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Estimating cure and risk of death from other causes of cancer patients: EUROCARE-6 data on head & neck, colorectal, and breast cancers

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ABSTRACT

Background: To estimate net survival and cancer cure fraction (CF), i.e. the proportion of patients no longer at risk of dying from cancer progression/relapse, a clear distinction needs to be made between mortality from cancer and from other causes. Conventionally, CF is estimated assuming no excess mortality compared to the general population.

Methods: A new modelling approach, that corrects for patients' extra risk of dying (RR) from causes other than the diagnosed cancer, was considered to estimate both indicators. We analysed EUROCARE-6 data on head and neck (H&N), colorectal, and breast cancer patients aged 40–79, diagnosed from 1998 to 2002 and followed-up to 31/12/2014, provided by 65 European cancer registries.

Findings: Young male H&N cancer patients have 4 times the risk of dying from other causes than their peers, this risk decreases with age to 1.6. Similar results were observed for female. We observed an absolute increase in CF of 30 % using the new model instead of the conventional one. For colorectal cancer, CF with the new model increased by a maximum of 3 % for older patients and the RR ranged from 1 to 1.2 for both sexes. CF of female breast cancer ranged from 73 % to 79 % using the new cure model, with RR between 1.2 and 1.4.

Interpretation: Not considering a RR> 1 leads to underestimate the proportion of patients not bound to die of their diagnosed cancer. Estimates of cancer mortality risk have an important impact on patients' quality of life.

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1. Introduction

Cancer patients often have, over and above the mortality risk associated with the diagnosed cancer, a higher risk of dying from other diseases, including other independent cancers, compared to the general population [1–5]. Estimating this risk in a population-based setting is important for public health, clinical follow-up, and the everyday life of cancer survivors. However, this estimation is hampered by the difficulty of accurately attributing from population-based data cancer and non-cancer risk of death. In principle this can be done in three different ways: considering the prevalence of risk factors for death in the patient cohorts and general population; using information on cause of death to separately calculate overall and cancer-specific survival; applying survival models to survival data from cancer registries including specific terms to capture the increased non-cancer mortality risk of patients compared to the general population.

All these approaches present problems. Information about mortality risk factors and their prevalence in both populations is partially known. To our knowledge, such an approach has been attempted only for smoking-related risks [6], and for deprivation [7]. Data on cause of death are not always available in population-based settings and their reliability is not well known [8]. Statistical models [9] do not suffer from the above problems, but are necessarily based on several hypotheses whose degree of validity is not easy to assess.

In this paper, we applied a new cancer mixture cure modelling approach for cancer patients, which accounts for the relative risk of death from other causes compared to the general population, be it caused (e.g. adverse effects of treatments) or not (e.g. independent second cancer, chronic disease related to the cancer risk factors) by the diagnosed cancer. This allows in addition to estimate the proportion of cancer-free patients, i.e. the cancer cure fraction (CF), no longer at risk of dying from primary cancer progression. Previous analyses have been published on the performance and robustness of a new cancer cure model developed to this end, based on simulated data [10]. This is the first extensive application of the new cure model to European data using EUROCARE-6 data.

Analyses focused on head and neck (H&N), colorectal, and breast cancers because they present different time patterns for death hazard and different risk factors. H&N are smoking and alcohol-related cancers, breast as a cancer site shares genetic and hormonal risk factors with other tumours, and colorectal cancer is associated with nutritional risk factors.

2. Materials and methods

We applied the modelling approach to Eurocare-6 data from patients aged 40–79, diagnosed in 1998–2002 and followed up to 31/12/2014, provided by 65 PBCR from 20 European countries: Austria, Bulgaria, Czechia, Denmark, Estonia, Finland, Ireland, Lithuania, Malta, Netherlands, Slovenia, Slovakia, Iceland, Norway, United Kingdom, with 100 % coverage, while Italy, Spain, Switzerland, France and Germany covered 26 %, 20 %, 16 %, 15 % and 4 % of their population, respectively. We selected malignant first primary tumours of the colon and rectum (ICD-O-3 C18-C20), H&N (including the larynx and nasal cavity: C01-C06, C09-C14, C30-C32), and female breast (C50).

