JOINT ACTION ON RARE CANCERS

WP4. Deliverable 4.4

Recommendations for the standardized estimation of rare cancers indicators at the European and country level

Co-funded by
the Health Programme
of the European Union

"This Deliverable is a part of the joint action "724161/JARC" which has received funding from the European Union's Health Programme (2014-2020)".

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1. Description

1.1 The Joint Action on Rare Cancers

The Joint Action on Rare Cancers (JARC) is aimed to integrate and maximize efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers.

The public health challenges posed by rare cancers include the limited professional expertise in the community, the difficulties in clinical research, the need of a timely and appropriate diagnosis and optimal treatment from the very beginning of the patient's journey. An accurate clinical, pathologic and biological assessment of the disease of the individual patient is key to survival and cure, as well as an expert clinical decision provided by a multidisciplinary team. To this end, proper referral of patients and effective clinical networking are crucial in rare cancers. This is the main reason why JARC decided to shape its efforts around the new European Reference Networks (ERNs) with the following objectives:

1. Improving epidemiological surveillance of rare cancers in the EU
2. Identifying standards of care for all families of rare cancers to ensure sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking
3. Improving the implementation at local level and within ERNs of clinical practice guidelines on rare cancers
4. Promoting integration of translational research innovations into rare cancer care
5. Improving education on rare cancers for medical and non-medical experts to ameliorate management of rare cancers and to improve rare cancer patients' empowerment in the EU
6. Identifying core strategies to incorporate in National cancer plans and Rare disease plans to address the specific needs of rare cancers across EU MSs

The JARC is structured in 10 work packages (WPs). Three cross cutting WPs (WP1 coordination, WP2 dissemination, WP3 evaluation) and 7 specific WPs based on the JARC objectives: WP4 epidemiology, WP5 quality of care, WP6 clinical practice guidelines, WP7 innovation and access to innovation, WP8 medical education, WP9 childhood cancers and, WP10 rare cancers policy. Patients work across all work packages, driving the JARC efforts along the needs of the only end users of all what we can do, in care and research as well.

1.2 Work Package 4 - Epidemiology

WP4 is aimed at improving data and information on rare cancer in Europe with the final objective to contribute to strengthen their epidemiological surveillance and to evaluate the impact of ERN on the care of rare cancer patients. Tasks of WP4 are: to revise, agree, and support the operational definition and the list of rare cancers; too develop recommendations to improve the quality of rare-cancer registration; to define recommendations for the standardized estimation of rare cancers indicators; to propose a model to evaluate the impact of ERNs using population-based CRs.

1.3 Aim and purpose of deliverable 4.4

Estimating epidemiological indicators of incidence, survival and prevalence for rare cancers may be challenging, particularly for the exceptionally rare entities and in countries with small population size. In these cases, the difficult alternative often arises between estimates directly based on very unstable empirical data and those derived from modelling approaches, inherently less intuitive, more complex, and to some extent dependent on subjective choices. On the basis of literature review and of the data provided by RARECAREnet, aims of this task are to discuss the major issues related to cancer burden estimates for rare cancers and to provide methodological recommendation on the most suitable methods, including classical, Bayesian and model based approaches. The final purpose of this task is to ensure a standardization of the way epidemiological indicators which will be provided at EU and country level.

1.4 The target group of the specific deliverable

Epidemiologists and statisticians involved in research and surveillance of rare cancers

1.5 Summary of the main conclusions of the deliverable

Data are assumed to be validated, complete and correctly coded, and only estimation problems due to, or enhanced by, the small number of events are considered. All available data on rare cancers are valuable and must be published, even if they present a high sampling variability. They should be provided with a correct measure of their variability, mainly in the form of true coverage 95% confidence intervals.

Incidence rates are reliable also for rare cancers. We suggest using the exact Poisson intervals for calculating corresponding confidence intervals. For very few (or even zero) observed cases, use Bayesian estimates when a reliable a priori is available. In incidence comparisons, age standardization of very low rates is more conveniently done by indirectly Standardized Incidence Ratios (SIR). Modelling, in particular under Bayesian approach, is also useful in geographical or multivariate comparisons. Clear model specification and sensitivity analysis of the assumptions are required.

Cancer mortality data do not report morphology, by which most rare cancers are classified. Use cancer registries data to adjust rare cancers mortality rates by morphological characteristics or, if this is not possible, apply incidence-based mortality methods or incidence-survival modelling to estimate rare cancers mortality.

