Population level cure of colorectal cancer in Malta: An analysis of patients diagnosed from 1995 to 2004

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Abstract

Aim: The aim of this study is to estimate the population level 'cure' of Maltese colorectal cancer patients diagnosed from 1995 to 2004, and to estimate the median survival time for the 'uncured' patients. **Methods and study population:** Analysis was conducted on 1,470 cases registered by the Malta National Cancer Register between 1995 and 2004 followed up to end of 2010. The mean age of the patients was 66.4 (95% CI 65.8 – 67.1) with an equal number of men and women. Background mortality for 1995 to 2010 was extracted from publicly available life tables. A mixture model with Weibull survival distribution and identity link was used to model 'cure'. **Results:** The overall 'cured' proportion for the patients diagnosed in 1995 – 1999 was 45.3% (95% CI 40.2 – 50.5) while the 'cured' proportion for the patients diagnosed in 2000 – 2004 was 52.3% (95% CI 47.2 – 57.5). Median survival time for the 'uncured' increased in the second calendar period from 1.25 years (95% CI 1.04 – 1.45) to 1.42 years (95% CI 1.15 – 1.76). **Conclusion:** In Malta, like the rest of Europe, improvements have been made in short and long term survival over a 15 year period under study. To continue this improvement, differences by age that still persist must be investigated and efforts focused to reduce any gaps between Malta and other European countries.

Keywords: Statistical cure, colorectal neoplasms, relative survival, population based registry

1. Introduction

Cancer is one of the leading causes of death worldwide and colorectal cancer is the fourth most common cause of cancer death. It is estimated that in Europe there were 214,700 deaths from colorectal cancer (12.3% of all cancer deaths) in 2012 (1). In Malta, in 2013, colorectal cancer was the second leading cause of cancer death amongst both men and women (2).

Relative survival analysis present survival estimates adjusted for the background risk of death at particular time points after diagnosis. An extension of the relative survival concept is the notion of 'statistical cure' or 'population cure'. This is defined at a group level and is different from the concept of individual cure where patients can be considered medically free of cancer (3). 'Population cure' relates to the tendency for some cancer relative survival curves to reach a plateau after a period of follow-up. This indicates that the excess mortality attributed to the cancer of the patient is equal to their background mortality and thus these cancer patients are no more likely to die than their counterparts in the general population. The analysis of 'cure' can expand our understanding of the pattern of cancer survival.

The EUROCARE project estimated the 'cured' proportion in Europe for patients diagnosed between 1978 and 1999 (4, 5) and found a 12% improvement in long term survival for the 'cured' proportion from 36% in 1978-1985, to 48.5% in 1997-1999. The study also showed a strong negative association between age and 'cure'. Studies conducted in Sweden, Finland and North West England have also made use of 'cure' models to assess survival trends for colorectal cancer and found similar results (6-8)

The aim of this study was to estimate the proportion of Maltese colorectal patients diagnosed from 1995 to 2004, who were statistically 'cured' and to estimate the median survival time for the uncured. This study is the first to apply 'cure' models on data from the Malta National Cancer Register.

2. Materials and Methods

2.1. Data sources

The data used in this study was taken from the Malta National Cancer Register which collects data for all incident cancers in the population resident in Malta and Gozo (9). Cancer notification is compulsory by the Notification of Cancer Act of 1957 (10). Data were collected for all patients diagnosed with colorectal cancer from 1995 to 2004 and followed up to the end of 2010. Colorectal cancers are coded by the registry using the International Classification of Diseases for Oncology (ICD-O-2) and codes C18 – C20 were included in this study.

Background mortality for the years 1995 to 2010 were obtained from life tables available publicly from the National Statistics Office. In these tables age is truncated to 85+ up to 1998 and 90+ from 1999 onwards. Since the risk of death increases exponentially after 85 years of age and because our cancer patients were aged up to 97 at the end of follow-up, it was necessary to impute age and sex specific rates of death for the older ages, for each of the years of follow-up. The available life tables were thus extended and smoothed up to 100 years of age using the Ewbank four parameter method (11), separately by year and gender. The standard life table used to smooth the data was that available for England and Wales from 1998 to 2000 since no reliable standard was available for Malta. To assess the goodness of fit of the derived life tables; the smoothed mortality rates and survival function in each table were plotted against the observed mortality rates.

