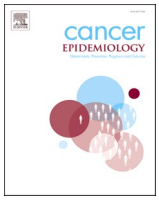
Cancer Epidemiology 76 (2022) 102085

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep



A way to explore the existence of "immortals" in cancer registry data – An illustration using data from ICBP SURVMARK-2

Therese M.-L. Andersson [a,*], Mark J. Rutherford [b,c], Tor Åge Myklebust [d,e], Bjørn Møller [d], Melina Arnold [c], Isabelle Soerjomataram [c], Freddie Bray [c], Hazem Abd Elkader [f], Gerda Engholm [g], Dyfed Huws [h,i], Alana Little [j], Lorraine Shack [k,l], Paul M. Walsh [m], Ryan R. Woods [n], D.Maxwell Parkin [o,p], Paul C. Lambert [a,b]

[a] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[b] Department of Health Sciences, University of Leicester, Leicester, United Kingdom
[c] Cancer Surveillance Branch, International Agency for Research on Cancer, Lyon, France
[d] Department of Registration, Cancer Registry of Norway, Oslo, Norway
[e] Department of Research and Innovation, Møre and Romsdal Hospital Trust, Ålesund, Norway
[f] Cancer Society of New Zealand, Wellington, New Zealand
[g] Cancer Surveillance and Pharmacoepidemiology, Danish Cancer Society Research Center, Copenhagen, Denmark
[h] Welsh Cancer Intelligence and Surveillance Unit, Knowledge Directorate, Public Health Wales, Cardiff, Wales, United Kingdom
[i] Swansea University Medical School, Swansea, Wales, United Kingdom
[j] Cancer Information and Analysis, Cancer Institute NSW, St Leonards, New South Wales, Australia
[k] Cancer Care Alberta, Alberta Health Services, Calgary, Alberta, Canada
[l] Preventative Oncology and Community Health Sciences, University of Calgary, Alberta, Canada
[m] National Cancer Registry, Cork, Ireland
[n] Cancer Control Research, BC Cancer, Vancouver, Canada
[o] School of Cancer & Pharmaceutical Sciences, King's College London, London, United Kingdom
[p] INCTR Challenge Fund, Prama House, Oxford, United Kingdom

ARTICLE INFO

Keywords:
Cancer registry
Cancer Survival
Immortals

ABSTRACT

Background: Accurately recorded vital status of individuals is essential when estimating cancer patient survival. When deaths are ascertained by linkage with vital statistics registers, some may be missed, and such individuals will wrongly appear to be long-term survivors, and survival will be overestimated. Interval-specific relative survival that levels off above one indicates that the survival among the cancer patients is better than expected, which could be due to the presence of immortals.
Methods: We included colon cancer cases diagnosed in 1995–1999 within the 19 jurisdictions in seven countries participating in ICBP SURVMARK-2, with follow-up information available until end-2015. Interval-specific relative survival was estimated for each year following diagnosis, by country and age group at diagnosis.
Results: The interval-specific relative survival levels off at 1 for all countries and age groups, with two exceptions: for the age group diagnosed at age 75 years and above in Ireland, and, to a lesser extent, in New Zealand.
Conclusion: Overall, a subset of immortals are not apparent in the early years within the ICBP SURVMARK-2 study, except for possibly in Ireland. We suggest this approach as one strategy of exploring the existence of immortals, and to be part of routine checks of cancer registry data.

1. Introduction

When estimating cancer patient survival based on cancer registry data, it is essential that vital status of the cancer patients is accurately recorded. In the absence of active follow-up of patients, information on vital status is usually obtained by linking the cancer register to death registers from vital statistics offices, and all cases without a match are assumed to be still alive. If some deaths are missed by this process, some

* Corresponding author.
E-mail address: therese.m-l.andersson@ki.se (T.M.-L. Andersson).

https://doi.org/10.1016/j.canep.2021.102085
Received 30 August 2021; Received in revised form 9 December 2021; Accepted 10 December 2021
Available online 24 December 2021

individuals will appear to be long-term survivors so-called "immortals". This will lead to survival being overestimated. Unsuccessful linkage to death registers (failure of matching) can occur in the absence of a unique personal ID, or if the individual died outside of the catchment area and therefore is not recorded in the death register, for example due to emigration. In countries with regional cancer registries for different provinces or states, e.g. Canada, movement out of the province/state could also lead to unability to find a death date for an individual if there is no formal record of emigration from a state and linkage to national vital statistics is not possible.