Net or relative survival are the most used population-based survival measures , but their statistical properties and performance in the rare cancer settings has been not yet sufficiently studied. Cases diagnosed in several years can be aggregated to strengthen the survival estimates, in the absence of strong time trends in survival. Efficient estimates of prognostic factors for rare cancers can be obtained by excess hazard modelling. Modelling is the only available way in a multivariable situation. A wide variety of models are available to this task and are referred to by the Report. Prevalence is directly available only using data from long standing cancer registries. It can be also estimated from incidence and survival, so considering all the related suggestions and cautions.

Lack of studies on the applicability of the standard statistical methods to the estimation of population-based indicators specific for rare cancers has been remarked, particularly for survival studies. There is need of further research to define the absolute thresholds, numbers-wise, below which the standard methods should not be applied.

2. Introduction

Aim of this document is to review the existing methods for the analysis of rare cancers as a support for surveillance and research activities. In particular for those related to the development of national cancer plans of the European Reference networks of rare cancers. Rare cancers are defined, according to the RARECARE and RARECAREnet definition, as those with incidence rate lower than 6 per 100,000 person/years. The topics are restricted to the estimation of population-based epidemiological estimators: incidence, mortality, survival and prevalence. If not otherwise stated, it is implicitly assumed that data will be those provided by cancer registries.

High quality of data is a pre-requisite for meaningful statistical analysis. Particularly for rare cancers, changes in coding or new diagnostic technologies which allow emerging previously undetected cases may have a relevant effect on incidence, survival and prevalence point estimation, and a huge impact on trends. Discussing the quality of CR data is the specific object of JARC task 4.2, is not under the aims of this report, and will be only marginally considered. We assume analyses to be carried out only on validated, complete and correctly coded data, and we consider estimation problems due to, or enhanced by, the small number of events. Throughout the text we outline synthetic recommendations with bullet points.

3. Material and method

The report has been made by review of the available literature and by discussion within a Working Group of statistician, epidemiologists involved in cancer registries and medical doctors expert in public health research. Le list of participant is in Annex. Method of work: literature review, expert discussion. Steps of the work were:

- Experts were identified within and outside the JA and invited on May 2017 to participate, joining the Working Group
- Expert who agreed were asked to indicate 2 or 3 relevant papers on the topics in discussion
- A first preliminary document based on our experience and on the papers was prepared and circulated on December 2017 for comments
- The preliminary document was then updated by mail circulation and versions 2 and 3 prepared on February and April 2018.
- A meeting of the WG was convened on 5 and 6 June 2018 in Milan to discuss all together the general layout and the details of the Report
- A final version was circulated in September 2018, and last remarks considered.

4. Incidence

4.1 Definitions

Basic methodology for the estimation of population-based cancer incidence rates is described by Estève et al (1994). The main indicator is the incidence rate. It is a fraction whose numerator is the number of incident cases observed in a given population (usually

characterized by age class, sex, and sometimes by other demographic characteristics such occupation or socioeconomic status) during a given period (usually one year), while the denominator is the corresponding population time at risk. International rules include in the numerator also cases known only from the death certificate (DCO) and multiple tumours. Population time at risk is usually taken from national statistics. It is estimated by the mid-year population, assuming that every person contributes a full year. Rates are often expressed as number of cases/100,000 person years. Direct age-standardised rates (ASR) are computed by a weighted sum of age-specific rates. Indirect Standardized Incidence Ratio (SIR) is defined (Breslow and Day, 1994; Estève et al, 1992) as the ratio between the number of observed cases in the observed area and those expected under the age-specific incidence rates in a reference region. The incidence estimators are the same for common and rare cancers, but reliability of direct estimates from observed data is decreased by low number of cases.

4.2 Incidence completeness

The completeness of registration is directly reflected on incidence estimates. DCO cases are not available for the majority of solid rare cancers, defined on the basis of both site of origin (topography) and histological type (morphology). The latter is not included in mortality records, apart from some rare cancers groups (haematological malignancies, mesotheliomas, skin melanomas). This leads to an underestimation in areas and cancer sites where DCO proportion is high. Another, often more important, source of incidence underestimation is given by cases with unspecified morphology, that hampers their attribution to a specific rare cancer group. A preliminary analysis of topography vs. morphology distribution in the considered database is needed to put in evidence possible lack of completeness problems.

- Look for possible incidence underestimation due to NOS morphology cases or to DCO.