2.2 Study population

In total 1,496 patients were eligible for analysis in this study. Of these, 25 were excluded because they were diagnosed only at death via death certificate (1.7%). Further to this, 1 more case was excluded since region of residence was unknown. In total 1,470 cases were examined. For each patient sex, age at diagnosis, date of diagnosis, date of death and region of residence were collected. Age at diagnosis was

grouped into 4 categories - <55, 55 – 64, 65 – 74 and 75+ years; while year of diagnosis was collapsed into two broad cohorts – 1995 – 1999 and 2000 – 2004. Vital status and date of death is collected by the registry through death certificates and linkage with the National Mortality Register. Since no variables directly measuring socioeconomic status were available, region of residence was used as a proxy for socio-economic status. The National Statistics Office (NSO) classifies the Maltese Islands into six broad geographic regions– the North Harbour, South Harbour, South East, West, North and Gozo. The North Harbour is the largest region with 28.9% of the total resident Maltese population living here while Gozo, Malta's sister island, is the smallest region at 7.5% (12). Studies on income and living conditions consistently show differences across region. The South Harbour region exhibits the highest percentage at risk of poverty and the lowest average household income (13).

2.3. Statistical analysis

The relative survival ratio (or relative survival), is a measure of survival from a particular disease of interest (e.g. cancer) in the absence of other causes of death. In our context, relative survival is the ratio of the survival observed among the cancer patients and the survival that would have been expected if they had experienced the same death rates as the general population from which they derive. Relative survival by age group, sex, calendar period of diagnosis and region of residence was estimated using the Ederer II method(14).

Cure models estimate the proportion 'cured' of their cancer; that is, the proportion of patients who experience no long-term disease related (excess) mortality. These models are only appropriate when it is believed that 'cure' is a reasonable assumption. This can be established by visual inspection of relative survival curves. A mixture model, which assumed a Weibull distribution and an identity link, was used to estimate 'cure'. We used the model estimates to derive a) the proportion 'cured'; b) the relative survival

curves for both the whole sample and the 'uncured' patients; and c) the median survival time of the 'uncured'. Estimation of the model parameters was obtained using the maximum likelihood method on individual-patient records.

The modelling strategy aimed to develop a parsimonious model to predict 'cure'. Initially all co-variables, as well as an interaction term between age group and year of diagnosis, were included to estimate the 'cure' fraction and two Weibull parameters. The likelihood ratio test was used to assess the number of co-variables included in the model. We also tested whether the Weibull shape and scale parameters varied by the co-variables included in the final model. In order to assess the fit of the final model, survival curves were derived from the model estimates and were compared graphically to the estimates obtained using the Ederer II method. All analyses were performed using Stata version 11. *strsmix* (3) was used to model cure.

3. Results

The mean age of the patients was 66.4 (95% CI 65.8 – 67.1). The proportion of men and women was similar in the two periods. Distribution of patients across the six regions reflects the relative population sizes of the regions (Table 1).

Five year relative survival for the whole study population (1995 – 2004) was 53.3% (95% CI 50.3 – 56.3). Survival estimates were similar for men and women and by period of diagnosis. The curves by age group indicated lower survival in the older age groups. Five year survival amongst those diagnosed at age 55 or younger was 63.3% (95% CI 58% - 68.2%) while for those diagnosed age 75+ survival was 47.2% (95% CI 41.5% - 52.9%). Due to small numbers with increasing years of follow up, relative survival showed wider variability after 11 years of follow up especially when subdividing by multiple categories such as region and age group (Figure 1).

On visual inspection, 'cure' did not appear to have been attained for the oldest age group (75+) therefore this group was excluded from the 'cure' analysis (1054 patients analysed). Initially all co-variables (age group, sex, region and year of diagnosis) were included in the model, with an interaction term between age and year of diagnosis. We found no association between the 'cured' proportion and sex (p=0.32) or region of residence (North reference group; North Harbour p=0.68; South East p=0.80; South Harbour p=0.64; West p=0.37 and Gozo p=0.52). Since the relative survival curves in general show better survival for Gozo compared to the five other regions forming the island of Malta, another regional categorization was created to compare Gozo to Malta (North Harbour, South Harbour, South East, North and West combined). However this new regional distribution did not improve the fit of the model, although the association between the cured proportion for the two islands was borderline significant (p=0.07). Our final model included age group, year of diagnosis and the interaction between age group and year of diagnosis. Allowing the scale parameter to vary by age group, year of diagnosis and the interaction term

improved the fit of the model ($p<0.01$), whereas this was not the case for the estimate of the shape parameter ($p=0.86$).

