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Bayesian estimates of the incidence of rare cancers in Europe

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ABSTRACT

Background: The RARECAREnet project has updated the estimates of the burden of the 198 rare cancers in each European country. Suspecting that scant data could affect the reliability of statistical analysis, we employed a Bayesian approach to estimate the incidence of these cancers.
Methods: We analyzed about 2,000,000 rare cancers diagnosed in 2000–2007 provided by 83 population-based cancer registries from 27 European countries. We considered European incidence rates (IRs), calculated over all the data available in RARECAREnet, as a valid a priori to merge with country-specific observed data. Therefore we provided (1) Bayesian estimates of IRs and the yearly numbers of cases of rare cancers in each country; (2) the expected time (T) in years needed to observe one new case; and (3) practical criteria to decide when to use the Bayesian approach.
Results: Bayesian and classical estimates did not differ much; substantial differences (> 10%) ranged from 77 rare cancers in Iceland to 14 in England. The smaller the population the larger the number of rare cancers needing a Bayesian approach. Bayesian estimates were useful for cancers with fewer than 150 observed cases in a country during the study period; this occurred mostly when the population of the country is small.
Conclusion: For the first time the Bayesian estimates of IRs and the yearly expected numbers of cases for each rare cancer in each individual European country were calculated. Moreover, the indicator T is useful to convey incidence estimates for exceptionally rare cancers and in small countries; it far exceeds the professional lifespan of a medical doctor.

1. Introduction

Because of their low numbers, rare cancers constitute particular challenges for diagnosis, treatment, and clinical decision-making; they are attracting increasing interest within the scientific, clinical, and public health community. Knowledge of the accurate numbers of rare cancer cases in each country is crucial to effectively planning care networks and high-quality healthcare programs, the cornerstones of

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which are efficiency and timeliness.

The RARECARE project [1] has provided an operative list of rare cancer entities [2] and rare cancer incidence, prevalence, and survival estimates. These indicators were updated by the RARECAREnet project [3], which also estimated country-specific annual incidence rates (IRs) per 100,000 subjects for rare cancers based on the cases recorded by population-based cancer registries (CRs) in each country. This approach gives potentially unstable and incorrect estimates because it is based on few observed cases, especially in countries with small populations. Also, incidence comparisons between populations or population groups by standard methods are hampered by over-dispersion. The alternative approach of applying European incidence rates (EUIRs) to the individual national populations leads to statistically stable incidence estimates even for very rare cancers, but hides the possible differences in incidence across European countries.

As neither of these approaches is fully satisfactory in providing reliable country-specific estimates and comparisons for very rare cancers, we propose an alternative strategy using a full Bayesian approach. This approach combines the strength of two sources of information—overall European data and country-specific data—and leads to increased precision in our understanding of the burden of a specific rare cancer in a specific country, providing reliable estimates and reducing the over-dispersion. This approach has been shown to outperform other methods which may fail when cancer rates and count data are low [4]. Full Bayesian analysis is often used for relative risk estimation in small-area mapping, where it borrows information about rates in surrounding geographical areas to estimate the rate in a given area [5]. We speculated that estimating epidemiological indicators for rare events was conceptually similar to that for small areas. We therefore considered that this approach might also be an effective way to estimate IRs of very rare cancers in each country [6].

In the present study, we took advantage of the RARECAREnet database, which comes from a large collection of real-world data, and applied the Bayesian method for estimating IRs and the yearly expected numbers of cases of rare cancers in individual European countries. Furthermore, we compared the results obtained by the classical and Bayesian approaches and assessed to what extent the latter is more appropriate with respect to frequentist inference. In addition to small-area estimation, the Bayesian approach has previously been applied for modeling rare events in clinical trial designs [7], but has seldom been used at the population level [8]. To our knowledge, this is the first paper providing estimates for all the rare cancers at the national level and for so many countries in Europe.