4.3 Incidence estimation in a single population

Incidence rate indicator gives unbiased point estimates of the risk of getting cancer but, in the case of rare events, it is highly subjected to random variation. Confidence intervals, that are usually very small in population based statistics on common cancers, become necessary in rare cancers statistics. The way to calculate standard errors of incidence rates and corresponding confidence intervals with correct coverage but as narrow as possible is therefore relevant. The most popular method for common cancers is the asymptotic normal approximation (Wald confidence intervals). This method has however a lower than the nominal coverage for low counts, say below 70 (Geert Silversmit, personal communication). Low counts conservative confidence intervals that give at least the nominal coverage can be calculated from quantiles of the Poisson distribution [Estève et al, 1994, pag. 63-64; Barker, 2002]. In the latter, the properties of several different confidence intervals when the expected number of events is ≤5 are discussed. The exact Poisson integer confidence limits is the most convenient solution for obtaining a correct coverage. Since these are not in closed form, the χ^2 approximation to the Poisson distribution is often applied, yielding non-integer lower and upper limits.

- Always provide confidence intervals of incidence rates, and calculate them by the exact Poisson method for incidence estimates with less than 70 observed cases

Bayesian methods can be conveniently used for estimating rare cancers incidence when there is a reasonable external belief on their expected levels. In this line, information

from previous studies such as incidence estimates from very large populations or from knowledge provided by experts can be easily incorporated through an informative prior distribution.

A special situation arises when no diagnoses with a specific rare cancer are observed during the considered study period, and the classical estimator of incidence rate is consequently zero. However, there is no reason to believe that the population is not at all at risk for that cancer, and a small but non-zero underlying incidence rate is likely to exist. The frequentist approach leads to a point estimate of zero and to the so called rule of three (Chen and McGee, 2008), i.e. to an approximate 95% confidence interval (0-3) for the numerator of the incidence rate. A Bayesian approach can provide more meaningful incidence and confidence interval estimates, if valid a priori knowledge can be included in the estimation (Winkler et al 2002, Botta et al 2018). Chen and McGee discuss consistent and reasonable Bayesian estimates for the zero-observed situation considering a range of different a priori distributions.

- Consider a 95% confidence intervals (0-3) for the estimated cases when the number of observed cases is zero and no other information exists; use Bayesian estimates when a reliable a priori is available

4.4 Comparisons of rare cancers incidence across areas (or population groups)

In statistical comparisons of rare cancers incidence between countries, simple confidence intervals around single estimates might be prone to case-mix confounding. Age standardization is therefore needed to avoid spurious differences due to different age distributions among the considered populations. Direct age-standardised rate (ASR) can be computed as usual by a weighted sum of age-specific incidence rates. As the ASR is the sum of independent random variables, it reaches a normal distribution for large enough counts. This “large enough” will also depend on how the counts are distributed over the age groups. Criteria to construct reliable confidence intervals using the normal approximation would be useful. As an indirect method of age standardization, standardized incidence rates (SIR) are frequently used for small geographical areas because the numbers are too small in each area to apply direct standardization, but there is sufficient numbers overall for the ‘reference’ set of age-specific rates. The disadvantage of SIR is that, as a relative measure, they are not informative about the absolute frequency of the disease. SIR estimates assume independence between age effects and area effects. Their exact confidence intervals are calculated from the chi-squared distribution (Sahai and Khurshid, 1993).

- Consider age-specific or indirect age-standardized rates in rare cancers incidence comparisons

The calculation of SIR can be of course generalized to multivariable stratification (for instance considering sex or time period in addition to age) if the total number of cases is sufficiently large. We will consider below a possible threshold value for “sufficiently large”. When the number of cases is low, random effects modelling is a more efficient way to estimate incidence variation adjusted by confounding variables. Geographical analysis of sparse events including random effects, specifically for small area incidence estimation, has been increasingly addressed by means of Bayesian approaches (see, among others, Mollié 1999, Leyland and Davies 2005, Blangiardo 2013). The Bayesian approach allows for smoothing SIRs based on unreliable data towards an overall mean SIR, but keeping SIR values closer to the original when based on large populations. In other words, incidence rates estimated from large areas tend to be closer to the empirically observed ones, while those from small areas will be closer to the prior mean value.

