171772021$*).
*The sum of the populations for all years included in the calculation of the associated rate.

Risk for a second primary tumour

Table 5 shows that, after EMPD, 75 cases of new primary tumours were observed (male to female ratio 1:2.3).

Table 4
5 yr relative cohort survival for invasive EMPD (1995–1999) with different indicators calculated using Hakulinen method.[17]

	N	Relative	95%CI
Overall	439	91.2%	83.5–95.4
Male	115	85.6%	66.4–94.3
Female	324	92.9%	83.6–97.0
Agecat 25–64	105	89.5%	80.1–94.6
Agecat 65+	334	91.9%	80.5–96.8
Northern Europe	102	84.0%	65.0–93.2
Central Europe	70	93.1%	54.9–99.2
Southern Europe	94	91.1%	73.4–97.2
UK and Northern Ireland	170	95.0%	72.2–99.2
EU Overall	439	91.2%	83.5–95.4
Low GDP 0–20,000	32	95.5%	16.6–99.9
Middle GDP 20,000–25,000	321	92.4%	82.7–96.8
High GDP > 25,000	85	83.6%	61.9–93.5
TNEH low 0–1500	32	95.5%	16.6–99.9
TNEH middle > 1501–2250	330	91.2%	81.8–95.9
TNEH high > 2250	76	88.4%	63.8–96.7

Table 5
Standardized incidence ratio (SIR) per indicator on developing a second primary cancer after EMPD.

All tumours		Cases observed	Cases expected	SIR	95%CI
Overall		75	53	1.39[a]	1.11–1.73
Age cat	0–60	9	5	1.82	0.83–3.45
	61–79	51	34	1.54[a]	1.14–2.02
	80–84	12	8	1.42	0.73–2.48
	85+	3	7	0.41	0.09–1.21
Sex	Male	23	18	1.24	0.79–1.87
	Female	52	35	1.47[a]	1.10–1.93
Years of follow up	0–1 yr	25	13	1.99[a]	1.29–2.94
	1–5 yr	37	31	1.17	0.93–1.63
	5–10 yr	12	9	1.33	0.66–2.23
	10–15 yr	1	1	1.81	0.05–10.11
EU region	Northern EU	13	12	1.11	0.66–1.77
	UK and Ireland	29	24	1.21	0.81–1.74
	Central EU	10	9	1.1	0.60–2.16
	Southern EU	23	10	2.31[a]	1.46–3.46
Topography	Colon	4	5	0.82	0.82–2.10
	Rectum	3	2	1.69	0.46–4.32
	Lung	3	5	0.61	0.13–1.77
	Connective tissue	1	8	0.13[a]	0.00–0.73
	Breast	13	7	1.87	0.99–3.20
	Female genital/other[b]	1	0	15.12	0.38–84.23
	Vulva	1	0	3.38	0.09–18.81
	Bladder	6	2	2.4	0.88–5.22

[a] Significant.
[b] Female only.

For females who had a second primary tumour after being diagnosed with EMPD ($n = 52$), it took an average of 37 months (range 0–129 months) before a second primary tumour was diagnosed. For males who had a second primary tumour after being diagnosed with EMPD ($n = 23$), this took an average of 26 months (range 0–64 months). Four women and two men were diagnosed with EMPD at same time as for the second primary tumour and therefore counted as 0 months between EMPD and their second primary tumour. The most frequent topographies, following the ICD-O-3, in which the second primary tumours occurred after being diagnosed with EMPD were the extragenital skin ($n = 21$), the breast ($n = 13$) and bladder ($n = 6$). The 21 cases of extragenital skin can be divided into several topographies; 6 cases on the skin of trunk, 4 cases on the skin of other and unspecified parts of the face, 3 cases on the skin of the lower limb and hip, 2 cases the eyelid and on the skin of scalp and the upper limb and shoulder. The other single cases represented a case on the external ear and on the overlapping lesion of skin.