The overall proportion 'cured' for the age group 55 to 64 was 12% lower when compared to those aged less than 55 ($p=0.062$),indicating a possible association . Figure 2 and 3 show the modelled estimates of relative survival for the total population together with the Ederer II estimates of relative survival with corresponding 95% confidence intervals by age and year of diagnosis.

Table 2 shows modeled estimates of the 'cured' proportion by age and year of diagnosis. The overall 'cured' proportion was 45.3% (95% CI 40.2 – 50.5) for the patients diagnosed in 1995 – 1999 and 52.3% (95% CI 47.2 – 57.5) for the patients diagnosed in 2000 – 2004. The higher cure proportion in the recent period suggests improvement with time (z-test $p<0.05$), which is primarily due to the improvements seen in the youngest and middle age groups.

In the 'uncured' group, we found evidence of a difference for patients aged 65 – 74 compared to those aged less than 55 ($p<0.01$). Older patients within the 'uncured' group exhibited poorer survival. Figure 4 shows the modelled estimates of relative survival for the 'uncured' proportion for both calendar periods separately.

Table 3 shows the modeled estimates of median survival time of the 'uncured' group by age and year of diagnosis. Median survival time in the 'uncured' group increased from 1.25 years (95% CI 1.04 – 1.45) in 1995-1999 to 1.42 years (95% CI 1.15 – 1.76) for patients diagnosed in 2000 - 2004. The median survival was lowest in patients aged 65-74 years; 0.80 years (95% CI 0.60 – 1.08) in 1995 – 1999 and 1.07 years (95% CI 0.80 – 1.43) in 2000 – 2004.

4. Discussion

This is the first study on population 'cure' for colorectal cancer in Malta. Comparable European level 'cure' estimates are only available for the period from 1994 to 1999 (5). The proportion of 'cured' patients in Malta for this same period was 45.3% (95% CI 40.2 – 50.5). The median survival time for the 'uncured' group was 1.25 years (95% CI 1.04 – 1.45). The proportion 'cured' in our study is slightly lower than the European estimate from the EUROCARE data for 1994 to 1999; 46.8% for patients in 1994 – 1996 (95% CI 45.5 – 48.1) and 48.5% for patients in 1997 – 1999 (95% CI 45.6 – 51.4). It is unclear if the results for the recent period (2000 – 2004) are similar to the European estimates since no comparable 'cure' data is available at this time. Comparison of the median survival time could not be conducted since mean rather than median time was calculated by the authors of the EUROCARE study (5).

Age at diagnosis and calendar period of diagnosis are the two main factors associated with survival amongst patients diagnosed with colorectal cancer in Malta between 1995 and 2004. Sex does not influence 'cure' in Malta despite the fact that studies suggest that females have an advantage in colorectal survival in Europe (15). This could partly be due to the smaller number of patients in Malta when compared to the large pooled dataset used by the EUROCARE. An internal analysis conducted by the Malta National Cancer Register for colorectal cancer patients diagnosed between 1999 and 2002 showed that women were diagnosed at a more advanced stage when compared to men which may cancel out any advantage associated with being female (16). The EUROCARE study suggests that a reason for the advantage may be due to differences in age at diagnosis. In our Maltese study population we did not find evidence of a difference in age at diagnosis by sex (p=0.83). While research conducted on socioeconomic differences in relative survival and 'cure' have shown major gaps amongst low and high socio-economic strata (6, 17), regional differences were not found in this study. However, this must be taken with caution since region of residence may be too broad to act as a proxy for socio-economic status even though studies show that there are differences in income and poverty levels at the regional level (13). A lack of regional

differences may suggest that the small size of the island allows for better physical access to care and highlights the universal and free for all availability of oncology care in the national health system. On the other hand regions may be too large to truly measure finer socio-economic differences. The North Harbour region of Malta, for example, encompasses nearly 30% of the population. A composite indicator at post code level containing data on factors such as education level, employment and deprivation may better outline differences between population sub-groups. If this data were available, analysis on socio-economic differences in survival would allow for richer understanding of survival. Indeed while it is true that oncology treatment is available to all patients in Malta, the fact that there is only one service provider offers no choice for patients and Malta, being an island, is restricted with respect to cross-border care options. These factors, though difficult to investigate, must be considered when comparing Malta to other larger European countries.

