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METHODOLOGY FOR ESTIMATION OF CANCER INCIDENCE, SURVIVAL AND PREVALENCE IN ITALIAN REGIONS

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Background: **The Italian health care system is based on a regional responsibility and organization. Incidence, survival and prevalence of cancer patients were estimated for major cancer sites by single regions in Italy within a collaborative project "I TUMORI IN ITALIA" aimed at providing epidemiological information in a web site, www.tumori.net, for health operators, health programmers, epidemiologists and the general public. The aim of this paper is to present the methodology used to derive regional estimates of cancer burden indicators in Italy for major cancer sites.**
Methods: **Estimates require a complex methodology to be used. We present herein the methodology to provide regional estimates that involves a combined use of multiple methods to model and extrapolate patient survival to derive incidence and prevalence estimates and future projections.**
Results: **Regional patient survival estimates in Italy are presented and discussed. Cancer survival has greatly improved over the years and differences between northern-central and southern regions have persisted. The fraction of patients cured from cancer is today over 50% for young men and women aged 15-44 and declines to 15%-25% at older ages (75-99).**
Discussion: **We integrated different methods to derive estimates of cancer burden in Italy, at a regional level, in order to take advantage of all information available and to obtain the most reliable estimates. The value of producing regional estimates of cancer burden indicators was motivated by the lack of such information systematically on the Italian national territory.**

Key words: cancer incidence, cancer mortality, cancer prevalence, cancer survival, statistical method.

Introduction

Estimation of cancer burden indicators is a complex research task that requires availability of multiple data sources and multiple statistical methods. Cancer registration is sparse in Italy, thus we need to extrapolate from the local to the national or regional scale the information on cancer incidence and patient survival. Most of the local cancer registries (CRs) in Italy are located in the northern-central part of the country[1]. Due to the partial coverage and no uniform distribution of CRs in Italy, we need methods to extrapolate information on cancer survival from local to regional or national levels. Furthermore, we need methods to derive regional incidence and prevalence estimates and projections able to use regional cancer mortality and patient survival estimates.

The aim of this paper is to present the methodology used to derive regional estimates for the project "I TUMORI IN ITALIA", established by the Fondazione IRCCS "Istituto Nazionale dei Tumori" and the Istituto Superiore di Sanità, in collaboration with the Italian Cancer Registries Association (AIRTum). The methodology presented in this paper refers to a) modeling patient survival and b) estimation and projection of cancer incidence and prevalence. Results on model-based survival used in the MIAMOD estimates presented in specific papers[2-7] are also discussed.

Methods

In order to estimate cancer incidence and prevalence at a regional level, a three-step procedure was used.

1) In the first step, a statistical approach to estimate patient survival for each Italian region and for Italy as a whole was developed[8] and used. 2) Regional cancer official mortality and patient survival estimates were used as input for a specifically designed statistical method (MIAMOD[9]) to estimate cancer incidence and prevalence at regional and national levels. 3) Cancer incidence estimates were then validated with available CR data in order to evaluate their reliability.

We present the methodology with reference to steps 1 and 2, whereas for step 3 we refer to an *ad hoc* paper on validation of incidence estimates[10].

Step 1. Cure mixture models to extrapolate patient survival from local to regional and national levels

According to a subdivision of the Italian territory into four geographical macro-areas (North-West, North-East, Center, South), survival data were modeled within each macro-area by a cure parametric mixture model[11,12]. This class of models assumes that a proportion P of patients is "cured" from cancer and will experience the same mortality risk as the general population of the same sex and age group. The relative survival for the remaining proportion of "uncured" cases (1-P) is as-

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sumed to be Weibull distributed, whereas it is equal to one for “cured” cases (*P*).

For projections up to 2010, cancer survival is assumed to increase at the same rate as that observed during the observational time window.

We present the application of this methodology aimed to estimate regional and national relative survival figures. The modeled regional and national survival is then used as an input to the MIAMOD method (step 2) aimed to estimate incidence and prevalence trends and projections.

a) Regional estimates of relative survival

Population-based cancer survival data were provided by the Italian CRs participating in collaborative studies[13,14]. Cancer survival data from CRs include patients diagnosed within the period 1978-1994, with different starting registration years among registries, and common closure of follow-up at December, 1999. The 13 considered CRs cover only about 16% of the whole national population, less than 9 million individuals of the over 57 million. Their territorial distribution does not follow statistical sampling criteria, being mostly concentrated in the northern and in the central part of the country.