A study specifically addressing incidence estimation of rare cancers in European

countries under a fully Bayesian approach (Botta et al, 2018) used a Poisson event distribution with a priori mean expected under the European average incidence rates and with a country-specific set of parameters without special structure. The two example applications on estimated incidence rates for a rare cancer (adenocarcinoma of trachea) and a common cancer (adenocarcinoma of colon) show two extreme examples in which the chosen prior influenced, respectively, very much and very little the final estimates. The same paper reports the empirical finding that classical and Bayesian estimates never differ by more than 10% if the number of expected cases is greater than 150. A large variety of models and methods have been proposed under the Bayesian methodology, depending from the model specification, the way the prior distribution is provided, the estimation method, and also the software used. A review of the extensive literature on Bayesian methods for geographical comparisons of rates is outside the scope of this document. This variety of possible approaches has the advantage of a high flexibility to the specific applications at the cost of being the result of subjective choices, often due to personal experience, availability of computer software, or limitations of computational time. It should be also considered that interpretation of Bayesian estimates is different from the frequentist ones and credible intervals have not the same meaning than the confidence interval. Bayesian methods are in most cases computationally heavy. Several methods and computer software are however available to this aim. See for example: Lunn et al, 2009; Brooks et al, 2011; Rue et al, 2009; Blangiardo et at, 2013.

- Bayesian estimates could be used, even with all the needed cautions, for areas with less than 150 cases expected from the overall incidence rates.

As previously outlined, rare cancers incidence estimation is conceptually similar to small area estimation, since both have to face the statistical problem of sparse event counts. However, some differences can arise. It is biologically plausible that, for many cancers, areas close to each other have (known or unknown) risk factors more similar than distant ones. Then, assuming a spatial structure often leads to more precise and accurate estimates. The same does not necessarily holds when studying rare cancers across large geographical units. Spatial structure is less likely to be relevant among large areas, such as neighbour countries, and not always can be used to strengthen estimates. In order to choose between a model accounting for spatial structure and another with independence of SIR, (Besag, York and Mollié, 1991), proposed a model allowing to test if SIR are spatially independent or, in alternative, if their extra variability can be attributed only to pure spatial dependence.

- Sensitivity analysis could be carried out to test the existence of spatial structure in rare cancers geographical analysis.

4.5 Time trends

Series of age-standardized, or age-specific, incidence rates estimated in different time periods are commonly used as input data for the analysis of time trends. Accounting for age is necessary because the population age structure is continuously changing worldwide. A popular trend indicator is the Annual Percent Change (APC), that gives a good summary measure of time variability if (age-standardized) incidence rates present a linear pattern over all the considered period or a log-linear one. The former occurs when rates change by a fixed *amount* each year. The log-linear trends is the most appropriate model when rates are supposed to vary by a fixed *proportion*. Both are strong assumptions, and more complex patterns can be decomposed into a series of connected broken lines, and a APC is calculated for each line segment. In this respect, the joinpoint method (Kim et al 2000) and the corresponding software (https://surveillance.cancer.gov/joinpoint/) are available, allowing to estimate both the

turning points (knots) and the corresponding APCs between each pair of them. When the standard errors of rates are not uniform across periods, weighted regression (also available under Joinpoint software) is desirable. Joinpoint analyses may produce appreciable differences according to period examined and number of knots selected. This may have a large impact on rare tumours. Careful data inspection and possibly also sensitivity analysis to different choices of these parameters are suggested.

- Annual Percent Change (APC) is a simple indicator of time trend, when this is linear in the natural or in the log scale.
- Joinpoint analysis, when validated by sensitivity analysis, provides well interpretable results in terms of a series of APCs.

Incidence trends can be also assessed directly from the raw data with Poisson modelling of logarithm of incident cases against time, with log of person-years at risk as constant, and possibly including age and other adjustment factors as covariates. Modelling approach is particularly useful when other covariates have to be included, and their association with incidence changes evaluated. In general, incidence rates change gradually over time within a same country. This means that, unless of some breakthrough change occurred in diagnosis or registration practices, rates in subsequent years are expected to be strongly correlated each other, thus posing less problems than modelling rates across countries, where the real effects may be quite different between countries. Bayesian approach can be applied also in the analysis of time trends (Cleries et al 2010, 2013). Moreover, the Bayesian approach to time trends allows for estimating probability measures for any model parameter, for example the probability that an APC surpass certain threshold percentage. The use of Bayesian models in time trend analysis is not in principle different from the case of geographical analysis, and the same considerations apply on model specification, priors definition, computational methods, interpretation of results. Autocorrelation of rates with respect to time should be considered, since it is very plausible and frequently found in empirical data.

- Modelling, including Bayesian approach and time autocorrelation of underlying rates, is an alternative efficient approach for estimating trends in terms of covariates.

