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Cancer

Cancer cure for 32 cancer types: results from the EUROCARE-5 study

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Abstract

Background: Few studies have estimated the probability of being cured for cancer patients. This study aims to estimate population-based indicators of cancer cure in Europe by type, sex, age and period.

Methods: 7.2 million cancer patients (42 population-based cancer registries in 17 European countries) diagnosed at ages 15–74 years in 1990–2007 with follow-up to 2008 were selected from the EUROCARE-5 dataset. Mixture-cure models were used to estimate: (i) life expectancy of fatal cases (LEF); (ii) cure fraction (CF) as proportion of patients with same death rates as the general population; (iii) time to cure (TTC) as time to reach 5-year conditional relative survival (CRS) >95%.

Results: LEF ranged from 10 years for chronic lymphocytic leukaemia patients to <6 months for those with liver, pancreas, brain, gallbladder and lung cancers. It was 7.7 years for patients with prostate cancer at age 65–74 years and >5 years for women with breast cancer. The CF was 94% for testis, 87% for thyroid cancer in women and 70% in men, 86% for skin melanoma in women and 76% in men, 66% for breast, 63% for prostate and <10% for liver, lung and pancreatic cancers. TTC was <5 years for testis and thyroid cancer patients diagnosed below age 55 years, and <10 years for stomach, colorectal, corpus uteri and melanoma patients of all ages. For breast and prostate cancers, a small excess (CRS < 95%) remained for at least 15 years.
Conclusions: Estimates from this analysis should help to reduce unneeded medicalization and costs. They represent an opportunity to improve patients' quality of life.

Key words: Cancer cure, time to cure, survival, life expectancy, population-based cancer registries, Europe, mixture cure models

Key Messages

- Cancer cure indicators are provided for European patients.
- Evidence suggests that several cancer types are curable diseases.
- For patients with some cancers (e.g. thyroid, testis), excess mortality becomes negligible in 2 years.
- Colorectal or endometrial cancer patients: half of them are cured in <10 years.
- Recognizing cancer patients as cured has relevant clinical, economic, and social implications.

Introduction

More than 50 years have passed since the first definition of 'cure' for cancer[1]: '...to connote that in time -probably a decade or two after treatment- there remains a group of disease-free survivors whose annual death rate from all causes is similar to that of a normal population group of the same sex and age distribution'. Several investigations have expanded such definition into the present 'cure fraction' (CF) indicator, i.e. the proportion of diagnosed cancer patients having the same death rates of the general population of the same sex and age.[2,3] The word 'cure' in oncology has been used with several other meanings if applied to individual patients or at population level, often without fitting the cited standard.[4] Moreover, patients with specific neoplasms may also remain relapse-free, or without any measurable sign of disease, for several years after initial treatment, with a small long-term excess risk of relapse or death.[5,6]

In populations of western countries, the number of individuals living after a cancer diagnosis (i.e. cancer prevalence) is growing by approximately 3% annually.[7–10] They currently represent more than 5% of the overall population in several countries. In addition, a large proportion of people living after a cancer diagnosis (i.e. 24% of cancer patients in Italy[6] and 29% in the USA[10]) are alive after 15 years or more since diagnosis. Patients living after a cancer diagnosis include: individuals currently in treatment; those who are relapse-free but remain at excess risk of recurrence or death[6]; and patients who have the same death rates as the general population (i.e. 'cured' ones).[11] Notwithstanding these growing evidences, few studies have categorized prevalent cancer patients according to the probability of being cured.[12–20]

This study aimed to provide reliable population-based estimates of three indicators of long-term prognosis and cure of cancer patients in Europe, by cancer type, sex and age. They serve as 'real-world' information addressed to health professionals for evaluating treatment effectiveness, to oncologists for planning follow-up[18,21] and to policy makers for allocating resources.[22] Moreover, they may be of special interest to the increasing number of people living after a cancer diagnosis.[23]

Methods

The EUROCARE-5 study included information on cancer patients diagnosed in 29 European countries and 99 population-based cancer registries (CRs).[24,25] Study

protocol, data quality checks, participating registries and national registration coverage in the EUROCARE-5 dataset have been extensively described elsewhere.[25]