Compared to the standard population all EMPD patients had an increased risk of developing a second primary tumour (SIR 1.4; 95%CI: 1.1–1.7; Table 5). This risk was particularly high in the South European countries (SIR: 2.3; 95%CI 1.5–3.5). In other areas, the SIR was also greater than 1, but not significant. Women had a significantly increased risk of developing a second primary cancer (SIR: 1.5; 95%CI: 1.1–1.9), for male patients there were no significant risks. In EMPD patients aged 61 to 79 the risk of developing a second primary tumour after an EMPD was significantly higher (age cat 61-79 SIR 1.5; 95%CI 1.1–2.0). People diagnosed with EMPD appear to have a lower risk of developing a new primary tumour in the connective tissue (SIR: 0.13; 95%CI 0.0–0.7). The risk is significant and strongly increased for women developing a second primary tumour on the female genitals (SIR: 15.1; 95%CI: 0.38–84.2), unfortunately only the results on the Connective tissue were significant.

Discussion

This study compiles a unique large number of patients diagnosed with EMPD using the data of the RARECARE database, enabling coverage of a mean population of 90,163,609 people over 13 years. Siesling et al. and Pierie et al. presented data on invasive EMPD as well EMPD in situ, reporting a distribution of 1:3.7 and 1:1.8 respectively.[7,18] We had to exclude the EMPD in situ for analyses as we have no information on how the different cancer CRs distinguished the EMPD in situ from invasive EMPD; some registries did not report any case of EMPD in situ, suggesting that those registries report the invasive EMPDs only. Cases of EMPD that were histologically confirmed were included. A much higher incidence in women than in men was revealed, which is consistent with previous literature describing the epidemiology of EMPD.[1,2,5,7] Pierie et al.[18] found a much greater predominance of EMPD in women than we did in our study, possibly due to the smaller sample size in his study. The preferred location in which most EMPD occurs is the anus and anal canal, extragenital skin, vulva in women and the male genitals (except penis), confirming findings in other studies.[2,5–7] The vulva and the male genital organs also includes the genital skin, as we were not able to differentiate for skin within these specific localisations.

Five-year relative survival in EMPD was higher in females than males, and almost the same for patients under the age of 65 and above. In this study, we found a difference in survival for people with EMPD between the different EU regions. This difference might be caused by the localisation of the EMPD. In the Northern EU region, a relatively high percentage of EMPD was located in the skin, in contrast to the UK and Ireland region. The opposite was found for the vulva, in which the Northern EU region had a relative low percentage of cases. Even more remarkable is the difference in survival between the patients included in the different levels of GDP and TNEH. In part this can be explained by the limitation that RARECARE presented GDP and TNEH as two separate indicators without making a correction for the difference in relative cost for healthcare per country. As this has never been described before, the relation between these results in survival needs further research.

The group with middle GDP and middle TNEH display almost similar 5-year survival rates, respectively based on 321 and 330 counts (95%CI 82.7–96.8 and 95%CI 81.8–95.9 respectively) (Table 4). EMPD is known as a slow growing disease with low mortality figures,[19] unfortunately we do not have any data on stage or extent of disease at the moment of diagnose. Therefore retrieving stage at diagnose and longer follow-up could probably of help to better explain our results.

Another finding in this study is the overall higher risk of developing a second primary tumour among people being diagnosed with EMPD compared to the standard population. Significant results of an increasing risk of developing a second primary tumour were found in patients aged 61–79 years old (SIR; 1.5 95%CI: 1.1–2.0). The part of the body most at risk of developing a second primary tumour after an EMPD is the female genital organs (SIR 15.1; 95%CI: 0.4–84.2) in contrast to the connective tissue, that has a strong decreased risk in comparison to the standard population (SIR 0.13; 95%CI 0.0–0.7). A twofold increased risk of developing a second primary tumour after an EMPD was found between the Northern EU region (SIR 1.1 95%CI 0.7–1.7) and the Southern EU region (SIR 2.3 95%CI 1.5–3.5). The same is found between the Central EU region (SIR 1.1 95%CI 0.6–2.2) and the Southern EU region. Unfortunately there are no other studies accessing EU data upon EMPD stratifying for the different EU regions to confirm our findings. As the number of cases used for analyses is very low, the difference group composition within the different EU regions can cause major effect in the results shown. The increased risk of developing a second primary tumour on the female genital organs after an EMPD was also found by Siesling et al.[7] Unfortunately we did not include data on histology type therefore we did not differentiate on morphology for the second primary tumours, it would be a good suggestion for future research to get more in detailed information on morphology even some pathological reviews for the secondary tumour is desirable.