5 Mortality

Mortality is an important indicator of cancer impact, and the most used one to compare the burden of different diseases worldwide. Mortality data are usually obtained from official death certificates. Cause of death is classified by International Classification of Diseases, mostly from its 10th revision (ICD-10), and therefore mortality data are unfortunately unsuited for the analysis of many rare cancers, simultaneously classified according to ICDO-3 topography and morphology. When the two classifications are partially overlapping (as for epithelial tumours of a give site), the bias due to using only ICD classification could be assessed by calculating mortality/incidence ratio from data provided by cancer registries, that usually classify incident cases by both ICD and ICDO. When ICD classification cannot be used (as for instance for neuroendocrine tumours), it is possible to link cause of death data with other cancer registry data and apply incidence-based mortality methods (Chu et al 1994). This however requires a long series of incidence data. Another alternative way is modelling mortality (and prevalence) via incidence and survival by the MIAMOD method and software (Verdecchia et al 1989, 2002).

- Use cancer registries data to adjust ICD-based mortality rates by morphological characteristics or, if this is not possible, apply incidence-based mortality methods or incidence-survival modelling to estimate rare cancers mortality.

When the number of deaths for a specific cancer can be known or estimated, the indicators, methods of analysis and problems are the same as for incidence.

6 Survival

6.5 Survival indicators

Three main survival measures are used in survival analysis: observed, cause-specific, and net survival. Observed survival (i.e. survival from all causes of death) can be used as a measure of cancer related survival only if mortality from other causes of death is negligible, as for childhood cancers, or it is controlled for, as in randomized clinical trials.

Cause-specific survival (i.e. only deaths for the disease of interest are considered as response, while the other are treated as censoring events) is directly calculated from cause of death information and is a standard end-point in clinical studies, where cause of death can be reliably determined. It is much more problematic for cancer registries, where cause of death (whose standard definition remains crucial) is sometimes not known, or not reliable, underwent changed in coding or finally, when death is not easily and unambiguously attributable to the cancer in study or to competing causes. These problems are particularly present for rare cancers, due to lack of information on morphology in death records.

In population-based studies, relative survival ratio or net survival are the indicators of choice in rare cancers survival analysis. They are provided respectively by the Ederer-2 (E2) and Pohar-Perme (PP) estimators. Both of them only need the knowledge of general population mortality data for all causes combined, and slightly differ in their interpretation. Relative survival is the ratio between observed survival and expected survival of a demographically comparable group of the general population. It is an estimator of cause-specific survival, under the reasonable assumption that, in the absence of cancer, patients would have the same mortality of the general population. Net survival indicator gives the hypothetical survival in the theoretical situation in which only the considered cancer were acting as possible cause of death. Net survival also removes the bias due to the early censoring of high risk patients (typically the oldest ones) due to causes other than cancer, and is therefore the reference indicator in comparison studies.

Whatever the chosen survival estimator, its desirable properties are to be unbiased with respect to the addressed measure, to have as small standard error as possible, and to be robust, thus meaning that the confidence interval is correct even when the underlying (normal, Poisson, etc) assumption is not exactly true. For a systematic comparisons between properties and performance of E2 and PP indicators, we refer to published works (Ederer and Heise, 1959; Pohar et al, 2011; Danieli et al, 2012; Roche et al, 2012, Seppä et al, 2015 and 2016), that however are generally addressing common cancers. In most cases, differences in estimated 5-year survival are not higher that 1-2 percent points.

- Choose a survival indicator mainly according to its meaning and consistency with the study purpose. As outlined below, their performance in rare cancers situation is largely unknown.

6.2 Survival analysis for rare cancers

Stability of estimates depends on the number of patients at diagnosis, on their subsequent hazard rates, and on the length of follow-up. Providing reliable survival estimates for rare cancers is challenging, however this should not prevent their publication, once a correct measure of the related random variability could be provided. Unfortunately,

no systematic study relating survival estimators' properties to the number of cases (or to the number of deaths) has been specifically carried out on rare cancers. A methodological study on survival estimated for English Cancer Networks (Ellis et al, 2007) found fairly stable 5-year survival estimates for breast cancer (242 incident cases per year on average) and substantial random fluctuations for colon cancer (about 122 cases per year), so suggesting two-year aggregation for current reporting. They show that aggregating several years of diagnosis (such as 3- or 5-years cohorts) is in most cases convenient and safe. Annual number of cases diagnosed with most rare cancers is far below these figures, even when analysed at a wider geographical level. Methodological studies on the robustness of relative or net survival standard errors and on the coverage of the related confidence interval have been carried, to our knowledge, only for common cancers (Seppä et al, 2016) or for large samples in simulation studies (Danieli et al, 2012).