This present study included 7.2 million adult (aged 15–74 years) cancer patients, with ≥15 years of registration during 1990–2007 and ≥18 years of follow-up as of 2008, collected by 42 CRs from 17 countries and 19% of the European population. Among them, 3.7 million were men and 3.5 million women (Supplementary Appendix 1, available as Supplementary data at *IJE* online). They included 1.2 million women with breast cancer and 0.7 million men with prostate cancer; 49% of men (1.8 million) and 37% of women (1.3 million) received a cancer diagnosis at age 65–74 years. All malignant tumours except non-melanomatous skin cancer (classified according to ICD-O-3), were eligible and the 32 most frequent cancer types or combinations were presented (Supplementary Appendix 1).

Relative survival (RS) between 0 and 18 years of follow-up and the corresponding 5-year conditional RS (CRS), conditioned on surviving at a given number (i.e. 1 to 13) of years of follow-up, were calculated using the Ederer II approach.[26] For each cancer type and sex, mixture cure models were applied to RS data, separately by age groups (15–44, 45–54, 55–64, 65–74 years), using a 3-year diagnostic period (1990–92 … 2005–07) as covariate. A Weibull distribution was obtained as parametric function for the excess mortality of fatal cases, with independent parameters (shape and scale of Weibull distribution, period) for each cancer type, sex and age stratum. All models were based on the assumption of linearity in the effect of the diagnostic period. The assumption seemed plausible within the examined diagnostic period, since sudden changes in RS trends were rarely observed at a population level. However, this assumption is questionable outside the study period.

The following indicators of long-term survival and cancer cure were estimated using described mixture cure models: (i) LEF is defined as the median life expectancy of fatal cases (i.e. the uncured) who will never reach the same death rates as the general population,[2] and it represents a measure of the death risk due to cancer only, as if the other causes of death were not present; (ii) cure fraction (CF) is defined as the proportion of cancer patients having the same mortality rates as those observed in the general population of the same sex and age[2,3]; and (iii) time to cure (TTC) is defined as the number of years after cancer diagnosis when the excess mortality due to cancer becomes negligible.[11,13] TTC was estimated as the number of years necessary for model-based 5-year CRS to reach 95%.

Validation

Cure models converged for every cancer type, sex and age group. In addition, a visual comparison of RS and CRS data with model-based estimates over an 18-year period of follow-up for all cancer types, age groups and period of diagnosis (Supplementary Appendix 2, available as Supplementary data at *IJE* online) was examined by the panel of experts involved in this study. The model fitting to the RS data was very good for most cancer types, sex and ages. TTC was considered uncertain when a difference between data and estimates of more than 10 percentage points of 5-year CRS at 10 years after diagnosis occurred.

A key assumption for the cure models is that the relative survival curves plateau at some point during the observed follow-up interval.[27] When excess mortality estimates (i.e. RS) show a non-negligible decrease until 15-years after diagnosis, CF should be read only as the proportion of diagnosed cancer patients that will die for causes other than the specific neoplasm and a cure is questionable. LEF was not reliable for thyroid cancer and in some age groups for Hodgkin lymphoma (HL) (≥45 years) and small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL) (<65 years), due to the small number of events in the tail of the distribution of fatal cases.

The observed RS was calculated by means of SeerStat software,[28] model-based estimation using the SAS NLIN procedure.[11]

Results

LEF spanned from 10 years for SLL/CLL patients (8.2 in men, 11.9 in women) at ages 65–74 years to less than 6 months for those with liver, pancreas, gallbladder, lung and brain cancer (Table 1). LEF was more than 5 years for breast cancer patients at all ages, prostate cancer patients aged 65–74 years, leukaemia patients aged 55–64 years and follicular non-Hodgkin lymphoma (NHL) patients aged 15–64 years. For most cancer types, LEF decreased with age in both sexes. A marked advantage for women emerged for NHL patients and skin melanoma patients. Only for bladder cancer, men showed more favourable LEF than women. Between 1990 and 2000, LEF in patients with breast or prostate cancer and for most lymphoid neoplasms increased by approximately 1 year (Supplementary Appendix 3, available as Supplementary data at *IJE* online). Conversely, a less than 2-month increase was estimated for all cancers combined and for the most fatal neoplasms (e.g. oesophagus, stomach, colon, liver, gallbladder, pancreas, lung and brain).