Amongst the oldest group (75 years and over); it seems that the survival curve did not show a plateau even after 15 years of follow up. The relative survival curve patterns may be explained by the small numbers of patients in our study or it may be indicating that patients over the age of 75 remain with elevated risk of death even after 10 years of follow up. The data suggest that while patients aged 55 to 64 experience better survival than their older counterparts in the short term (up to 5 years after diagnosis), these gains in survival do not persist over time. Patients in this age group take longer to reach 'cure' indicating that their elevated risk of death remains comparably high. The explanation for this is unclear. It may be due to different stage at diagnosis by age or possibly the treatment protocols used locally. At the time of analysis comprehensive data on stage were not available. While notification of cancer cases is governed through a legal act, the law does not stipulate the compulsory collection of data such as stage or treatment. Published reviews on treatment practices in Malta are limited and an adequate review of diagnosis and treatment protocols, which may influence survival outcomes, is not available. A study by Brincat and colleagues (18) reviewed recurrence of rectal cancer in patients

diagnosed in 2001 – 2003 with the specific aim of reviewing treatment and management protocols. The study found a local recurrence rate of 16% which was noted to be "disappointingly" high when compared to other studies using different treatment protocols. The authors suggest a need to implement new treatment protocols using appropriate imaging followed by the referral of selected patients for pre-operative radiation or chemo-radiation and adequate surgery. Since no other studies were found following this publication, it is not clear if new protocols have been put into place for the treatment and management of rectal cancer following this audit. The outcomes of this present study may also be related to other factors that have not been considered here, however it seems clear that this age group should be the topic of further research.

Analysis of cancer data in Malta are based on a small number of patients due to the small population size and this is evident when analysis is conducted across multiple categories and after extended follow-up. To mitigate the problem, categories for age, year of diagnosis and follow up time were compiled in such a way that they made sense for the purpose of comparison, while being large enough to ensure statistical power. A limitation of this study is the fact that background mortality smoothing had to be conducted against a standard population that was not a Maltese population, though the smoothed data for all the tables fitted the observed data well after smoothing. It would have been better to have had regional life tables to adjust for regional differences in background mortality. However, it was not possible to produce these since data on mortality at regional level are not available. One of the major strengths of this study is that the data analysed represent coverage of the entire national population. According to EUROCARE, the average percentage coverage of the population of the cancer registries in Southern Europe (36%) is far lower than the coverage of registries in Northern Europe, Ireland and the UK (all with 100%)(19). This research therefore is a valuable source of information available on national level survival in Southern Europe.

While improvements have been made in survival over the past 15 years, the data suggests that age differences still persist for both short term and long term survival and need to be investigated further. The 'cure' models in this study have outlined that the technique can be incorporated into survival analysis as a complimentary and informative method of measuring progress in cancer survival. The 'cure' models have also highlighted the importance of looking at long-term survival as a measure of improvement in survival and not just focusing on the benchmark of 5 year survival that is usually taken when comparing results over time.

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The funding source did not have any role in the design of the study, in the collection, analysis or interpretation of the data, in the writing of the report or in the decision to submit the paper.

Conflict of interest statement

The authors declare no potential conflict of interest.

Ethical approvals

Local ethical approval to conduct this study was obtained from the Malta University Research Ethics Committee in December 2011 (reference number 91/2011) and subsequent ethical approval was acquired on the 9th April 2012 from the London School of Hygiene and Tropical Medicine Ethics Committee (reference number 011/36).