- Aggregate cases diagnosed in several years of diagnosis, in the absence of strong time trends in survival

6.3 Survival by regions or patients groups

Often survival comparisons between different regions or patient groups, instead of single point estimates of survival, is the main objective of the analysis. In principle, they can be carried out by the usual statistician armamentarium, through standard errors of survival estimates, confidence intervals or the logrank test (see Graffeo et al, 2016), the latter to compare the entire distribution instead of survival at given time points. Correct comparisons of survival estimates depends of course on the validity of corresponding standard errors or confidence intervals that, as outlined before, is not well known in the case of rare cancers.

Standardization by age at diagnosis is opportune. Direct standardization is the most popular method in population-based survival studies, but stratification by age and population often breaks down if cases in analysis are few because lack of cases in one or more age classes precludes the calculation. Interpretation of multiple stratified survival rates becomes difficult and direct standardization unfeasible. Alternative methods can be used, based on flexible age class definition (Gondos et al 2006) or on indirect methods with "internal" weighting (Brenner et al 2014; Sasieni and Brentnall 2016).

- Adjustment by age at diagnosis can be done, with decreasing number of cases, by direct standardization, indirect standardization, or modelling.

A modelling approach based on biologically plausible assumptions (such as, for example, the continuity of the variable-survival relationship) will in general strongly reduce the number of quantities to be estimated (the model parameters) and will give a more parsimonious and interpretable representation of the data. The majority of excess hazard models, the counterpart of the net survival, are based on the additive assumption that the patients' death hazard is the sum of a background hazard, taken from the general population statistics, and the excess hazard due to the cancer in study. The latter is usually modelled through a piecewise constant or a continuous excess hazard function of time from diagnosis combined with a linear function of covariates. A wide variety of survival models have been used, for which we refer to the related literature. They include additive and multiplicative models (Buckley, 1984), discrete, continuous and flexible models (Hakulinen and Tenkanen 1987, Giorgi et al. 2003, Dickman et al 2004, Nelson et al 2007, Remontet et al, 2007), cure models (De Angelis et al 1999, Lambert et al 2007, Yu et al 2013), multilevel and random effect models (Dasgupta et al, 2014). Bayesian survival models have been used as a tool to allow geographical comparisons of survival after removing random effects variability, and either neglecting or including (Farley et al, 2008; Cramb et al, 2016; Cleries et al 2016) spatial autocorrelation of survival between

neighbouring areas.

- Efficient estimates of prognostic factors for rare cancers can be obtained by excess hazard modelling. A wide variety of models are available to this task.

A funnel plot method (Spiegelalter, 2005a, Quaresma 2011) could be a sounder way to compare estimates from different countries than simply estimating confidence intervals around each estimate and seeing whether estimates are over-lapping or not. Funnel plot mothod postulates that there is an average for all the countries, and examines if there are 'outliers' from this mean (rather than comparing countries bilaterally), accounting for the different precision of the estimates (fixed effects model). When there is over-dispersion, i.e. more variation in the funnel plot than expected with the fixed effects model, a refinement of this method (Spiegelhalter, 2005a) is to use a random effects model, which assumes that every country has its own survival and the standard error of an estimate made of two components: a natural variation of baseline survival between countries (random effects), due to unknown variation in prognostic factors, and a within country sampling variation depending on sample size. The aggregation of several years will only affect the within country variation, not the between country variation, and so there is a upper threshold to what aggregation can do. To reduce the between countries variation, greater standardisation by survival drivers (stage, performance status) may be required. This could suggest the cancer registry to make a greater effort to collect prognostic information for rare cancers.

6.4 Survival trends

Comparing survival point estimates of different incidence years among each is affected by age at diagnosis distribution. This varies within and across areas, due not only to changing age distribution of the population, but also to health care related factors, as screening, diagnostic intensity, heath assurance regimen. Then, standardisation to the same age distribution is desirable when comparing survival among different incidence years/periods to filter out the time trend. When this is possible, the use of APC indicator for linear trends and the Joinpoint method for non-linear ones can be carried out, similarly to the analysis of incidence trends. Standardisation to more factors (gender, stage) could be also needed. For rare cancers, age or multivariable standardization might be difficult: due to the low number of cases some strata might have no observations and the standardisation breaks down. Modelling might bring us further, adding period of incidence as a covariate in a survival regression model. Flexible parametric modelling (Nelson et al, 2007, Uhry et al, 2017) might include spline functions to capture time trends. Important factors influencing survival (age at diagnosis, sex, stage, etc.) can be included in the model to take differences in case mix into account.