The CF was >60% in 2000 for patients with testicular cancers (94%), skin melanoma (76% in men and 86% in women), thyroid cancer (70% in men and 87% in women), HL (67% in men and 75% in women), corpus uteri (76%), breast (66%), cervix uteri (64%) and prostate cancers (63%) (Figure 1). Conversely, a CF ≤ 15% in both sexes

Table 1 Life expectancy of fatal cases (years)a at diagnosis by cancer type, sex and age in Europe

Cancer type[b]	Age at diagnosis (years)							
	15–44		45–54		55–64		65–74	
Sex	M	W	M	W	M	W	M	W
All types	1.2	2.7	1.0	2.3	1.0	1.6	1.0	1.0
Oral cavity and pharynx	1.7	2.4	1.8	2.7	1.8	2.4	1.5	2.2
Oesophagus	0.7	0.8	0.7	0.7	0.6	0.7	0.5	0.6
Stomach	0.7	0.7	0.7	0.7	0.6	0.6	0.5	0.5
Colorectal	1.5	1.6	1.6	1.7	1.6	1.5	1.3	1.2
Colon	1.3	1.5	1.3	1.5	1.3	1.3	1.1	1.0
Rectum	1.8	2.0	2.0	2.0	1.9	1.9	1.6	1.6
Liver	0.4	0.6	0.3	0.4	0.3	0.4	0.3	0.3
Gallbladder	0.8	0.7	0.7	0.6	0.6	0.5	0.4	0.3
Pancreas	0.4	0.4	0.3	0.4	0.3	0.4	0.2	0.3
Larynx	2.2	3.0	2.9	4.0	4.1	10.3	4.7	5.2
Lung	0.6	0.7	0.6	0.6	0.5	0.6	0.4	0.4
Skin melanoma	3.1	4.4	2.9	3.6	2.5	3.1	2.4	2.7
Connective tissue	1.6	1.9	1.6	1.7	1.3	1.7	1.1	1.4
Breast		7.1		6.4		5.6		6.4
Vagina		3.2		2.6		2.1		1.7
Cervix uteri		1.9		1.8		2.0		1.7
Corpus uteri		2.9		2.4		2.4		2.1
Ovary		2.0		2.1		1.6		1.1
Prostate	2.2		3.7		4.8		7.7	
Testis	1.3		7.0		2.6		2.0	
Kidney	1.6	1.3	1.9	1.9	1.9	2.0	1.6	2.7
Bladder	2.0	1.0	2.6	1.5	3.5	2.1	3.5	2.2
Brain	2.3	2.7	0.8	0.8	0.5	0.5	0.3	0.3
Hodgkin lymphoma[b]	3.6	3.9	–	–	–	–	–	–
Non-Hodgkin lymphoma	1.3	1.6	7.2	8.9	9.4	15.1	5.7	7.3
Multiple myeloma	4.6	3.7	4.0	4.2	3.5	3.5	2.2	2.4
Leukaemias	1.3	1.1	5.0	2.7	5.9	5.8	2.9	3.0
SLL/CLL[b]	–	–	–	–	–	–	8.2	11.9
NHL, diffuse large-B cell	1.0	1.3	1.8	2.2	2.0	2.2	1.6	2.1
NHL, follicular	5.3	4.8	5.1	6.5	5.7	5.4	4.2	4.9

M, men; W, women; NHL, non-Hodgkin lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.

[a]Median life expectancy of fatal cases at diagnosis was calculated in years as the median (50th percentile) RS estimated through the best fitting model-based distributions centred at 2000 as the year of diagnosis.