2. Material and methods

There are two different approaches in the Bayesian framework. The full Bayesian approach deals with uncertainty of the hyper-parameters, whereas the empirical Bayesian approach requires reliable estimates of these estimates. We chose to use the full Bayesian approach as it is more effective when dealing with rare events based on low counts [6]. The Bayesian approach combines background understanding (*prior*) with further information supplied by observed data to obtain a *posterior* knowledge that updates our prior. In this paper we considered the EUIR, calculated on the entire RARECAREnet database, as a valid *a priori* to merge with the data recorded by national CRs or national pools of CRs.

We analyzed rare cancer data from all patients diagnosed in the period 2000–2007, provided by 83 CRs from 27 European countries covering a population of about 217 million (48% of the total population of those countries). Nineteen countries had nationwide CR coverage, while in Germany, Portugal, Spain, France, Belgium, Switzerland, Italy, and Poland the observed cases came from pooling regional CRs (population coverage range: 13-71%). RARECAREnet data came from the EUROCARE-5 database and so had already been validated by centralized and standardized checking procedures [9]. In our analysis we used tumor-specific IRs from the RARECAREnet data of 198 rare cancers, by *j-th* 5-year age classes (0–4, 5–9… 85+), for Europe (Λ_j) and for each *i-th* country (Λ_{ji}). For each rare cancer we estimated E_i, the country-specific number of cases expected on the basis of the EUIR:

$$E_i = \sum_{j=1}^{18} Y_{ij} * \Lambda_j$$

where Y_{ij} were the person-years at risk during 2000–2007 in the CR areas of the *i-th* country, in the *j-th* age group, and Λ_j was the specific *j-th* EUIR, assumed to be constant in the period 2000–2007.

The cancer-specific standardized incidence ratio R_i for each *i-th* country in the study period was then calculated from E_i and the corresponding C_i, the observed number of cases for the area of the country covered by the CRs:

$$R_i = \frac{C_i}{E_i}$$

To compare C_i and E_i with a corresponding Bayesian estimate C_i' we applied full Bayesian methodology. Assuming C_i followed a Poisson distribution with mean $R_i x E_i$, we specified the following log-linear model:

$$\log(R_i) = \mu + \nu_i \quad (1)$$

where μ was the intercept quantifying an estimate of the theoretical European average incidence ratio (exp μ) and ν_i represented the unstructured residual for each country [10], and we measured how the log-standardized IR in each country differs from the European mean.

We assumed that the prior distribution for the parameters μ and ν_i followed a normal distribution with mean 0. The prior distributions between these parameters differed in their precision (the inverse of the variance). For μ the precision was set to a value close to 0, assuming a large prior variance. Since the choice of the prior for ν_i might have a considerable impact on the posterior smoothed estimates, we used a non-informative *gamma* prior distribution for τ with shape and inverse-scale hyper-parameters 0.00001. We also did a sensitivity analysis with different values for these hyper-parameters and found no substantial differences in the posterior estimates of R_i (R_i') (see Supplementary material 2). From here onward the apostrophe (') identifies the estimates obtained with the full Bayesian method.

Once the model (1) was fitted, we obtained the posterior distribution of R_i and calculated the median and 2.5% and 97.5% percentiles. R_i' and its distribution were used in the equations below in order to provide Bayesian estimates of C_i:

$$C_i' = R_i' x E_i$$

and their upper and lower bounds. The Bayesian model for each cancer entity was estimated using integrated nested Laplace approximations (INLA), a computational alternative to the Markov chain Monte Carlo method, through the R-interface [11]. We ran a sensitivity analysis, estimating the two rarest entities using uniform distribution as the prior distribution for the standard deviation of random effects. This sub-analysis was done using WinBUGS [12] on account of its adaptability to differences in modeling. We compared INLA with the WinBUGS results and found no substantial differences in the outcomes (see Supplementary material 3).