We estimated cumulative and interval-specific (yearly) relative survival (RS) by 5-year age groups. We calculated RS using the Ederer II estimator [11] of expected mortality, linking the general population life table by calendar year, age, sex, and registry area.

We then used these grouped results to fit the new mixture cure model which included the increased risk of non-cancer death [9]:

$$RS(t,x) = [\pi(x) + (1-\pi(x))\, S_u(x,t)]\, S_e(x,t)^{\alpha(x)-1} = NS(t,x)\, S_e(x,t)^{\alpha(x)-1} \quad (1)$$

where t is time from diagnosis, x is age at diagnosis, $\pi(x) = [1 + \exp(-\phi(x))]^{-1}$ indicates the CF as a function of age ($-\phi(x)$ with the logistic link), and $S_u(x,t)$ represents the relative survival function of the uncured patients, $S_e(x,t)$ the expected survival of a comparable group in the general population between ages x and x + t, and α indicates the relative risk of death from causes other than the primary cancer of all cancer patients compared to the general population (RR). The expression in square brackets represents the survival to the death risk from the diagnosed cancer, usually indicated as net survival (NS). Note that the conventional mixture cure model is obtained from the above expression by setting $\alpha(x) = 1$. [12].

We tested several parametric survival functions for S_u (Loglogistic, Lognormal, Weibull, Exponential Weibull), two parameterisations of the π (linear by age or categorically by 3 age group: 40–59, 60–69, 70–79 years), and four parameterisations of α equal to one, constant across ages, linear by age, categorical in the 3 age groups).

For each of the selected sites and each sex, we fitted the 32 models defined by the combination of these different characteristics to the

Table 1
Head and Neck cancer: Number of cases, parameter estimation of the uncured survival distribution and cure fraction for the new and conventional cure model, and the relative risk of non cancer death (α) estimated by the new cure model by sex.

		Females						Males					
		New cure model[a]			Conventional model[a]			New cure model[a]			Conventional model[a]		
		parameter	95 % CI		parameter	95 % CI		parameter	95 % CI		parameter	95 % CI	
Cases	40-59			7920						39,104			
	60-69			5443						25,360			
	70-79			5577						16,247			
Cure fraction			categorical			categorical			linear			linear	
	40-59	49.3 %	45.7 %	52.8 %	0.0 %	0 %	100 %	45.9 %	44.7 %	47.1 %	14.9 %	13.2 %	16.7 %
	60-69	55.1 %	52.2 %	57.9 %	8.0 %	0.9 %	26.2 %	52.1 %	51.0 %	53.2 %	10.9 %	8.9 %	13.1 %
	70-79	53.8 %	51.1 %	56.5 %	11.2 %	2.6 %	27.0 %	56.3 %	54.8 %	57.7 %	8.8 %	6.4 %	11.5 %
α			linear						linear				
	40-59	4.48	4.01	4.95				3.96	3.82	4.10			
	60-69	2.90	2.69	3.11				2.56	2.50	2.63			
	70-79	1.85	1.74	1.95				1.64	1.59	1.68			
Uncured Function			Lognormal			Lognormal			Lognormal			Lognormal	
	Scale	1.30	1.19	1.40	2.27	2.20	2.33	1.06	1.02	1.09	1.90	1.85	1.94
	Shape	0.33	0.24	0.43	1.77	1.69	1.84	0.12	0.10	0.15	1.08	1.03	1.14
	Delta	-0.46	-0.54	-0.39	-0.34	-0.41	-0.28	-0.20	-0.24	-0.17	0.05	0.01	0.08