It is difficult to know the size of the problem with "immortals" in cancer registries, but there are a number of approaches in which the issue can be further explored. One means is to perform active follow-up tracing a random sample of individuals who are assumed to be alive and check if this actually is the case, although this can be a costly and time-consuming task. Another option is to assess if the survival of long-term survivors is the same as that of the general population. "Statistical" cure has been reported for certain cancer sites such as colon cancer, where patients still alive 7–8 years after diagnosis experience little or no excess mortality relative to the general population [1,2]. The interval-specific, or conditional relative survival, for these cancer patients should therefore level off at 1. If the interval-specific relative survival is greater than unity it indicates that the survival among the cancer patients is better than expected, which could be due to the inclusion of a subset of immortals, as described earlier.

In this study we estimate the interval-specific relative survival for colon cancer within the jurisdictions and countries that are part of the ICBP SURVMARK-2 study [3–7], to investigate whether there is reason to suspect that a subset of immortals exists in the contributing registry datasets.

2. Materials and methods

We included all cases of colon cancer diagnosed in the years 1995–1999 within the 19 jurisdictions in seven countries participating in ICBP SURVMARK-2[7], with follow-up information on death until 31 Dec 2015. The participating countries are: Australia (New South Wales, Victoria, and Western Australia), Canada (Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan), Denmark, Ireland, New Zealand, Norway, and the United Kingdom (England, Northern Ireland, Scotland, and Wales). The reason for not including diagnoses from more recent calendar years was to ensure that all cases had a potential follow-up of at least 15 years. Interval-specific relative survival was estimated for each year following diagnosis, separately for each country and by age group at diagnosis (15–44 years, 45–54, 55–64, 65–74, 75–99). Individuals younger than 15 or older than 99 years at diagnosis were excluded from the analysis. All analyses were performed using the statistical software Stata and interval-specific relative survival estimates were obtained using the command strs [8].

3. Results

Fig. 1a–g shows the interval-specific relative survival by years since diagnosis for each country and age group. The equivalent interval-specific survival together with 95% confidence intervals, for year 1, 5, 10 and 15 after diagnosis, as well as the number of individuals still at risk at the start of each interval (year), is presented in Table 1. For the first year, the interval-specific relative survival is the same as the 1-year relative survival, and differs across both age groups and countries. However, over time the differences diminish, and the interval-specific relative survival levels off at 1 for most countries and age groups. For Ireland the age group 75 + levels off above 1, indicating that this group has a higher survival than the general population, and this is statistically significant (Table 1). This can also be seen for New Zealand, although to a lesser extent. For Canada and Denmark, the interval-specific relative survival for the age group 75 + is above 1 for the last few years, but only for Canada is this statistically significant by year 15.

4. Discussion

In this study, we have presented an approach to explore the presence of immortals in cancer registry data. As a word of caution, the method can only suggest the existence of "immortals", and cannot provide a quantitative estimate of the extent of the problem. Registries can however use this as one of the initial checks and investigate further if a potential problem was detected. On the basis of the datasets within the ICBP SURVMARK-2 study, we can conclude that there is little evidence of the existence of a subset of immortals in the vast majority of contributing registry datasets, although the oldest age group warrants further assessment in certain countries, notably in Ireland. There were indications of a problem in Canada in the last few years, which could partly be due to changes in legislation which has led to difficulty in linking to the national vital statistics. The problem with "immortals" could therefore be larger in Canada in later years, which is not observed in this study since we only included cases diagnosed in 1995–1999.