- Excess hazard modelling is a convenient way also to estimate survival trends
- Annual Percent Change (APC) indicator, applied to age-standardized survival, can be used as an alternative way to present rare cancers survival trends without modelling

6.5 Non-parametric point estimates and modelling.

The non-parametric approach to the estimation of survival, as provided for example by E2 and PP estimators is simple, does not require specific assumptions, and is therefore objective and comparable across studies. Non-parametric approach should still be the preferred way to provide current and comparable statistics, provided that the patients group is large enough to be stratified into homogeneous subgroups. In principle, this approach becomes less and less applicable with decreasing incidence of the cancer and decreasing size of the population. However, to what extent such limitation becomes relevant in connection with data sparseness has not been sufficiently investigated.

The modelling approach allows to draw inference from sparse data with greater efficiency, but needs the specification of the different model components (hazard functional form, covariates definition, link between hazard and covariate functions, distributional assumption, etc.). All these choices are up to the free investigator evaluation, and depend on research aims and investigator's skill and also subjective preferences. Efficiency with modelling would greatly benefit from the availability of a transparent fixed analytic protocol, applicable to and robust for the analysis of rare cancers. Sensitivity analysis might find that basic results are largely insensitive to 'choices' which are debatable refinements. Good model could predict standardised survival estimates directly by averaging model based survival estimates over a fixed covariates distribution.

- Reduce as much as possible subjective choices (for example, by using simple models, non-informative priors.
- Sensitivity analysis should be carried out in the lack of evidence in favour of a single among different alternative models, to test how much results depend from the particular assumptions made.

7 Prevalence

Prevalence measures the number of persons alive in a population with a past diagnosis of cancers. For rare as well as for common tumours, it is an indicator of health care needs of survivors. Specifically for rare tumours, prevalence drives the definition of orphan diseases and orphan drugs.

Prevalence is measured from cancer registry data by counting the number of past diagnosed persons still alive at a given time, the prevalence index date. Incidence series are seldom sufficiently long to provide a complete measure of prevalence. In Europe, only the Nordic countries and Slovenia registries have 50 years or more of registration, so assuring a sufficiently complete estimate (Engholm 2010). The comparability of cancer definition throughout such a long period is however uncertain, particularly for rare cancers defined by ICD-O-3 classifications that have encompassed many revisions in the last years.

Limited duration prevalence can be estimated including in the count only persons diagnosed within a given period (e.g. 5 years, 10 years, 15 years …) prior to the prevalence date. Complete prevalence can be estimated from limited duration prevalence by a regression model with log-link function (Maddams et al, 2009), or by a model-based adjustment factor (completeness index) dependent by age, sex and cancer (Capocaccia et al 1997, Merrill et al 2000). The latter adjustment can be done by a SEER*Stat compatible software COMPREV (SRP-NCI 2009). Estimation of standard errors and confidence intervals for limited duration prevalence are described by Clegg et al (2002), showing a good performance also in two rare cancers. A method for calculation of complete prevalence confidence intervals is described in Gigli et al (2006).

In alternative, complete prevalence can be entirely estimated from incidence and survival functions, modelled across the available data series and extrapolated in the past to a sufficiently long period (Verdecchia et al 2002, Guzzinati et al 2018, Colonna et 2015). It should be considered that modelization of incidence rates for the extrapolation of values before the observation period may have an huge impact on the prevalence estimates.

For most cancers, the number of prevalent cases alive at a given date is higher (usually from five- to ten-fold higher) than the number of incident cases observed in one year. Therefore, the usual method used for the comparing prevalence of common cancer across populations or population groups are frequently applicable also to the prevalence of rare cancers. However, also prevalence figures can be sparse, particularly for rare lethal

cancers. In this case, the same methods considered for rare cancers incidence estimation can be applied (Martuzzi and Elliott, 1996).