[b]Not estimable for thyroid cancer and some age groups for HL and SLL/CLL.

was estimated for cancers of the pancreas, liver, lung, SLL/CLL, oesophagus, myelomas, brain and gallbladder. The CF increased by a different extent during 1990–2000 for all cancer types (except bladder), in particular for patients with prostate cancer (from 22% to 63%) and (>10%) for breast, thyroid, colorectal cancers and follicular NHL (Figure 1). Two-thirds of cancer patients diagnosed at age 15–44 years (CF = 65% in men and 69% in women), and one-third of patients aged 65–74 years (CF= 33% in men and 38% in women) were expected to be cured (Supplementary Appendix 4, available as Supplementary data at *IJE* online). CF for all cancer types combined increased in Europe from 23% in 1990 to 39% in 2000 among men and from 41% to 51% among women (Figure 1).

The TTC was less than 1 year for thyroid and testicular cancer patients below the age of 45 years (Table 2). Conversely, a small but not negligible excess risk of death was present even after 10 years since diagnosis for women with breast cancer and for men with prostate cancer. In particular, TTC of approximately 10 years was found in women aged 45–64 years with breast cancer, but it was 15 years or more for those aged below or above 45–64 years. A relevant long-term excess risk of death (TTC $\geq$ 15 years) remained for patients aged 65–74 years with laryngeal, liver (in men), prostate, bladder and kidney cancers, and for all haemolymphopoietic neoplasms, but HL below age 45 years had TTC $\leq$ 3 years in both sexes.

TTCs based on a threshold of 90% were also calculated (Supplementary Appendix 5, available as Supplementary data at *IJE* online), and they occurred 3–5 years earlier than those based on threshold of 95% for most cancer types.

CF and TTC in the most frequent age groups of individual cancer types showed an inverse correlation except for the most fatal cancer types (Figure 2). Possible clusters of cancer types were: (i) those with CF >70% and TTC $\leq$ 6 years, including HL, skin melanoma, thyroid, testicular and cervix uteri cancers; (ii) those with CFs between 30% and 70% and TTC of <10 years, including corpus uteri, colorectal, and connective tissue; (iii) those with CFs between 30% and 70% and TTC of $\geq$10 years, including prostate, kidney, and bladder cancers; (iv) those with CFs <30%, including cancers with severe prognoses (e.g. stomach, gallbladder, lung, pancreas) and those with long-term excess risk of death (e.g. most NHL types, myelomas, liver, larynx, ovary).

Discussion

This study provides further insights on long-term cancer survivors in Europe using cure indicators, in addition to traditional survival measures.[12,24] Our findings strengthen and are consistent with previous national studies, albeit they were derived from different mathematical models, in Europe[11–16,19] or elsewhere.[18,20]

According to estimates of CF and TTC, four major clusters of cancer types emerged. The first included testicular or thyroid cancer patients, for whom surveillance may be warranted only for the first 1–2 years, since no relevant