The impact of immortals will differ across age groups, and thus we chose to estimate the interval-specific survival by age. At younger ages, the number of expected deaths are few, and the impact of failing to ascertain all deaths is likely to be small. The interest is predominantly in assessing older age groups, but due to a high mortality, there could be few individuals left for long-term follow-up. This approach is feasible in cancer registries with large population, however, it is more challenging in cancer registries with small catchment populations when there are few observations with long-term follow-up. In these circumstances, one option would be to pool cancer sites for which there is evidence of statistical cure as a means to better understand potential problems with linking information on deaths. Cancer sites for which statistical cure has previously been assumed are for instance rectal cancer [9] and melanoma [10]. Even though statistical cure is not reasonable for all cancer sites, it is not necessary to apply this approach to more sites as long as the procedure for ascertaining and linking deaths can be assumed the same across cancer sites within a cancer registry.

There may be other explanations as to why interval-specific relative survival values are consistently above unity, for instance as a result of healthy survivor bias, e.g. those that survive cancer are healthier than the general population. Another is the use of a population mortality file that does not correctly reflect the background mortality in the population of cancer patients. For older ages the population mortality files are sometimes smoothed and extrapolated, which could lead to less reliable estimates on the oldest age group. It is also worth noting that interval-specific relative survival estimates of one or below one do not necessarily demonstrate an absence of immortals. Even so, this approach do offer an option to registries seeking to detect whether such biases exist in the underlying dataset, and should be done routinely in efforts to develop comparable estimates of population-based cancer survival.

Funding

The ICBP-SurvMArk-2 project and its data collection were supported by the ICBP which is funded by the Canadian Partnership Against Cancer; Cancer Council Victoria; Cancer Institute New South Wales; Cancer Research UK; Danish Cancer Society; National Cancer Registry Ireland; The Cancer Society of New Zealand; NHS England; Norwegian Cancer Society; Public Health Agency Northern Ireland on behalf of the Northern Ireland Cancer Registry; DG Health and Social Care, Scottish Government; Western Australia Department of Health; Public Health Wales NHS Trust.