To provide the annual number of observed C_i^{yearly} and expected E_i^{yearly} cases in each country, the country-specific Λ_{ji} and age-specific EUIRs Λ_j were applied to P_{ij}, the national annual population of the entire country in 2003, the central year for 2000–2007.

$$E_i^{yearly} = \sum_{j=1}^{18} P_{ij} * \Lambda_j$$

$$C_i^{yearly} = \sum_{j=1}^{18} P_{ij} * \Lambda_{ji}$$

For exceptionally rare cancers, the expected annual number of cases might be less than one: for example, one tenth of a case per year; as this is a clumsy quantity to communicate, we proposed to use its inverse (T_i). *T* is a more comprehensible indicator that represents the expected time, in years, needed to observe one new case in the *i-th* country, specified as:

$$T_i = \frac{1}{C_i^{yearly}}$$

The Bayesian method enabled us to work out the incidence rate (IR') for each rare cancer and each country; the annual number of cases:

$$C_i^{year\,\prime} = R_i' x E_i^{yearly}$$

and the time needed to observe one case, expressed in years:

$$T_i' = \frac{1}{C_i^{yearly\,\prime}}$$

In the RARECARENet study each country contributed less than 9% to the European population covered, with the exception of England (about 25%). So we deleted nine rare cancers for which ≥ 40% of all cases came from a single country other than England (see Appendix Table footnotes in Supplementary material).

To decide in which cases Bayesian estimates should be preferred to the frequentist approach we established three pragmatic criteria:

1) when the number of observed cases of a specific rare cancer in the entire period in a country was 0;
2) when the number of observed cases of a specific rare cancer in the entire period in a country, C_i, did not fall within the 95% credible interval of the Bayesian estimates;
3) when C_i and C_i' differed by more than 10%.

Criterion 1 is a theoretically special case and comes from a well reported problem in the literature, the zero-numerator problem [13], a situation in which we estimate the probability for an event that is possible but has not yet occurred in the available time window. Here, the Bayesian method combines the a priori with the only empirical information available (i.e. the person years of observation that were not sufficient to observe a single case) providing a posteriori meaningful estimates C_i' and T_i'. The second criterion is equivalent to assessing statistically significant differences between two estimates. The third criterion consists in an arbitrary cut point to select when the Bayesian and classical estimated values substantially differed. Our primary goal was to give correct and reliable numbers, thus we decided that 10% was a good threshold.

3. Results

We applied this method to 189 rare cancers in each of the 27 countries considered. Fig. 1 and Fig. 2 present as examples the results for mucinous adenocarcinoma of the ovary (EUIR = 0.77) and adenocarcinoma of the trachea (EUIR = 0.01). The bars represent on the log scale the number of cases C_i recorded by CRs, their expected numbers E_i under the EUIR and the Bayesian estimates C_i' with their 95% credibility intervals.

Mucinous adenocarcinoma of the ovary (Fig. 1) had wide geographic variability in terms of incidence, as in many cases the C_i differed substantially from the E_i. The Bayesian estimates, bound by definition between the expected and the observed values, were generally close and in many cases identical to the observed figures. The only exceptions were for Iceland (–15%), and Malta (+12%). T_i's were < 1 year for all the countries, so this is not reported in Fig. 1.

For adenocarcinoma of the trachea (Fig. 2), Bayesian estimates were in most cases closer to the European average than to the locally observed cases. The resulting corrections exceeded 10% in 21 of the 27 countries and ranged from +113% in Ireland to –78% in Iceland. For Malta, Switzerland and Northern Ireland, the Bayesian method provided non-zero incidence estimates even though no cases were observed in the whole period. Estimates of T_i', the time needed to observe one case, are reported on the left side of the figures and ranged from 37 years in Iceland (95% credible interval from 15 years to > 50 years) to < 1 year in France, England, Italy, Germany and Poland, with a 95% credibility interval ranging from 0 months to a maximum of 5 months. For very rare cancers and small countries, this interval can easily exceed the professional life-span of a medical doctor (see Appendix Table for further details in Supplementary material) and we support the use of this indicator for very rare cancers in order to understand the burden and the importance of the network at European level for very rare cancers. A systematic presentation of the whole set of the Bayesian results—including *IR'*, $C_i^{year\prime}$, and T_i' by rare cancer and individual European country—is too large to be considered in this paper, and can be found in the Appendix Table (Supplementary material).