[a] chosen among all those included in Appendix Table 1

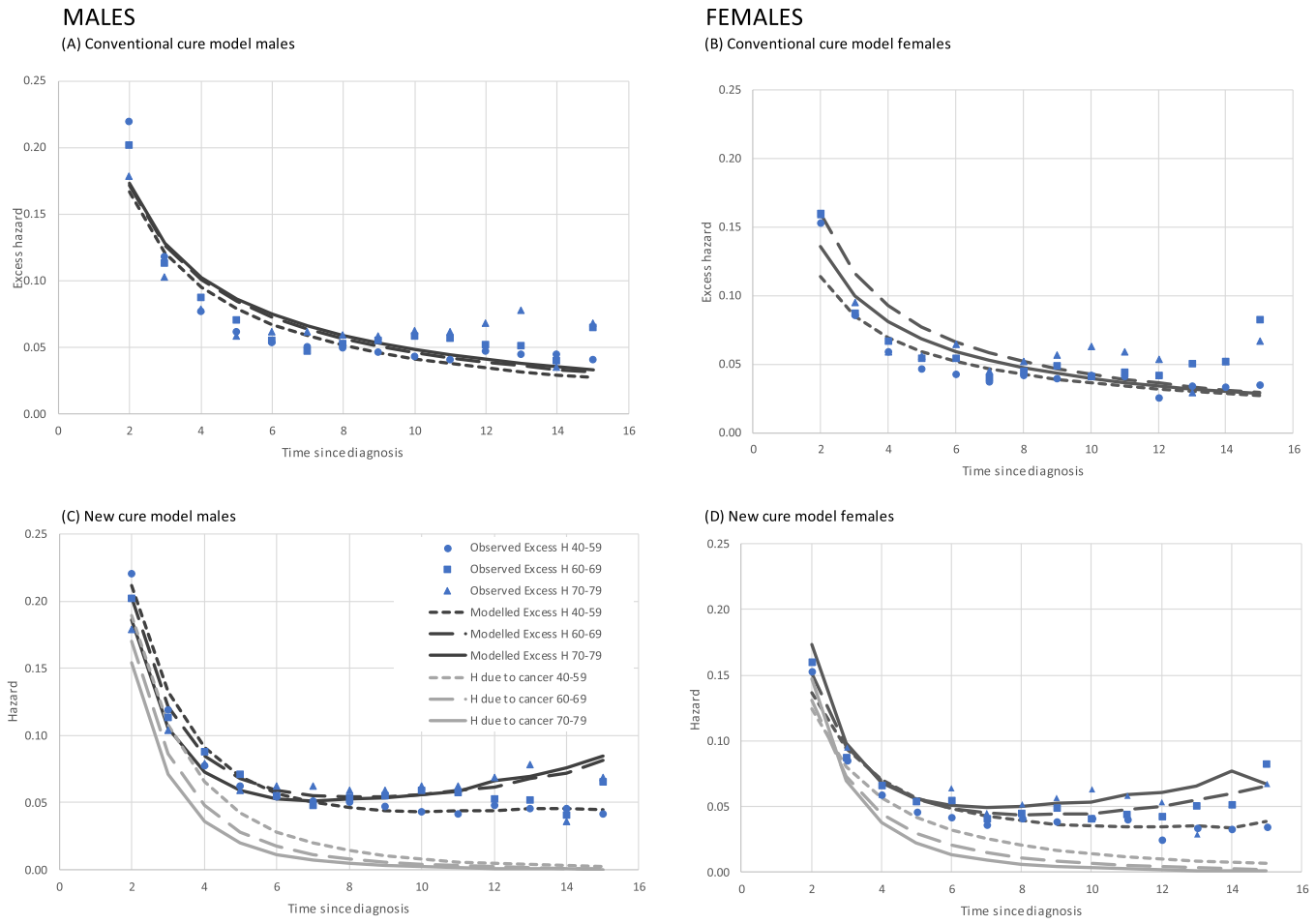

Fig. 1. H&N cancer data. Fitting of the excess hazards of death of the Conventional (black lines in A and B) and New Cure models (black lines in C and D), the observed excess hazards of death (geometric shapes) and the Hazard of death due to cancer (grey lines, only in C and D) by age group and sex. The first time point was excluded due to the very high hazard observed, which would excessively reduced the Y-axis scale.

observed data (Appendix Table 1), selecting the best model by jointly evaluating several classification criteria (qualitative and quantitative): the Akaike Information Criterion (AIC), a visual inspection of the model fit and residuals on the hazard scale, and correlation matrix of the estimates of the parameters involved in the model. We used Stata version 17 for the analysis.