CRediT authorship contribution statement

Therese M-L Andersson: Formal analysis, Methodology, Writing –

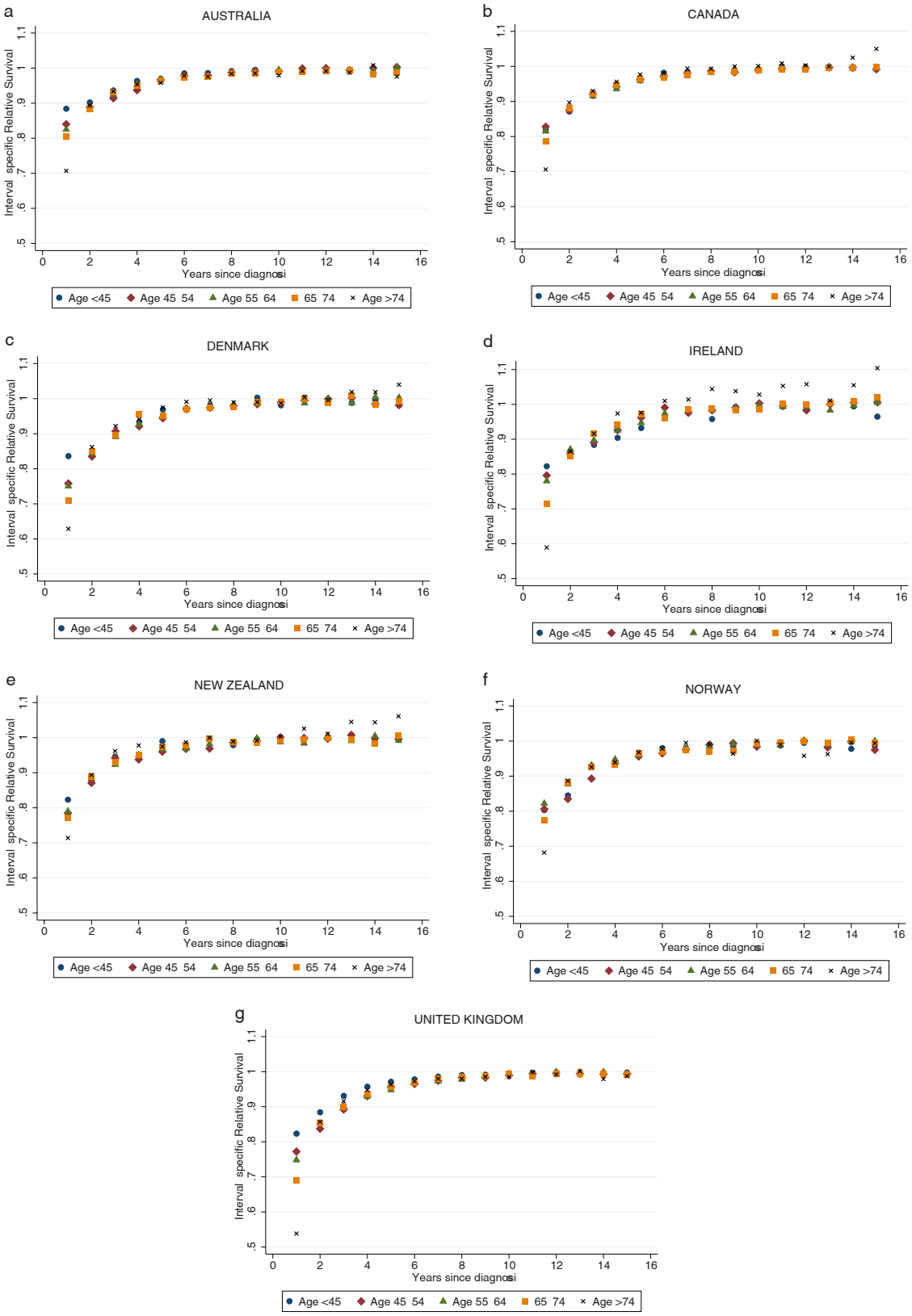


Fig. 1. a-g. Interval-specific relative survival over years since diagnosis and by age groups for colon cancer patients diagnosed 1995–1999 in a) Australia, b) Canada, c) Denmark, d) Ireland, e) New Zealand f) Norway and g) United Kingdom. (Australia includes New South Wales, Victoria, and Western Australia; Canada includes Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan; and the United Kingdom includes England, Northern Ireland, Scotland, and Wales).

Table 1
Interval-specific relative survival (IRS) with 95% confidence intervals (CI) at 1, 5, 10 and 15 years after diagnosis by age group and country* for colon cancer patients diagnosed in 1995–1999. The interval-specific relative survival is estimated in yearly intervals, and the number of individuals included in each interval (i.e., still at risk at start, after 4 years, after 9 years and after 14 years) are included in the table (N).