We took advantage of the fairly extensive dataset to find a practical criterion among the three listed in the Methods section to decide when Bayesian estimates should be preferred to frequentist ones.

Table 1 presents, for each country, the number of rare cancers with no observed cases (criterion 1), with the observed cases not falling within the credible interval (criterion 2), and with a difference between observed and Bayesian estimates > 10% (criterion 3). For 60 rare cancers there were no observed cases in 2000–07 in Iceland and Malta, and fewer than five occurred in England, The Netherlands, Germany and Italy. According to criterion 2, the observed value is out from the credibility interval of the Bayesian approach for 19 rare cancers in Iceland but none in England. The maximum number of observed cases for which the Bayesian estimate was better than the frequentist strategy was 53. Finally, when we considered the difference between C_i and C_i' as defined in the third criterion (last column in Table 1), there were more rare cancers in all the countries. The number of rare cancers in which C_i' differed from C_i by more than 10% ranged from 77 in Iceland (population about 300,000) to 14 in England (about 50 million) (Table 1). Only in 11 countries we found one rare cancer with more than 50 observed cases in the study period worth a Bayesian approach because it led to a substantial difference (> 10%).

With this third criterion the maximum number of observed cases for which the Bayesian estimate was better than the frequentist figure was 137 (Table 1).

As expected, and regardless of the criterion employed, the relationship between the numbers of rare cancers that profit from the Bayesian approach were inversely related to the size of the population of the country.

4. Discussion

Country-specific IRs of rare cancers are important for public health, research and clinical organization. Here we propose a full Bayesian approach to provide incidence estimates of each rare cancer in individual European countries. The classical estimates based on locally observed rates are reliable from a statistical point of view for the majority of rare cancers, and are not substantially changed when using the Bayesian method. Thus we are confident that most of the rare cancer estimates provided up to now with the RARECARENet project are not particularly biased. Nevertheless, in some cases they can be unreliable, and this paper may suggest practical indications on where Bayesian methods could actually lead to different and unbiased results compared to classical estimations. We suggest the Bayesian method when there are < 150 observed cases of a specific rare cancer in a country, and recommend it for < 50 cases. These thresholds resulted from the least conservative criterion: the third one which included all the rare cancers emerging from the second criterion. Furthermore we suggest to use T_i' as an easy indicator to communicate and interpret the burden of rare cancers, especially for very rare cancers.