Table 2
Colorectal cancer: Number of cases, estimated parameters of the distribution of uncured survival and cure fraction for the new cure and the conventional model, and the relative risk of non-cancer death (α) estimated by the new cure model by sex.

		Females						Males					
		New cure model[b]			Conventional model[b]			New cure model[b]			Conventional model[b]		
		parameter	95 % CI		parameter	95 % CI		parameter	95 % CI		parameter	95 % CI	
Cases	40-59			34,576						46,975			
	60-69			45,173						70,092			
	70-79			70,056						84,521			
Cure fraction			categorical			categorical			categorical			categorical	
	40-59	52.3 %	51.6 %	53.0 %	51.8 %	51.2 %	52.3 %	46.5 %	45.7 %	47.3 %	46.2 %	45.6 %	46.7 %
	60-69	54.6 %	53.9 %	55.2 %	52.2 %	51.7 %	52.8 %	50.7 %	50.0 %	51.3 %	47.8 %	47.3 %	48.3 %
	70-79	49.8 %	49.2 %	50.5 %	46.9 %	46.4 %	47.4 %	48.6 %	47.9 %	49.4 %	44.8 %	44.8 %	45.4 %
α			categorical						categorical				
	40-59	1.01	0.90	1.13				0.97	0.89	1.05			
	60-69	1.21	1.17	1.26				1.16	1.13	1.20			
	70-79	1.14	1.11	1.16				1.11	1.09	1.13			
Uncured Function			Weibull			Weibull			Weibull			Weibull	
	Scale	0.52	0.52	0.53	0.51	0.51	0.52	0.51	0.50	0.52	0.50	0.49	0.50
	Shape	0.86	0.85	0.88	0.83	0.82	0.84	0.85	0.84	0.86	0.82	0.81	0.82
	Delta	-0.35	-0.37	-0.33	-0.29	-0.31	-0.27	-0.31	-0.34	-0.29	-0.25	-0.26	-0.23

[b] chosen among all those included in Appendix Table 1

3. Results

In the following paragraphs, we describe the results yielded by the best fitting models by cancer sites and sex. Table 1 reports the estimates of the RR of death from other causes (α), of CF, and of the uncured survival parameters for Head & Neck cancers. The corresponding estimates obtained by the conventional model (setting $\alpha = 1$) are also reported for comparison. The α parameter, stood for female patients at 4.5, 2.9, and 1.8 at ages 40–59, 60–69, and 70–79, respectively. The corresponding estimates for males were 4.0, 2.6, and 1.6. The cancer CF estimated increased in by age group from 49 % to 55 % in females and from 46 % to 56 % in males (Table 1). The corresponding CFs values from conventional ($\alpha = 1$) model were much lower: from 0 % to 11 % in females and from 15 % to 9 % in males.

Inspection of the observed and predicted annual excess hazard rates (Fig. 1a–d) shows that, compared to the general population, the excess hazard of death no longer decreased after 7 years of diagnosis, tending instead stabilize or to rise again (geometrical shape, representing the observed excess hazard). This pattern cannot be captured by the conventional model, which is built to assume monotonically decreasing excess hazard of death over time (Figures 1a and 1b), but can be fitted by the new model through the α parameter (Figures 1c and 1d).

Our analysis of residuals (Appendix Figure 1a–d) showed that over time the conventional model increasingly underestimated the excess hazard, due to model assumption. Conversely, this bias is not present in the new corrected model estimates, whose residuals by age group, when plotted by against time since diagnosis, appeared almost flat (for females) or slightly increasing (for males).