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh J, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. European journal of cancer 2013;49(6):1374-1403.
2. Directorate for Health Information and Research. National Mortality Registry Annual Report 2012. In.
3. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. Biostatistics 2007;8(3):576-94.
4. Verdecchia A, De Angelis R, Capocaccia R, Sant M, Micheli A, Gatta G, et al. The cure for colon cancer: results from the EUROCARE study. Int J Cancer 1998;77(3):322-9.
5. Francisci S, Capocaccia R, Grande E, Santaquilani M, Simonetti A, Allemani C, et al. The cure of cancer: a European perspective. Eur J Cancer 2009;45(6):1067-79.
6. Eloranta S, Lambert PC, Cavalli-Bjorkman N, Andersson TM, Glimelius B, Dickman PW. Does socioeconomic status influence the prospect of cure from colon cancer--a population-based study in Sweden 1965-2000. Eur J Cancer 2010;46(16):2965-72.
7. Lambert PC, Dickman PW, Osterlund P, Andersson T, Sankila R, Glimelius B. Temporal trends in the proportion cured for cancer of the colon and rectum: a population-based study using data from the Finnish Cancer Registry. Int J Cancer 2007;121(9):2052-9.
8. Shack LG, Shah A, Lambert PC, Rachet B. Cure by age and stage at diagnosis for colorectal cancer patients in North West England, 1997-2004: A population-based study. Cancer Epidemiol 2012.
9. IARC. EUROREG List of registries. In.
10. Government of Malta. Notification of Cancer Act. In; 1957.
11. Ewbank DC, Gomez De Leon JC, Stoto MA. A reducible four-parameter system of model life tables. Popul Stud (Camb) 1983;37(1):105-27.
12. National Statistics Office. Census of population and housing 2011 - Final report. In: National Statistics Office Malta; 2014.
13. National Statistics Office Malta. Statistics on income and living conditions 2010. In.
14. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23(1):51-64.
15. Micheli A, Ciampichini R, Oberaigner W, Ciccolallo L, de Vries E, Izarzugaza I, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer 2009;45(6):1017-27.
16. Ministry for Health the Elderly and Community Care. The National Cancer Plan 2011 - 2015. In. Malta.
17. Coleman MP, Rachet B, Woods LM, Mitry E, Riga M, Cooper N, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer 2004;90(7):1367-73.
18. Brincat S, von Brockdorff L, Said J. Recurrence of rectal cancer: a study on patients with rectal cancer referred to Sir Paul Boffa Hospital during 2001-2003. Malta Medical Journal 2009;21(3):32-35.
19. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. The lancet oncology 2014;15(1):23-34.

Table 1: Patient characteristics

		Year of Diagnosis		
		1995 - 1999	2000 - 2004	Total
		N (%)	*N (%)*	*N (%)*
Total		***658 (45)***	***812 (55)***	***1,470 (100)***
Characteristic	***Category***			
Age (years)	*<55*	127 (19)	139 (17)	266 (18)
	55 - 64	148 (22)	185 (23)	333 (23)
	65 - 74	195 (30)	260 (32)	455 (31)
	75+	188 (29)	228 (28)	416 (29)
Sex	*Male*	324 (49)	418 (51)	742 (50)
	Female	334 (51)	394 (49)	728 (50)
Region	*North*	56 (9)	95 (12)	151 (10)
	North Harbour	222 (34)	279 (34)	501 (34)
	South East	76 (12)	108 (13)	184 (13)
	South Harbour	151 (23)	174 (21)	325 (22)
	West	88 (13)	86 (11)	174 (12)
	Gozo	65 (10)	70 (9)	135 (9)

Table 2: Predicted proportion 'cured' in 1995 - 1999 and 2000 - 2004, by age. Z-test compares proportions for total and age groups across year of diagnosis.

		Year of Diagnosis				
		1995 - 1999		*2000 – 2004*		
		Proportion 'cured' %	***95% CI***	***Proportion 'cured' %***	***95% CI***	**z-test**
Total		***45.3***	***40.2 – 50.5***	***52.3***	***47.2 – 57.5***	***p=0.008***
Age (years)	***<55***	47.4	38.2 - 56.5	58.0	46.5 - 69.6	p=0.08
	55 - 64	35.3	26.4 – 44.2	49.9	41.4 – 58.4	p=0.007
	65 - 74	53.1	45 – 61.2	50.9	43.3 – 58.5	p=0.65

Table 3: Median survival time of the "uncured" in 1995 - 1999 and 2000 - 2004 by age

		Year of Diagnosis			
		1995 - 1999		*2000 – 2004*	
		Median survival time of uncured (years)	*95% CI*	*Median survival time of uncured (years)*	*95% CI*
Total		***1.25***	***1.04 – 1.45***	***1.42***	***1.15 – 1.76***
Age (years)	***<55***	1.32	0.96 – 1.81	2.40	1.39 – 4.16
	55 - 64	1.71	1.29 – 2.29	1.46	1.06 - 2.02
	65 - 74	0.80	0.60 - 1.08	1.07	0.80 - 1.43

Figure 1: Relative Survival Ratio (%) up to 16 years after diagnosis (a) by gender (b) by region of residence (c) by year of diagnosis (d) by age at diagnosis

Figure 2: Relative Survival Ratio (%) estimates derived from the model and using Ederer II with corresponding 95% CI for patients diagnosed 1995-1999, by age at diagnosis. Horizontal lines indicate point where statistical cure is reached.