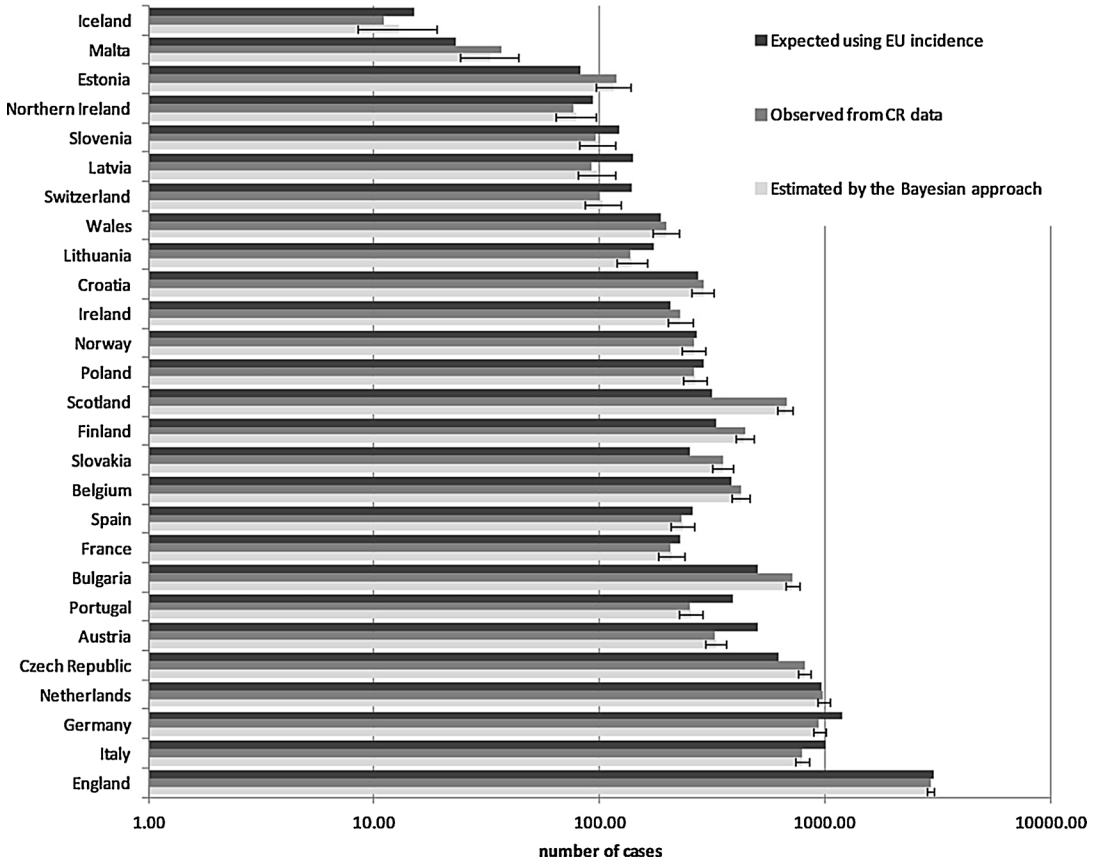

Fig. 1. Expected number of incident cases by country E_i, the corresponding number of cases observed (by CR) C_i and the estimates with the Bayesian approach C_i' for mucinous adenocarcinoma of the ovary (IR 0.77). Period of diagnosis 2000–2007. Numbers are plotted on a logarithmic scale.

Ti'	Ti' LL	Ti' UL
37	15.2	> 50
29	12.4	> 50
7	3.4	16.9
8	3.7	18.9
5	2.3	10.4
3	1.6	6.6
2	0.9	4.5
3	1.5	6.2
3	1.6	6.8
2	1.0	3.7
4	1.9	8.5
2	1.3	4.9
<1	0.1	0.4
2	1.2	4.4
2	1.1	4.3
2	1.3	5.3
1	0.5	1.6
<1	0.1	0.4
<1	0.1	0.3
1	0.6	1.9
1	0.4	1.1
1	0.6	1.9
1	0.5	1.5
1	0.5	1.5
<1	0.1	0.3
<1	0.0	0.1
<1	0.2	0.4