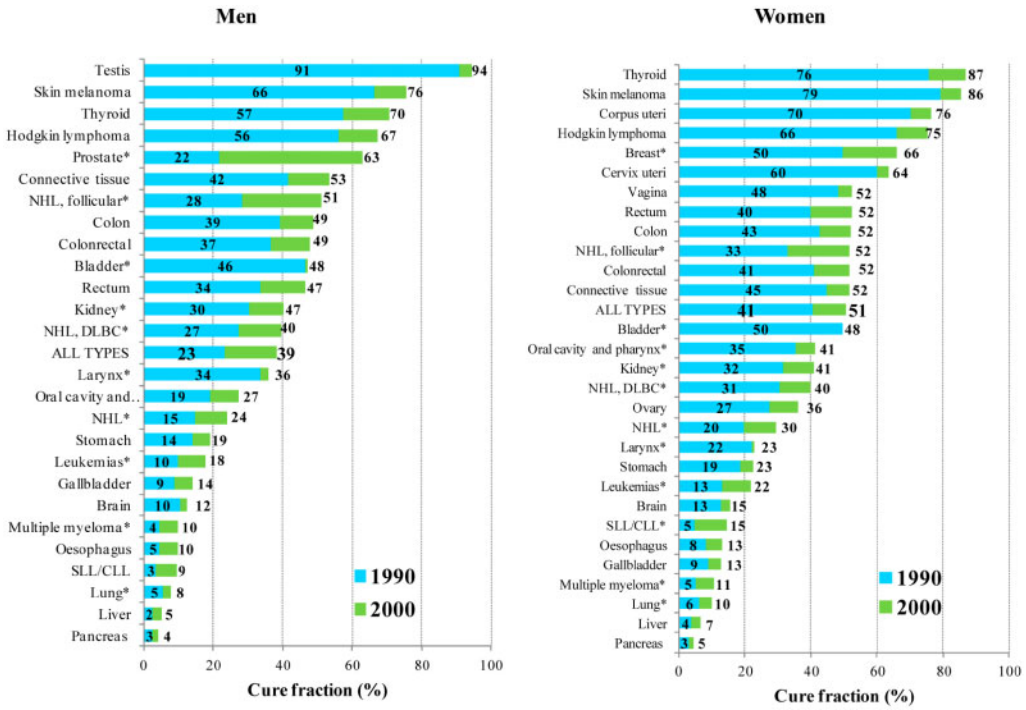

Figure 1 Cure fraction (%)[a] by sex, cancer type and period in Europe. NHL, non-Hodgkin lymphoma; DLBC, diffuse large-B cell non-Hodgkin lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.
[a]Calculated as means of corresponding cure fractions estimated for the four age groups (Supplementary Appendix 4, available as Supplementary data at *IJE* online) weighted by number of incident cases (Supplementary Appendix 1, available as Supplementary data at *IJE* online). Patients aged 15–74 years. *Cancer types with a non-negligible long-term excess mortality rate, in comparison with general population. In this case, CF should be interpreted as long-term relative survival (i.e. ≥20 years since diagnosis)

excess mortality would persist later on.[15,18] Cure was also reached by more than two-thirds of patients with melanoma, HL and cancer of the cervix uteri. The second cluster included patients with colorectal and endometrial cancers, for which a cure is reached by approximately half of patients with TTC < 10 years, suggesting the need of a medium-term surveillance.[15,18,29] A third cluster included patients with breast, bladder and prostate cancers since, consistently across studies: 50-70% of them were not expected to die because of their neoplasms,[12,15,19,30] but a small risk of death persisted for at least 15 years.[5,6,15,19] For most cancer types, prognosis varied considerably according to stage at diagnosis[18] and expression of tumuor markers,[6] suggesting that further detailed information is needed for an accurate stratification of follow-up. The fourth major cluster included patients with liver, lung and pancreatic cancers,[14,15,19] with a median 4–6-months survival. Furthermore, these cancers showed small CF changes during the observation period. For patients with these cancer types, as well as most lymphomas and leukaemias who have longer survival, an excess mortality in comparison with the general population persisted for a very long period, suggesting that lifelong oncology surveillance is needed.[18]

Strengths and limitations

The accuracy of the presented population-based indicators of cancer cure depends on the size of the study population, length and completeness of follow-up and the goodness-of-fit of models used. The large population size allowed estimates of long-term prognosis for some relevant histological subtypes (i.e. diffuse large-B cell and follicular NHL, and SLL/CLL), rarely examined.[31,32] The follow-up period was adequate to provide reliable LEF, CF and TTC estimates for most cancer types. This can also be seen as a limitation, as long-term follow-up cannot be obtained for recent diagnoses. Inevitably, validated indicators represent observations from the distant past. Projections of cancer survival and cure for more recent cases depend necessarily on questionable assumptions, and are beyond the scope of present report.

Our present results pertain to the pool of populations for which sufficiently long time series of registry data were available. Even though populations from all parts of Europe were included, the overall study population is certainly not fully representative of the overall European population. Also, given the major variation in survival rates between European populations,[24] the presented cure measures are likely to vary substantially among European countries as well.