Figure 3: Relative Survival Ratio (%) estimates derived from the model and using Ederer II with corresponding 95% CI for patients diagnosed 2000-2004, by age at diagnosis. Horizontal lines indicate point where statistical cure is reached.

Figure 4: Relative Survival Ratio (%) estimates for the uncured patients only derived from the model. Vertical lines indicate median survival time.

Figure 1

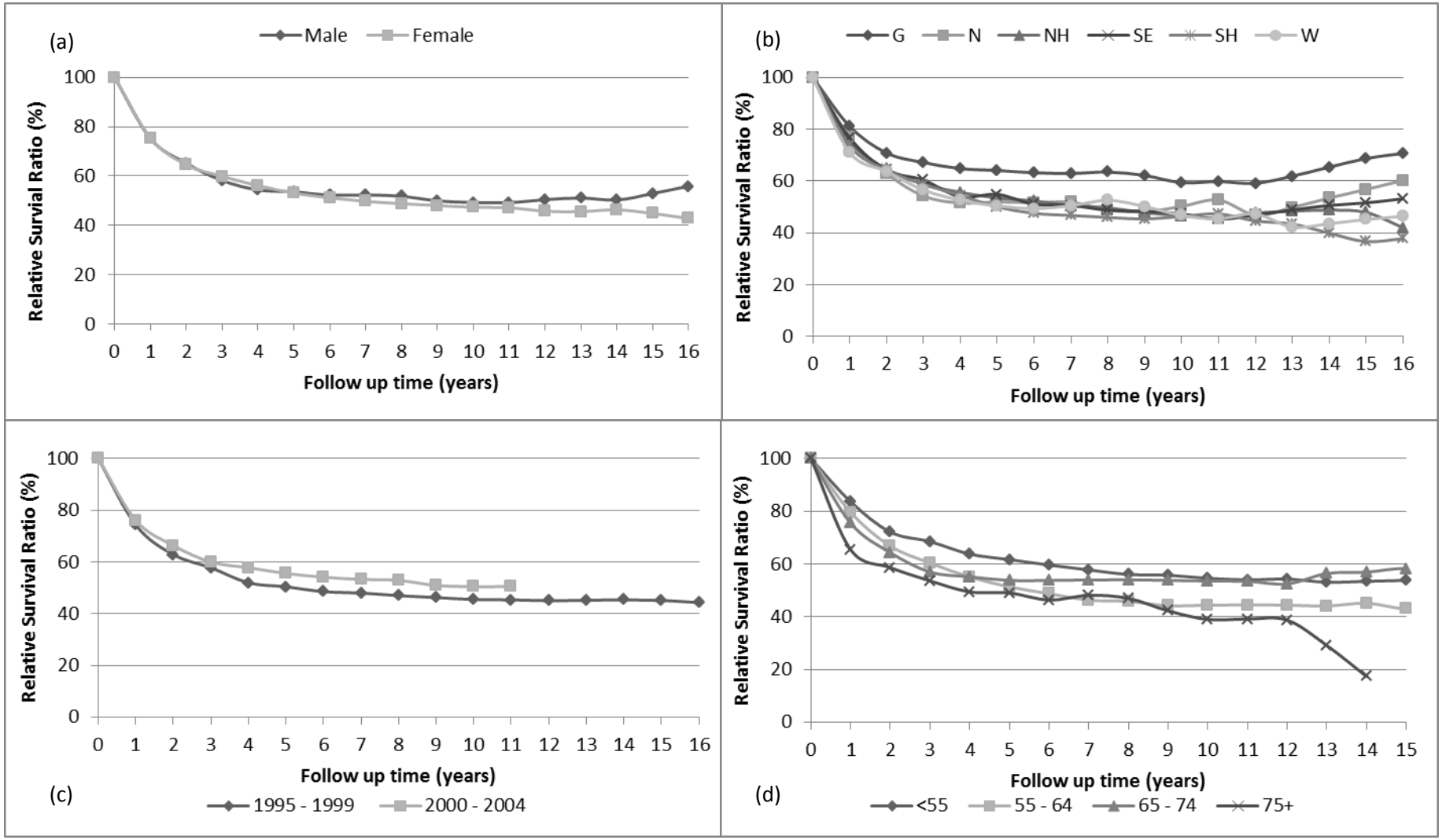
(a)
Male
Female
Relative Survial Ratio (%)
Follow up time (years)
(b)
G
N
NH
SE
SH
W
Relative Survival Ratio (%)
Follow up time (years)
(c)
1995 - 1999
2000 - 2004
Relative Survival Ratio (%)
Follow up time (years)
(d)
<55
55 - 64
65 - 74
75+
Relative Survival Ratio (%)
Follow up time (years)