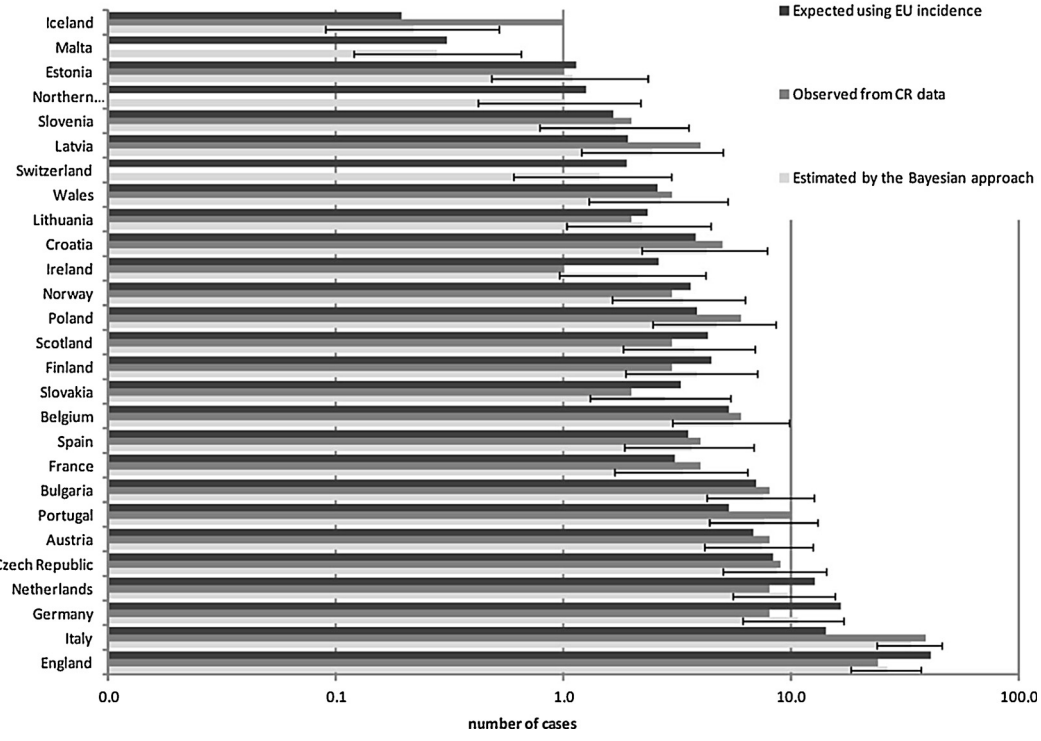

Fig. 2. The time in years needed to observe one case, T_i' by country with lower (LL) and upper (UL) bound of the 95% credible interval, the expected number of incident cases by country E_i, the corresponding number of cases observed (by CRs) C_i and the number estimated with the Bayesian approach C_i' for adenocarcinoma of the trachea (IR 0.01). Period of diagnosis 2000–2007. Numbers are plotted on a logarithmic scale.

Table 1
Number of rare cancers by country, and corresponding range of observed cases (when sensible), selected for Bayesian estimates by selection criterion.

		Criterion 1[a]	Criterion 2[a]		Criterion 3[a]	
Country	2007 population[b]	No. of rare cancers	No. of rare cancers	Range of observed cases	No. of rare cancers	Range of observed cases
Iceland	0.3	60	16	(1–14)	77	(1–43)
Malta	0.4	59	9	(1–15)	69	(1–37)
Estonia	1.3	31	6	(1–17)	58	(1–100)
Northern Ireland	1.8	49	3	(1–5)	45	(1–68)
Slovenia	2	20	4	(1–3)	58	(1–105)
Latvia	2.3	24	9	(1–10)	67	(1–51)
Switzerland[c]	2.3	18	2	(5–9)	53	(1–30)
Wales	3	23	3	(2–9)	44	(1–116)
Lithuania	3.4	24	7	(1–5)	51	(1–49)
Ireland	4.4	21	6	(1–3)	41	(1–22)
Croatia	4.4	29	11	(1–4)	61	(1–137)
Norway	4.7	17	4	(1–6)	40	(1–60)
Poland[c]	4.9	18	5	(1–2)	61	(1–39)
Scotland	5.1	14	3	(1–20)	37	(1–27)
Finland	5.3	25	10	(1–14)	61	(1–51)
Slovakia	5.4	19	7	(1–53)	40	(1–53)
Belgium	6.1	6	2	(2–3)	37	(1–27)
Spain[c]	6.3	10	2	(1–1)	37	(1–29)
France[c]	6.5	7	3	(1–7)	49	(1–29)
Bulgaria	7.7	15	4	(1–5)	46	(1–33)
Portugal[c]	8	10	5	(1–5)	48	(1–92)
Austria	8.3	9	3	(2–7)	33	(1–32)
Czech Republic	10.3	7	6	(1–18)	38	(1–89)
Netherlands	16.4	5	2	(1–9)	32	(1–40)
Germany[c]	18.5	1	2	(1–4)	15	(1–9)
Italy[c]	18.5	2	1	(1)	17	(1–39)
England	51.1	5	0		14	(1–24)

[a] Criterion 1, zero observed cases in the study period (2000–2007); criterion 2, observed cases outside the Bayesian credible interval; criterion 3, Bayesian estimates differing by more than 10% from the classical estimates.
[b] Annual population in millions covered by cancer registration.
[c] Countries not completely covered by cancer registration.