All cancers included were histologically confirmed, a relative easy procedure for EMPD. Therefore, confusion with other diagnosis, such as Bowen's disease, superficial spreading melanoma and pagetoid spread of visceral carcinoma[20,21] is not expected. The only complexity that might occur is determining the original localisation of the tumour, as this requires specialised immunostaining techniques. Therefore we cannot exclude that bias might have occurred for the primary localisation of the EMPD used for analyses. For example we cannot rule out that metastases might have been included accidentally.

For EMPD we can state that differences between countries in incidence, survival and standardized incidence ratios can be seen. However, as we cannot rule out that the reliability of data may vary between cancer registry (CR) and regions, partly explains the reported differences. It is important to state that we need to be cautious giving and interpreting the results related to the different European regions.

Finally we analysed relative recent data with a limited follow-up period: we expect some patients to develop new primaries in over 15 years after initial treatment.[21] Nevertheless, the highest SIR in follow-up was found in the first year after diagnosing the EMPD, indicating that the existence of other primaries at the time the EMPD was diagnosed is very likely.

In conclusion, the risk of a new primary tumour after EMPD is increased compared to the standard population. Consequently, a thorough search for other tumours during the follow-up of EMPD patients should be considered. The risk of a second primary tumour is present mainly in women, predominantly affecting the genital tract, and most commonly presents within the first year of follow-up after being diagnosed with EMPD.

Conflict of interest

None.

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Appendix

Austria: M Hackl, N Zielonk (Austrian National Cancer Registry); ***Belgium:*** E Van Eycken, M Verstreken (Flemish Cancer Registry); Jan Geissler (European Cancer Patients Coalition); ***Croatia:*** A Znor (Croatian National Cancer Registry); ***Estonia:*** M Magi (Estonian Cancer Registry); ***Finland:*** T Hakulinen (Finnish Cancer Registry); ***France:*** G Hedelin, M Velten (Bas-Rhin Cancer Registry); I Tron, E Le Gall (Bretagne Childhood Cancer Registry); G Launoy (Calvados Digestive Cancer Registry); AV Guizard (Calvados General Cancer Registry); J Faivre, AM Bouvier (Cote d'Or Digestive Cancer Registry); M Maynadié (Cote d'Or Haematological Malignancies Registry); A Danzon (Doubs Cancer Registry); A Buemi (Haut-Rhin Cancer Registry); B Tretarre (Hérault Cancer Registry); M Colonna (Isere Cancer Registry); F Molinié (Loire Atlantique Breast and Colon Cancer Registry); B Lacour, E Desandes (Lorraine Childhood Cancer Registry); S Bara (Manche Cancer Registry); C Schvartz (Marne and Ardennes Thyroid Cancer Registry); O Ganry (Somme Cancer Registry); P Grosclaude (Tarn Cancer Registry); E Benhamou (Public Health Department, Institut Gustave Roussy); ***Germany:*** B Holleczek (Saarland Cancer Registry); Markus Wartenberg (Global GIST Network); ***Iceland:*** L Tryggvadottir