Figure 2

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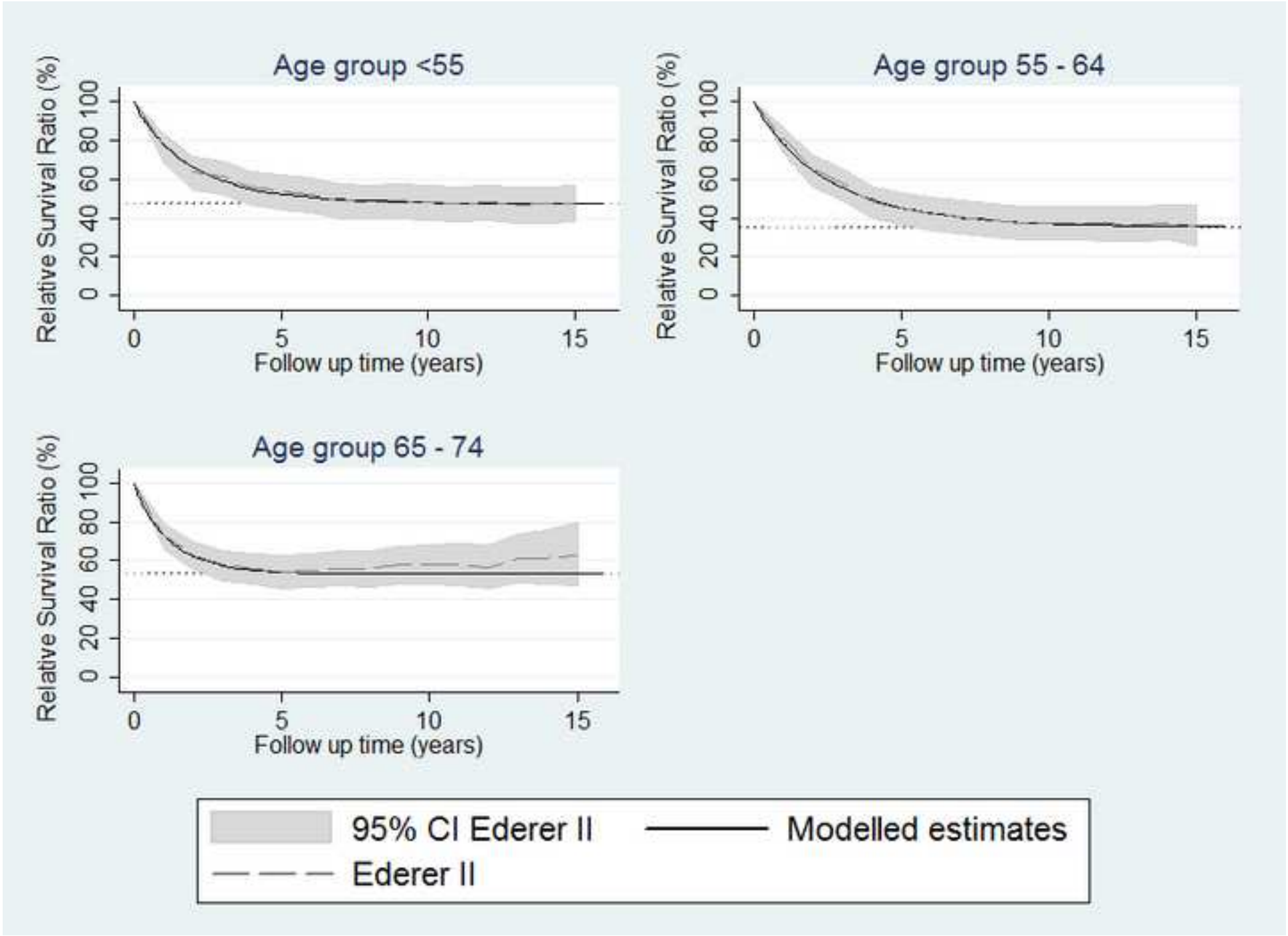