Country	Age group	1-year		5-year		10-year		15-year	
		N	IRS (CI)	N	IRS (CI)	N	IRS (CI)	N	IRS (CI)
Australia	< 45	1113	0.88 (0.86;0.90)	796	0.97 (0.95;0.98)	732	0.99 (0.98;1.00)	702	1.00 (0.99;1.00)
	45–54	2439	0.84 (0.82;0.85)	1539	0.97 (0.96;0.98)	1365	0.99 (0.98;1.00)	1299	1.00 (1.00;1.01)
	55–64	5331	0.82 (0.81;0.83)	3291	0.97 (0.96;0.97)	2775	1.00 (0.99;1.00)	2447	1.00 (0.99;1.01)
	65–74	9027	0.80 (0.79;0.81)	5138	0.97 (0.96;0.97)	3859	0.99 (0.98;1.00)	2816	0.99 (0.98;1.00)
	75 +	9655	0.71 (0.70;0.72)	3905	0.96 (0.95;0.97)	2025	0.98 (0.96;1.00)	904	0.98 (0.94;1.01)
Canada	< 45	1462	0.82 (0.80;0.84)	894	0.97 (0.95;0.98)	803	0.99 (0.98;1.00)	777	0.99 (0.98;1.00)
	45–54	3610	0.83 (0.82;0.84)	2237	0.96 (0.95;0.97)	1940	0.99 (0.98;0.99)	1819	0.99 (0.99;1.00)
	55–64	7706	0.81 (0.81;0.82)	4556	0.96 (0.95;0.97)	3772	0.99 (0.99;1.00)	3311	1.00 (0.99;1.00)
	65–74	13,566	0.79 (0.78;0.79)	7399	0.96 (0.96;0.97)	5437	0.99 (0.98;1.00)	4016	1.00 (0.99;1.01)
	75 +	17,022	0.71 (0.70;0.71)	6884	0.98 (0.97;0.99)	3743	1.00 (0.99;1.01)	1765	1.05 (1.03;1.07)
Denmark	< 45	254	0.84 (0.78;0.88)	150	0.97 (0.92;0.99)	134	0.98 (0.94;1.00)	126	0.98 (0.93;1.00)
	45–54	844	0.76 (0.73;0.79)	436	0.94 (0.92;0.96)	361	0.99 (0.97;1.00)	333	0.98 (0.96;1.00)
	55–64	1839	0.75 (0.73;0.77)	908	0.95 (0.93;0.97)	720	0.99 (0.97;1.00)	610	1.00 (0.99;1.01)
	65–74	3291	0.71 (0.69;0.73)	1475	0.95 (0.93;0.96)	1008	0.99 (0.97;1.01)	686	0.99 (0.97;1.01)
	75 +	4804	0.63 (0.61;0.64)	1482	0.97 (0.95;0.99)	687	0.99 (0.95;1.02)	266	1.04 (0.97;1.09)
Ireland	< 45	229	0.82 (0.77;0.87)	129	0.93 (0.87;0.96)	107	0.99 (0.94;1.00)	103	0.96 (0.90;0.99)
	45–54	511	0.80 (0.76;0.83)	283	0.96 (0.93;0.98)	249	1.00 (0.98;1.01)	236	1.01 (0.98;1.01)
	55–64	1169	0.78 (0.75;0.80)	627	0.95 (0.92;0.96)	510	1.00 (0.98;1.01)	439	1.01 (0.99;1.02)
	65–74	1965	0.72 (0.69;0.74)	899	0.97 (0.95;0.99)	641	0.99 (0.96;1.00)	466	1.02 (0.99;1.04)
	75 +	2170	0.59 (0.57;0.61)	646	0.98 (0.94;1.00)	355	1.03 (0.98;1.06)	170	1.10 (1.03;1.16)
New Zealand	< 45	275	0.82 (0.77;0.86)	177	0.99 (0.96;1.00)	165	0.99 (0.95;1.00)	160	1.00 (1.00;1.00)
	45–54	763	0.79 (0.75;0.81)	454	0.96 (0.94;0.98)	389	1.00 (0.99;1.01)	376	1.00 (0.98;1.00)
	55–64	1928	0.79 (0.77;0.81)	1132	0.97 (0.95;0.98)	955	0.99 (0.98;1.00)	844	0.99 (0.98;1.00)
	65–74	3050	0.77 (0.76;0.79)	1658	0.98 (0.96;0.99)	1275	0.99 (0.98;1.00)	925	1.01 (0.99;1.02)
	75 +	3111	0.71 (0.70;0.73)	1314	0.97 (0.95;0.99)	677	1.00 (0.97;1.03)	322	1.06 (1.01;1.10)
Norway	< 45	248	0.80 (0.75;0.85)	145	0.97 (0.92;0.99)	129	0.99 (0.94;1.00)	120	0.99 (0.94;1.00)
	45–54	675	0.81 (0.77;0.83)	374	0.96 (0.93;0.97)	323	0.98 (0.96;1.00)	296	0.98 (0.95;0.99)
	55–64	1450	0.82 (0.80;0.84)	886	0.96 (0.94;0.97)	735	0.99 (0.98;1.00)	644	1.00 (0.98;1.02)
	65–74	2972	0.77 (0.76;0.79)	1568	0.96 (0.95;0.98)	1110	0.99 (0.98;1.01)	806	1.00 (0.97;1.01)
	75 +	4631	0.68 (0.67;0.70)	1675	0.97 (0.95;0.99)	801	1.01 (0.97;1.03)	300	0.99 (0.93;1.05)
United Kingdom	< 45	3171	0.82 (0.81;0.84)	2043	0.97 (0.96;0.98)	1861	0.99 (0.99;1.00)	1800	1.00 (0.99;1.00)
	45–54	7815	0.77 (0.76;0.78)	4115	0.96 (0.95;0.96)	3459	0.99 (0.98;0.99)	3194	0.99 (0.99;1.00)
	55–64	18,966	0.75 (0.74;0.75)	9668	0.95 (0.94;0.95)	7648	0.99 (0.99;1.00)	6666	1.00 (0.99;1.00)
	65–74	36,862	0.69 (0.68;0.69)	16,052	0.96 (0.95;0.96)	11,348	0.99 (0.99;1.00)	7961	0.99 (0.99;1.00)
	75 +	51,940	0.54 (0.53;0.54)	14,206	0.96 (0.96;0.97)	6849	0.98 (0.97;0.99)	2883	0.99 (0.97;1.00)