Table 2 Time to cure measured as years to reach 5-year conditional relative survival (5-year CRS) >95%[a] by cancer type[b], sex and age in Europe

	Age at diagnosis (years)							
	15–44		45–54		55–64		65–74	
Cancer type	Men	Women	Men	Women	Men	Women	Men	Women
All types	6	8	9	9	10	10	13	12
Oral cavity and pharynx[b]	8	7	12	13	15	15	17	18
Oesophagus[b]	6	6	6	6	7	6	7	6
Stomach	7	7	7	7	7	7	7	8
Colorectal	6	6	7	7	8	7	8	8
Colon	6	6	7	6	7	6	8	7
Rectum	7	7	8	7	9	8	9	9
Liver	10	9	13	10	15	11	20	14
Gallbladder	7	6	7	6	9	7	8	7
Pancreas	8	6	7	6	6	6	6	6
Larynx	9	9	13	18	21	>25	>25	>25
Lung	5	5	7	6	8	8	9	9
Skin melanoma	6	2	6	4	6	4	6	5
Connective tissue	6	7	7	8	7	10	9	12
Breast		16		11		10		15
Vagina		8		9		10		10
Cervix uteri		4		6		10		14
Corpus uteri		5		4		5		7
Ovary		7		9		9		10
Prostate	6		8		9		17	
Testis	<1		1		1		5	
Kidney	7	5	12	9	15	13	17	>25
Bladder	4	3	8	6	14	10	19	16
Brain[b]	18	20	8	10	5	6	5	5
Thyroid	<1	<1	3	<1	8	1	24	8
Hodgkin lymphoma	3	2	14	7	>25	18	>25	>25
Non-Hodgkin lymphoma	7	7	>25	23	>25	>25	>25	>25
Multiple myeloma	21	16	25	24	>25	>25	25	>25
Leukaemias	7	7	>25	20	>25	>25	>25	>25
SLL/CLL	>25	>25	>25	>25	>25	>25	>25	>25
NHL, diffuse large-B cell	5	5	11	11	16	15	22	>25
NHL, follicular	10	9	13	14	19	17	19	21

NHL, non-Hodgkin lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.
[a]Calculated using model-based 5-year CRS estimates of time to cure, centred at 2000 as the year of diagnosis.
[b]A poor fitting between observed and model-based CRS emerged for patients with oral cavity, oesophagus and brain cancers.

The cure models we used may have potential limitations. For cancers with long-term excess mortality risk in particular, the available follow-up period may have been insufficient to observe the deaths of all fatal cases, i.e. the plateau in the relative survival curve, a general key assumption of cure models.[15,27] This means that there might have been an identifiability issue with the CF.[27] Hence, patients above 75 years of age at diagnosis were excluded from the analyses, as cure models are less reliable for older age groups.[3] Other biases may have affected RS and cure indicators, including lead time and length biases.[33,34] Notably, we defined as cured those patients reaching the same mortality rate as that of a comparable group without cancer, with the assumption that cancer patients were exposed to the same risk factors of the general population. However, this is a 'prudent' assumption, since cancer patients, even those cured, could have been exposed to risk factors that contributed to causing their cancer and, in turn, were associated with excess risk of death for competing causes.[35] Recent studies[36–38] have suggested that this effect may lead to underestimating CF and overestimating TTC for several cancer types. No confidence intervals for LEF, CF and TTC have been presented, nor sensitivity analyses for different TTCs[11] or their variability,[19] in order