3.1. Colorectal cancer

The relative risk of death from other causes was estimated close to 1 for colorectal cancer patients (Table 2). For males, estimates were 0.97 for ages 40–59, and of 1.16 and 1.11 for ages 60–69 and 70–79, respectively. Therefore, conventional and new models yielded similar results. The CF estimated by both models was 46 % in the youngest patients, slightly differing for the other age groups, with the new model providing a 3–4 % points higher CF compared to the conventional model. Similar results were obtained for female patients, with a slightly higher estimated relative risk (1.01, 1.21 and 1.14) and CF (52 %, 55 %, and 50 %) for the three increasing age groups. The corresponding CFs estimated by the conventional $\alpha = 1$ model were 52 %, 52 %, and 47 %, respectively. Plots of observed and model-based values showed some underestimation of excess hazard from the conventional model in the oldest age group, after 10 years' follow-up (Fig. 2a-d). This was due to slight increases in excess hazard captured by the new but not by the conventional model. Analysis of residuals (Appendix Figure 2a-d) confirmed that new cure model better fitted the long-term survival data.

3.2. Female breast cancer

The RR of death from other causes of breast cancer patients was estimated (Table 3) as 1.3 at ages 40–59, 1.4 at ages 60–69, and 1.2 at ages 70–79. The corresponding CF estimates were 74 %, 79 %, and