4.1. Possible issues related to the statistical methods

Usually in Bayesian analysis the correlation between adjacent areas sharing risk factors is measured with a model that accounts for extra variability in adjacent areas assuming both spatial and non-spatial residuals [6]. We chose not to include spatial structure in our model, in the belief that the use of structured variability has epidemiological sense when applied to small adjacent areas within the same country, but is harder to justify when comparing countries. We also did not consider possible incidence correlations between adjacent areas due to shared risk factors, as the provided estimates regard many rare tumors for which in general the risk factors and their variability between countries are largely unknown.

Inclusion of covariates measuring risk factors (such as deprivation index, health expenditure and so on) can be specified by simply adding a linear predictor in the covariates into expression (1), and then performing an ecological regression analysis [12]. If the covariates are available, standardized and associated with a specific cancer incidence, this may lead to improved estimates of the underlying relative risk. In our analysis we avoid using explicative variables as we are dealing with many and different rare cancers for which general relation is impossible to define. Another important problem in the formulation of Bayesian log-linear models is the specification of the prior distribution for the random effects. Since this may substantially influence the posterior estimates of R_i, we ran a sensitivity analysis considering different priors [11] (Supplementary material 2). In almost all the cancer sites we found no substantial differences in the posterior estimates with any of the priors tested.

The Poisson model with random effects (which account for under/over-dispersion) fits perfectly with the problem of estimating incidence when the observed counts are small or even zero [14,15] and confidence bounds of estimators are hard or impossible to derive. However, these advantages become evident only for the estimation of very infrequent events. Although this paper focuses on rare cancers, the posterior estimates of R_i did not differ from the observed ones for most of the entities and countries.

4.2. Possible issues related to the quality of the data

All these results are valid assuming the absence of quality problems. Bayesian estimates are not the solution if the geographical patterns of the data indicate that some entities are not identified or are incorrectly classified in some countries. If locally observed IRs appear unreliable, as when the number of observed cases is too big or too small compared with the expected number, we firmly support providing national estimates based only on the pooled EUIRs.

The definition of a rare cancer is based on a combination of site and morphology, which is why their specification must be accurate. A pathologist having difficulties in reaching a precise diagnosis or in assigning a specific morphological category, or inadequate documentation supplied to the CR at the time of registration, can increase the proportion of unspecified morphology [16] and underestimate the true incidence. Since the quality, completeness and standardization of data collection is beyond the scope of this paper we suggest that each country, knowing its own specific problems, should carefully comment and use the results.

Knowing this limitation, when we see wide variability between observed and expected cases we have to be careful about ascribing it only to true differences in incidence. Unfortunately neither data management nor statistical analysis of any kind will correct bias due to data quality, or differences between countries, health organizations and expertise on specific rare cancers.

5. Conclusions

This study provides for the first time Bayesian estimates for incidence rates and the yearly expected numbers of cases of every rare cancer in individual European countries. We identify simple indications when using Bayesian estimates instead of observed country-specific cases, and offer some advice on detecting probable data quality problems affecting the application of Bayesian estimation. In addition, the estimate of the waiting time T_i' could serve as a simple and appropriate indicator to easily communicate the occurrence burden for exceptionally rare cancers in each country.

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Author's contribution

Regarding the manuscript "Bayesian Estimates of the incidence of rare cancer in Europe":

L Botta and R Capocaccia contributed to the study design and the manuscript editing;

L Botta, R Cleries and R Capocaccia contributed to the statistical analysis and manuscript preparation;

L Botta, R Cleries, R Capocaccia, A Trama and G Gatta contributed to the study concepts and data interpretation;

L Botta, R Capocaccia, A Trama, G Gatta, S Mallone and R De Angelis contributed to data acquisition and quality control of the data;

All the authors contributed to the manuscript review.

Conflict of interest statement

The authors have declared no conflicts of interest.

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Appendix. A Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2018.04.003.

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