(Icelandic Cancer Registry); ***Ireland:*** H Comber, S Deady (National Cancer Registry of Ireland); ***Italy:*** F Bellù (Alto Adige Cancer Registry); A Giacomin (Biella Cancer Registry); C Pascucci (Childhood Cancer Registry of Marche); S Ferretti (Ferrara Cancer Registry); D Serraino (Friuli Venezia Giulia Cancer Registry); M Vercelli, A Quaglia (Liguria Cancer Registry); S Vitarelli (Macerata Province Cancer Registry); M Federico, C Cirilli (Modena Cancer Registry); M Fusco (Napoli Cancer Registry); A Traina (Palermo Breast Cancer Registry); M Michiara, F Bozzani (Parma Cancer Registry); G Pastore (Piedmont Childhood Cancer Registry); R Tumino (Cancer Registry Azienda ospedaliera "Civile MP Arezzo" Ragusa); L Mangone (Reggio Emilia Cancer Registry); F Falcini, F Foca (Romagna Cancer Registry); G Senatore, A Iannelli (Salerno Cancer Registry), M Budroni (Sassari Cancer Registry); S Rosso (Torino Cancer Registry); S Piffer, S Franchini (Trento Cancer Registry); E Crocetti, A Caldarella (Tuscan Cancer Registry); F La Rosa, F Stracci (Umbria Cancer Registry); P Contiero, G Tagliabue (Varese Cancer Registry); P Zambon, A Fiore (Veneto Cancer Registry); F Berrino, PG Casali, G Gatta, L Licitra, M Ruzza, S Sowe, A Trama (Fondazione IRCCS Istituto Nazionale dei Tumori); R Capocaccia, R De Angelis, S Mallone, A Tavilla (Centro Nazionale di Epidemiologia, Istituto Superiore di Sanità); AP Dei Tos, J Fleming (Azienda Ulss N.9 Regione Veneto); ***Malta:*** K England (Malta National Cancer Registry); ***Norway:*** F Langmark, F Bray (Cancer Registry of Norway); ***Poland:*** J Rachtan (Cracow Cancer Registry); R Mezyk (Kielce Cancer Registry); M Zwierko (Warsaw Cancer Registry); M Bielska-Lasota (National Institute of Public Health - National Institute of Hygiene, Warsaw); J Slowinski (Department of Neurosurgery in Sosnowiec, Medical University of Silesia); ***Portugal:*** A Miranda (Southern Portugal Cancer Registry); ***Slovenia:*** M Primic-Žakelj (Cancer Registry of Slovenia); ***Slovakia:*** M Ondrusova (National Cancer Registry of Slovakia); ***Spain:*** A Mateos (Albacete Cancer Registry); I Izarzugaza (Basque Country Cancer Registry); A Torella-Ramos, O Zurriaga (Comunitat Valenciana Breast and Childhood Cancer Registry); R Marcos-Gragera (Girona Cancer Registry); MJ Sánchez (Granada Cancer Registry); C Navarro, MD Chirlaque (Murcia Cancer Registry); Eva Ardanaz, C Moreno (Navarra Cancer Registry); R Peris-Bonet (Spanish National Childood Cancer Registry); J Galceran (Tarragona Cancer Registry); JA Virizuela-Echaburu, R Gonzalez-Campora (Hospital Macarena); C Martinez-Garcia, JM Melchor (Escuela Andaluza de Salud Pública); ***Sweden:*** Å Klint, M Talbäck (Cancer Registry of Sweden); Jan Adolfsson (Stockholm-Gotland Cancer Registry); M Lambe (Uppsala Regional Cancer Registry), TR Möller (Lund University Hospital); Ulrik Ringborg (Karolinska Institute); ***Switzerland:*** G Jundt (Basel Cancer Registry); M Usel, C Bouchardy (Geneva Cancer Registry); H Frick (Grisons Cancer Registry); SM Ess (St. Gallen Cancer Registry); A Bordoni (Ticino Cancer Registry); JC Luthi (Valais Cancer Registry); S Dehler, NM Probst-Hensch (Zurich Cancer Registry); JM Lutz (Co-ordinating Center); ***The Netherlands:*** O Visser (Amsterdam Cancer Registry); R Otter, JM van der Zwan, S Siesling (Comprehensive Cancer Centre North East, Groningen/Enschede, the Netherlands); JWW Coebergh (Eindhoven Cancer Registry); ***UK-England:*** DC Greenberg (Easter Cencer Registration and Iinformation Centre); D Forman (Northern and Yorkshire Cancer Registry); M Roche (Oxford Cancer Intelligence Unit); C Stiller (Childhood Cancer Research Group); J Verne (South-West Cancer Intelligence Service); D Meechan (Trent Cancer Registry); G Lawrence (West-Midlands Cancer Intelligence Unit); MP Coleman (London School of Hygiene and Tropical Medicine); ***UK-Northern Ireland:*** A Gavin (Northern Ireland Cancer Registry); ***UK-Scotland:*** DH Brewster, RJ Black (Scottish Cancer Registry); I Kunkler (The University of Edinburgh); ***UK-Wales:*** J Steward (Welsh Cancer Intelligence & Surveillance Unit).

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