8 Estimation for areas without cancer registration

The easiest method used to estimate incidence rates in a single area without cancer registration is to apply the age-specific rates of neighbouring regions to the target area population. The dimension of the reference region could be chosen according to the cancer: the lower the incidence rates, the wider the region. A more refined approach might consider testing a possible geographical structure of the incidence rates. In this case age-specific rates in the area will be estimated by a weighted average of the neighbouring areas with registry data available (Antoni et al 2016). In some other cases an ecological regression models in terms of known risk factors (e.g. smoking, nutrition, deprivation) or of possible proxy variables (such as mortality for related cancer sites, or gross domestic product) can be fitted to the neighbouring areas and projected to the target one. Both frequentist (Belot et al, 2008) and Bayesian models (Schmid et al, 2004) can be used.

Survival and prevalence estimation might follow the same approaches. Survival has been shown to be highly correlated to economy- social- or health care system-related variables (Woods et al 2006, Quaglia et al 2013). Modelling approaches have been proposed that use the relationships between incidence and mortality (Clèries et al 2012) in a certain area to estimate cancer incidence in an area without cancer registration but having information about cancer mortality, or incidence, prevalence and survival (Mariotto et al 2002) to estimate one of these indicators from the knowledge of the other two. They have been only applied to common cancers, however they use parsimonious parametric representations of the corresponding functions that are in principle suitable also for the analysis of rare tumours.

- Estimating rare cancers incidence and prevalence for areas without registration is to a large extent a guessing exercise, that might be useful (with cautions) for planning purposes or for the design of clinical studies, but not for studying causal relationships.
- Survival projections have to be always presented as such with extreme transparency and caution. Survival is usually taken as an outcome evaluator, and clear definition of methods used are necessary to a correct dissemination of cancer survival projections to clinicians and patients.

9 Topics for research

Studies are lacking on the applicability of the standard statistical methods to the estimation of population-based indicators specific for rare cancers. This is true for incidence estimation, but even more for survival analysis. Many papers have analysed the performance of survival indicators for common cancers, in terms of desired statistics properties (robustness, unbiasedness, and others), transparency, simplicity, relative ease of calculation, software ability. Few evidence is available on the analysis of patients' cohorts diagnosed with less than 200 patients at diagnosis. Such sample size if out of reach for most rare cancers, particularly in medium-low population countries. A research priority is therefore to evaluate standard methods and, when they do not perform appropriately, developing new ones specifically for rare cancers survival estimation. Some possible topics are listed below.

- Determine when the number events is sufficiently high to allow a safe application of standard methods (e.g. normal approximation of age specific and standardized incidence rates, Poisson distribution for estimation of confidence intervals, etc), and when special methods or additional cautions are necessary. Studies should be done by both simulation and based on real world applications.
- Bayesian methods can be evaluated using a priori information and smoothing to produce a map of incidence which can be compared with heat maps of potential risk factors for epidemiological insight.
- Sensitivity analyses to be conducted with various spatial correlation structure, perhaps sampling (and so making rare the considered cases) from a common cancer population with known spatial correlation. Test various types of spatial correlation structures, and estimate in which cases the results are sensitive or not to the structure.
- While there are many papers describing survival estimation methods there is less work done on defining the absolute thresholds, numbers-wise, below which the methods should not be applied. Establishing these thresholds for population-based rare cancer statistics will be invaluable in guiding how many years of diagnosis (or how large areas) are required to be used to make survival estimates credible.
- Exploring the relative contributions, to the standard error of a survival statistic, given by the random effects variation between countries and by the within country sampling. The results would inform whether more effort is required to standardise for prognostic factors distribution by collecting more information (reducing between countries variation), or simply increasing the sample size (expanding the diagnosis period, reducing sampling variation component to standard error).
- Explore the performance on rare cancers of an indirect method of standardisation (Sasieni, 2016) to compare survival estimates similar to standardized incidence ratios. Indirect methods in general are used for small populations or rare entities because the numbers are too small in each population to standardise, but there is sufficient numbers overall for the ‘reference’ set of factor-specific rates.
- Exploring incidence/survival models that can increase efficiency (less variation) over non-parametric methods, but not at the expense of consistency (i.e. becoming more biased). The hope might be that reasonable and parsimonious models can be fit to sparse data, avoiding instability in a non-parametric estimate. Under particular situations, where certain assumptions are safer, a more sophisticated method may be more efficient and allow the numbers threshold to be lower.
- Regarding Bayesian methods, it seems that if a country has really sparse data, then its Bayesian estimate will be influenced more by the a priori information. However, if we want each countries statistic to be somewhat “official”, then the threshold sample size, above which all countries estimates in a study are robust and stand alone, needs to be identified.

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