* Australia includes New South Wales, Victoria, and Western Australia; Canada includes Alberta, British Columbia, Manitoba, New Brunswick, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan; and the United Kingdom includes England, Northern Ireland, Scotland, and Wales

original draft, Writing – review & editing. **Mark J Rutherford:** Methodology, Writing – review & editing. **Tor Åge Myklebust**: Methodology, Writing – review & editing. **Bjørn Møller**: Methodology, Writing – review & editing. **Melina Arnold**: Methodology, Writing – review & editing. **Isabelle Soerjomataram**: Methodology, Writing – review & editing. **Freddie Bray**: Methodology, Writing – review & editing. **Hazem Abd Elkader**: Writing – review & editing. **Gerda Engholm**: Writing – review & editing. **Dyfed Huws**: Writing – review & editing. **Alana Little**: Writing – review & editing. **Lorraine Shack**: Writing – review & editing. **Paul M Walsh**: Writing – review & editing. **Ryan R Woods**: Writing – review & editing. **D Maxwell Parkin**: Methodology, Writing – review & editing. **Paul C Lambert**: Methodology, Writing – review & editing.

Acknowledgements

The ICBP-SurvMArk-2 project and its data collection were supported by the International Cancer Benchmarking Partnership. The authors would also like to thank Cancer Research UK for managing the programme and the ICBP Programme Board for their oversight and direction.

Authors' contributions

Conception and design: TMLA, MR, TÅM, BM, PCL, Development of methodology: TMLA, MR, TÅM, BM, PCL, MA, IS, FB, MP, Analysis of data: TMLA, Writing, review and/or revision of paper: All authors.

Conflict of interest

The authors declare no competing interests.

Author statement

Where authors are identified as personnel of the International Agency for Research on Cancer/WHO, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/WHO.

References

[1] X.Q. Yu, R. De Angelis, T.M. Andersson, P.C. Lambert, D.L. O'Connell, P. W. Dickman, Estimating the proportion cured of cancer: some practical advice for users, Cancer Epidemiol. 37 (6) (2013) 836–842.

[2] S. Eloranta, P.C. Lambert, N. Cavalli-Bjorkman, T.M. Andersson, B. Glimelius, P. W. Dickman, Does socioeconomic status influence the prospect of cure from colon cancer–a population-based study in Sweden 1965-2000, Eur. J. Cancer 46 (16) (2010) 2965–2972.