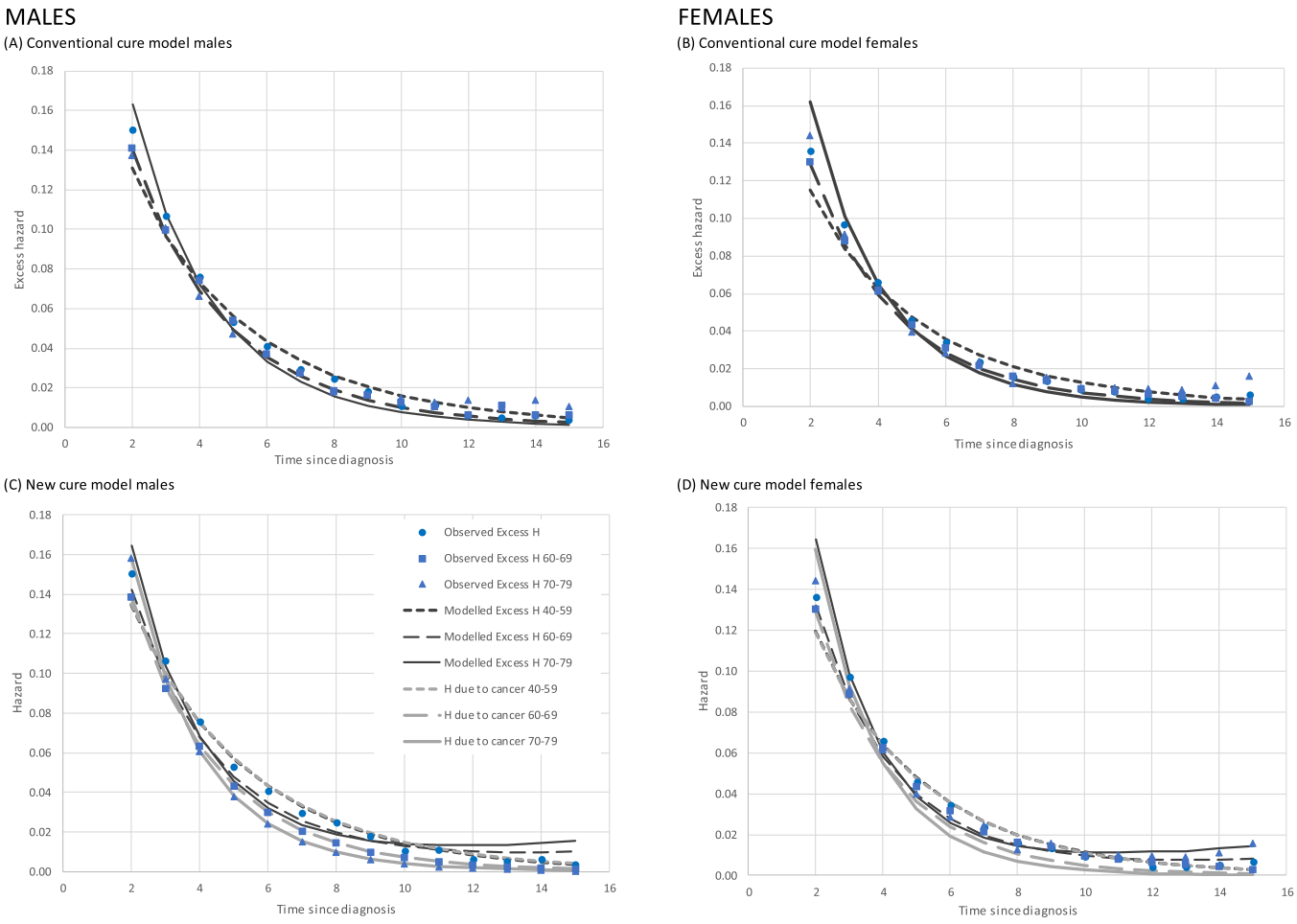

Fig. 2. Colon and rectum cancer data. Fitting of the excess hazards of death of the Conventional (black lines in A and B) and New Cure models (black lines in C and D), the observed excess hazards of death (geometric shapes) and the Hazard of death due to cancer (grey lines, only in C and D) by age group and sex. The first time point was excluded due to the very high hazard observed, which would excessively reduced the Y-axis scale.

Table 3
Female Breast cancer: Number of cases, estimated parameters of the distribution of uncured survival and cure fraction for the new cure and the conventional model, and the relative risk of non-cancer death (α) estimated by the new cure model.

		Breast					
		New cure model[c]			Conventional model[c]		
		parameter	95 % CI		parameter	95 % CI	
Cases	40-59			204,315			
	60-69			109,473			
	70-79			97,613			
Cure fraction			categorical			categorical	
	40-59	74.2 %	73.2 %	75.2 %	69.0 %	68.5 %	69.5 %
	60-69	79.0 %	77.9 %	80.1 %	68.7 %	68.0 %	69.3 %
	70-79	72.8 %	71.4 %	74.1 %	57.4 %	56.5 %	58.2 %
α			categorical				
	40-59	1.31	1.22	1.40			
	60-69	1.40	1.36	1.43			
	70-79	1.24	1.22	1.27			
Uncured Function			Weibull			Weibull	
	Scale	0.15	0.14	0.15	0.12	0.12	0.12
	Shape	1.12	1.11	1.14	1.03	1.02	1.05
	Delta	-0.39	-0.42	-0.36	-0.20	-0.22	-0.18

[c] chosen among all those included in Appendix Table 1.