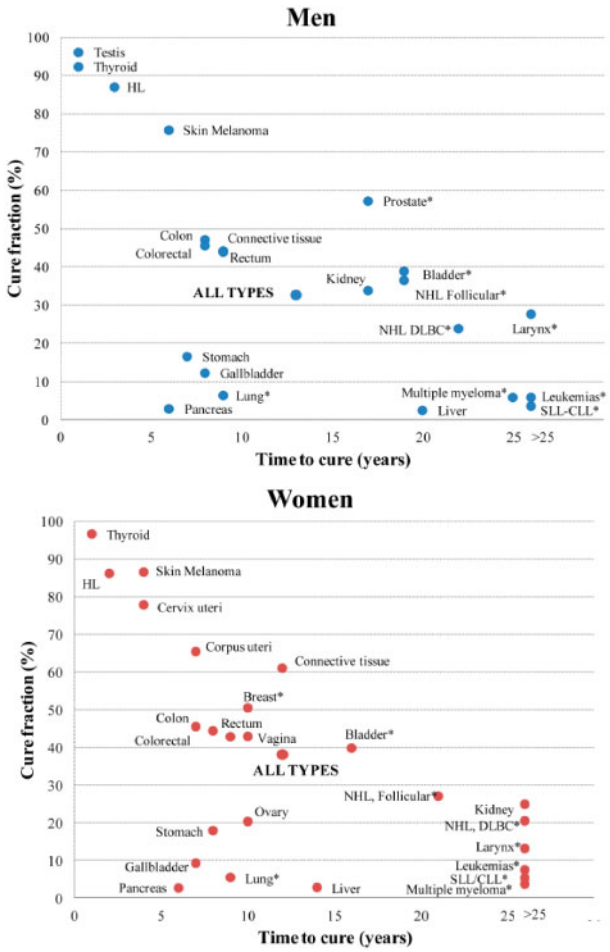

Figure 2 Combination of the cure fraction (%) and time to cure[a] by sex for the most frequent age group in Europe. HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; DLBC, diffuse large-B cell non-Hodgkin lymphoma; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.

[a]Calculated in 2000 for age 65–74 years; but oral cavity, skin melanoma and breast: 55–64 years; and cervix uteri, testis, thyroid and Hodgkin lymphoma: 15–44 years. *Cancer types with a non-negligible long-term excess mortality rate, in comparison with general population. In this case, CF should be interpreted as long-term relative survival (i.e. ≥20 years since diagnosis)

to avoid overemphasized estimates of 'precision' by means of still largely debated variability measures. The threshold to define TTC (i.e. a low risk of recurrence/death) is arbitrary and may be based on different assumptions or statistical models.[13] Moreover, it should be noted that the estimation of TTC is sensible to the choice of the CRS threshold (i.e. a low risk of recurrence/death or the margin of clinical relevance) and to the use of different definitions and statistical models,[11,13,18,,19,39] in particular for prostate or breast cancer. Most importantly, information on prognostic factors (i.e. stage, treatment, recurrence, socioeconomic status), which should have been taken into account as covariates or stratified in our models, is not routinely collected by most European CRs. For breast cancer patients, detailed estimates of long-term prognosis by stage and receptor status have been provided in some countries, as well as first attempts to estimate the risk of recurrence, a kind of information not usually reported by CR.[6,13,40–42] These studies have reported that the prognostic effect of stage or cancer subtype lessens with increasing time since diagnosis, suggesting that present indicators may underestimate cancer cure for subtypes with less advanced stages.

Finally, the presented indicators of cure and survival estimates may have been influenced by overdiagnosis (increasing detection of cancer cases that would not otherwise result in causing symptoms or deaths, without difference in mortality rates as compared with the general population).[43] Overdiagnosis that may have had a relevant impact on CF changes emerged for prostate and thyroid cancer in Europe.

Conclusions

The results from the present study confirm the need to reconsider the current paradigm of survivorship as a never-ending experience that 'lasts throughout the lifespan'.[44] This definition of survivorship, indeed, fails to recognize the increasing number of patients who have already reached a life expectancy similar to that of the general population.

The awareness that some cancer patients are cured has relevant clinical, economic, and social implications; first of all, it provides an opportunity to improve quality of life by changing the way 'former' patients view themselves.[23] In a context of the considerable resources needed for care of people living after a cancer diagnosis, our findings call for risk-stratified follow-up care for cancer patients.[21,45]

Supplementary data

Supplementary data are available at *IJE* online.

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Author contributions

L.D.M. and S.Francisci drafted the study protocol and designed the study with the support of S.G. and D.S. A.T., S.M., R.C., M.C., G.G., V.J., P.M., R.D.A. and the EUROCARE Working Group revised the study protocol, collected data and prepared cleaned data for the study database. C.P. and A.T. did the statistical analyses with the support of L.D.M., S.G. and S.Francisci D.S., S.M., L.B., O.B., R.C., M.C., E.C., T.D., G.G., A.G., F.G., V.J., P.M., L.N., G.R., M.Z. and R.D.A. contributed to validation of statistical models and revised statistical analyses. A.D., S.Franceschi, D.S. and M.Z. specifically discussed social and clinical implications of study results. All authors contributed to the interpretation of study results and reviewed and approved the final version.

Conflict of interest

None declared.

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