[3] C.J. Cabasag, J. Butler, M. Arnold, M. Rutherford, A. Bardot, J. Ferlay, E. Morgan, B. Møller, A. Gavin, C.H. Norell, S. Harrison, N. Saint-Jacques, M. Eden, B. Rous, A. Nordin, L. Hanna, J. Kwon, P.A. Cohen, A.D. Altman, L. Shack, S. Kozie, G. Engholm, P. De, P. Sykes, G. Porter, S. Ferguson, P. Walsh, R. Trevithick, H. Tervonen, D. O'Connell, F. Bray, I. Soerjomataram, Exploring variations in ovarian cancer survival by age and stage (ICBP SurvMark-2): a population-based study, Gynecol. Oncol. 157 (1) (2020), 234-44.

[4] M. Araghi, M. Arnold, M.J. Rutherford, M.G. Guren, C.J. Cabasag, A. Bardot, J. Ferlay, H. Tervonen, L. Shack, R.R. Woods, N. Saint-Jacques, P. De, C. McClure, G. Engholm, A.T. Gavin, E. Morgan, P.M. Walsh, C. Jackson, G. Porter, B. Møller, O. Bucher, M. Eden, D.L. O'Connell, F. Bray, I. Soerjomataram, Colon and rectal cancer survival in seven high-income countries 2010-2014: variation by age and stage at diagnosis (the ICBP SURVMARK-2 project), Gut 70 (2020) 114–126.

[5] E. Morgan, I. Soerjomataram, A.T. Gavin, M.J. Rutherford, P. Gatenby, A. Bardot, J. Ferlay, O. Bucher, P. De, G. Engholm, C. Jackson, S. Kozie, A. Little, B. Møller, L. Shack, H. Tervonen, V. Thursfield, S. Vernon, P.M. Walsh, R.R. Woods, C. Finley, N. Merrett, D.L. O'Connell, J.V. Reynolds, F. Bray, M. Arnold, International trends in oesophageal cancer survival by histological subtype between 1995 and 2014, Gut 70 (2020) 234–242.

[6] S. Pilleron, H. Charvat, M. Araghi, M. Arnold, M.M. Fidler-Benaoudia, A. Bardot, et al., Age disparities in stage-specific colon cancer survival across seven countries: an ICBP SURVMARK-2 population-based study, Int. J. Cancer (2020).

[7] M. Arnold, M.J. Rutherford, A. Bardot, J. Ferlay, T.M. Andersson, T.Å. Myklebust, H. Tervonen, V. Thursfield, D. Ransom, L. Shack, R.R. Woods, D. Turner, S. Leonfellner, S. Ryan, N. Saint-Jacques, P. De, C. McClure, A.V. Ramanakumar, H. Stuart-Panko, G. Engholm, P.M. Walsh, C. Jackson, S. Vernon, E. Morgan, A. Gavin, D.S. Morrison, D.W. Huws, G. Porter, J. Butler, H. Bryant, D.C. Currow, S. Hiom, D.M. Parkin, P. Sasieni, P.C. Lambert, B. Møller, I. Soerjomataram, F. Bray, Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study, Lancet Oncol. 20 (11) (2019), 1493-505.

[8] P.W. Dickman, E. Coviello, Estimating and modeling relative survival, Stata J. 15 (1) (2015) 186–215.

[9] P.C. Lambert, P.W. Dickman, P. Osterlund, T. Andersson, R. Sankila, B. Glimelius, Temporal trends in the proportion cured for cancer of the colon and rectum: a population-based study using data from the finnish cancer registry, Int. J. Cancer 121 (9) (2007) 2052–2059.

[10] T.M. Andersson, H. Eriksson, J. Hansson, E. Månsson-Brahme, P.W. Dickman, S. Eloranta, M. Lambe, P.C. Lambert, Estimating the cure proportion of malignant melanoma, an alternative approach to assess long term survival: a population-based study, Cancer Epidemiol. 38 (1) (2014) 93–99.