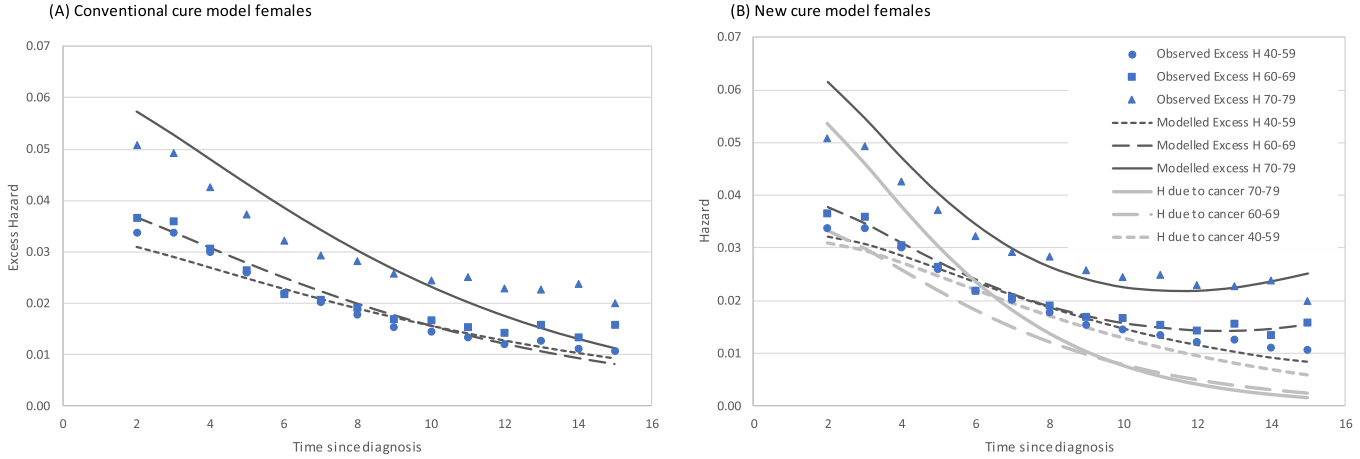

Fig. 3. Female Breast cancer data. Fitting of the excess hazards of death of the Conventional (black lines in A) and New Cure models (black lines in B), the observed excess hazards of death (geometric shapes) and the Hazard of death due to cancer (grey lines, only in B) by age group and sex. The first time point was excluded due to the very high hazard observed, which would excessively reduced the Y-axis scale.

73 %. They were significantly higher than those obtained from the conventional ≡ model (69 %, 69 %, and 57 %, respectively). The plots of observed excess hazard (Figure 3a-b) showed a flattening trend over the 10 years after diagnosis. The conventional cure model did not capture this tendency to flatten, providing excess hazard rates rapidly approaching zero. The new cure model provided a better fit, behaved better, but tended in the long run to overestimate the excess hazard in the oldest and to underestimate it in the youngest age classes. In the youngest age group, the hazard of cancer death fell by one third at 6 years after diagnosis and by half at 9 years compared with the hazard of death observed at 2 years. Our analysis of residuals confirmed the new cure model's better fit (Appendix Figure 3a-b) during the final years of follow-up.

4. Discussion

This is the first time that the new mixture cure survival model, which provides estimates of the extra risk of death from other causes and the subsequent corrected cancer cure fraction has been applied to EUROCARE-6 data. The cure fraction in this context can be interpreted as the proportion of patients who are no longer at risk of dying due to progression or recurrence of the diagnosed cancer [13].

We estimated a high relative risk, compared to the general population, for other causes of mortality for H&N cancer patients, which was particularly high in the young and decreased with age. Lower RRs with similar age patterns were found for breast cancer patients. The estimates for colorectal cancer were very close to 1, indicating small or negligible extra risk. These conclusions were yielded through observation of a long-term persistence or rise in excess hazard in patients, particularly in the elderly. The decreasing age pattern can be explained by higher levels of unspecific risk factors in people getting cancer at younger age, and/or by more aggressive and toxic treatments given to younger patients. The impact of ignoring an existing relative risk of death from other causes (estimated by the α parameter) higher than 1 is relevant, as shown by the results obtained from the conventional cure models with $\alpha = 1$, resulting in underestimation of cancer cure fraction [14,15]. This because a fraction of deaths from other diseases would be erroneously attributed to the diagnosed cancer.

4.1. Comparison with the literature

Similar results were obtained applying the same method to US-SEER data. The estimated relative risk of non-cancer death for patients versus the general population was 1.11 for colorectal patients of both sexes and

1.16 for breast [9]. The literature on cause-specific mortality of cancer patients is sparse. A comprehensive study on patients diagnosed with all the most frequent cancers [16], but limited to 5 years from diagnosis, found a higher risk of other causes mortality for H&N, but not for colorectal and breast cancers. In a specific study on colorectal cancer patients [17], the standardised mortality ratio (SMR) of mortality from other causes was estimated at around 2, i.e. significantly higher than that experienced by the general population. Moreover, for breast cancer the SMR calculated for causes other than BC in the cohort at 10 years, reported by Ameijide and colleagues in a similar period, was 1.2 [18].