Figure 3

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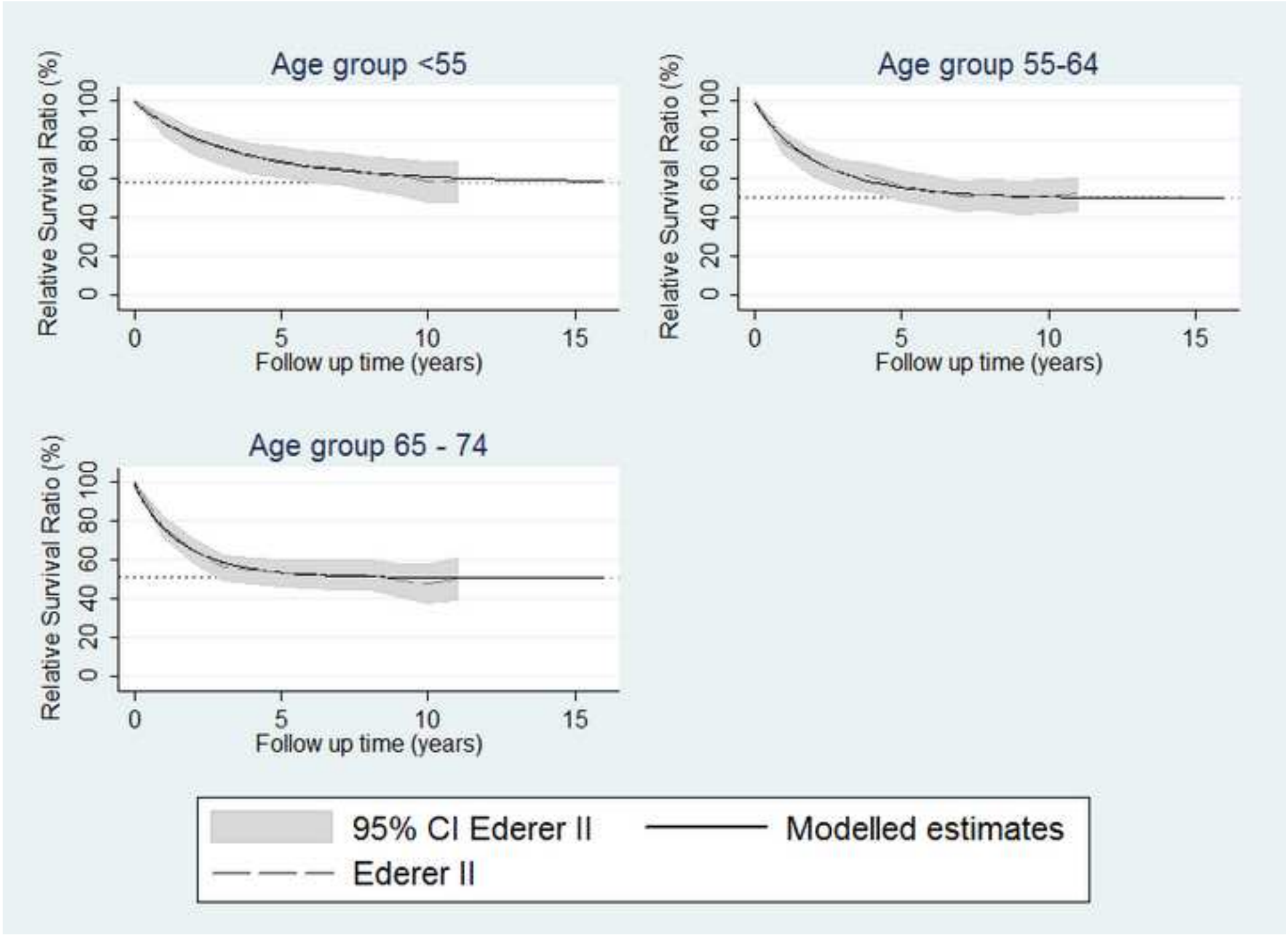

Figure 4

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