4.2. Cure model specifications

In the present application we selected the best fitting distribution of times to cancer deaths from among several options and important differences among the considered models in the estimation of α and all other model parameters were observed. The choice of the uncured cancer survival distribution is therefore crucial [12]. We found not sufficient to use AIC as a single criterion so we stress the importance of analysing residuals in the hazard scale [12]. The sensitivity of CF estimates to the choice of distribution can be partially mitigated by forfeiting its asymptotic definition and considering instead the proportion of patients not expected to die from cancer before some extreme age, such as 100 years [19].

4.3. Strengths

This is the first study aimed at estimating other causes mortality in a large population-based European dataset. The new cure model applied in this paper addresses the issue of disentangling cancer-specific and background mortality of the cancer cohort. It estimated the proportion of patients at risk of death from progression or relapse of the diagnosed cancer and those expected to die from other causes, either due (e.g. adverse effects of treatments) or not (e.g. other diseases possibly linked with risk factors associated with the tumour or second cancers) to the cancer included in the analysis. A previous simulation-based analysis [10] showed that the method performed fairly well, with a good degree of robustness with respect to the partial failure of the model assumptions.

4.4. Weaknesses

To avoid over-parametrisation, we chose to keep the model structure as simple as possible, without including other covariates, interactions, or time-dependent variables. The impact of including these terms in mixture cure models in terms of covariance and interpretability of parameters warrants further study.

Relapse is not routinely actively collected by PBCR. Having this information would be useful to validate model results through the application of a new multistate model [20] proposed to estimate the excess risk of non-relapse mortality for cancer patients compared to the general population, most likely due to other causes. Cause of death information are not always available in European population-based cancer registries and their reliability is not well known because attributing death to cancer or other causes is sometimes difficult and arbitrary where comorbidities are present. In future, cause of death information can be used to empirically investigate the existence of this increased risk of non-cancer death in cancer patients.

We did not explore the geographical and time variability of the excess mortality from other causes. This should be planned for future analysis. Caution is therefore needed in extrapolating our estimates to other populations and to more recent times.

5. Conclusions

We believe that CF and the relative risk of death from other diseases (including other independent cancers) are important indicators. They should be communicated to patients to improve awareness of their health status, to enable them to better plan their lives and to facilitate their return to a normal existence. Furthermore, these indicators could be useful in public health decision-making to improve the planning of health services for cancer survivors, including long-term clinical follow-up, focusing more on preventing or treating the long-term effects of treatments and addressing risk factors for cancer that are shared with other chronic diseases [21].

Estimates of time to cure, derived from these models, also have practical implications in legislation addressing cancer patients' "Right to be Forgotten" (https://ecpc.org/policy/the-right-to-be-forgotten/) and should be considered in discussions with insurance companies [21].

Patients and their insurers are already aware of the presence of comorbid conditions potentially increasing the risk of death, since they are included in health claims, and would in any case influence access to loans etc. Overestimating an individual's cancer mortality risk may result in undue additional burden on cancer survivors' quality of life.

Ethics approval

We analysed pseudonymised data collected from 65 population-based cancer registries, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT 73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analyses agreed on in the EUROCARE-6 protocol, available at http://www.eurocare.it.

Author contributions

Laura Botta, Riccardo Capocaccia, Gemma Gatta and Valerie Jooste contributed to the study conception and design. Silvia Rossi, Gemma Gatta and Laura Botta contributed to data acquisition. Data collection was performed by all members of the EUROCARE-6 Working Group. Data preparation was performed by Laura Botta, Riccardo Capocaccia, Silvia Rossi, and Gemma Gatta. Analysis was performed by Laura Botta and Riccardo Capocaccia. The first draft of the manuscript was written by Laura Botta, Riccardo Capocaccia and Valerie Jooste. All authors commented critically on important intellectual content in previous versions of the manuscript. All authors read, approved, and had final responsibility for the decision to submit for publication.

Data statement

We are not permitted to share individual data. Aggregated level data, in the form of counts, rates, or survival proportions, can be only shared after express permission from the participating registries. These data should be requested by contacting the corresponding author or Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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Declaration of Competing Interest

The sponsor have no role in the study design; in the collection,

analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114187.

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