For estimation purposes, the 20 Italian regions have been aggregated into four geographical macro-areas as follows: North-West (Liguria, Lombardia, Piemonte, Valle d’Aosta), North-East (Emilia Romagna, Friuli Venezia Giulia, Trentino Alto Adige, Veneto), Center (Lazio, Marche, Toscana, Umbria), South (Abruzzo, Basilicata, Calabria, Campania, Molise, Puglia, Sardegna, Sicilia), reflecting the standard classification of the Italian territory. According to this classification, three CRs belong to the North-West, five to the North-East, three to the Center and only two to the South. The two registries in the South are actually located in islands Sardegna and Sicilia, whereas no CR is available in the continental southern part of the country. For this reason, the Latina CR, located on the border between the Center and South, has been considered for the estimation of survival in both areas, with the only exception of breast cancer survival estimates.

Modeling cancer patient survival with mixture models makes it possible to consider covariates. Two categorical covariates (geographical area and age) and one continuous covariate (period of diagnosis) have been included in the model, which was estimated for each sex separately. Let us consider a macro-area. The relative survival $S_{x,j}(d,t)$ at follow-up time *d* and period of diagnosis *t,* for the j^{th} region with at least one CR (within the macro-area) and for the age class *x*, is given by:

$$S_{x,\,j}\,(d,t) = [S_x(d)]^{\exp[\beta j(\mathrm{t}-\bar{\mathrm{t}})+RRj]} \qquad [1],$$

with

$$S_x\,(d) = P_x + (1\text{-}P_x)\exp[-((\lambda_x d)^{\gamma_x})] \qquad [2],$$

where $S_x(d)$ represents the baseline modeled survival in a macro-area. The constant $\bar{\mathrm{t}}$ is set equal to 1986, the central value of the calendar period 1978-1994. Model parameters are: P_x (proportion of cured cases at age class *x*), λ_x and γ_x (scale and shape of Weibull’s parameters), β_j (log relative risk of dying) and RR_j (log relative excess death risk for the j^{th} area). The mean survival time of fatal cases for the age class *x,* T_x, is given by $\lambda^{-1}\Gamma\,(1+1/\gamma)$, where Γ is the gamma function. For regions with no CR inside we used the relative survival of the macro-area (see Table 1: macro-area). For regions with one or more CRs we derived specific regional estimates (see Table 1: regional).

According to trends observed in survival for specific macro-area cancer sites, whether homogeneous or variable between regions, the time trend parameter β may be unique or specific.

All cancers combined supported the modeling of relative survival for regions sufficiently covered by cancer registration[15].

b) National estimates of relative survival

The national survival estimates have been obtained as the weighted geometric average (A) of the macro-area specific survival estimates by using the following two equations[8]:

$$S_{x,\,A}\,(d,t) = \prod_{j\in\{NW,NE,C,S\}} S_{x,j}(d,t)^{w_j} \qquad [3]$$

$$S_{x,\,j}\,(d,t) = [S_x(d)]^{\exp[\beta_A(\mathrm{t}-\bar{\mathrm{t}})+RR_A]} \qquad [4]$$

The w_j are normalized weights assigned to the four macro-areas and are defined as the percentage proportion of expected incident cases for each geographic macro-area (Table 2). The values w_j are obtained as the ratio between the number of incident cases estimated in all regions belonging to the *j*-th macro-area and the total number of incident cases estimated for Italy.

By combining equations [3] and [4] and applying the natural logarithm to both members, we obtain the following equation:

$$\exp\left\{\beta_A\left(t-\bar{t}\right)+RR_A\right\} = \sum_{j\in\{NW,NE,C,S\}} w_j\exp\left\{\beta_j\left(t-\bar{t}\right)+RR_j\right\} \qquad [5]$$

Taking the first degree Taylor’s approximation based on the fact that the arguments of the exponential functions in equation [5] are small, we can simplify the estimation of β_A and RR_A. Estimates of β_A and RR_A are consequently derived as weighted arithmetic averages of the area-specific parameters:

$$\beta_A = \sum_{j\in\{NW,NE,C,S\}} w_j\beta_j \qquad RR_A = \sum_{j\in\{NW,NE,C,S\}} w_j RR_j \qquad [6]$$

In the particular case that in the defined areas, and consequently in the whole country, there is a unique pe-

Table 1 - Regional coverage of the Italian Cancer Registries (CRs) included in the study, with the reference period of survival data, and model used for survival estimation. The type of period-trend coefficient is reported for each cancer site

Regions	% of regional population covered by CRs	Period	Survival MODEL					
			Lung	Colon-Rectum	Stomach	Breast	Prostate	All cancers
(time trend parameter)			(unique)	(area-specific)	(unique)	(area-specific)	(area-specific)	(area-specific)
North-West								
Piemonte	21.8	1985-1994	regional	regional	regional	macro-area	macro-area	macro-area
Valle d'Aosta	-	-	regional	regional	regional	macro-area	macro-area	macro-area
Lombardia	9.0	1978-1994	regional	macro-area	regional	macro-area	regional	regional
Liguria	39.5	1986-1994	regional	regional	regional	macro-area	macro-area	macro-area
North-East								
Trentino Alto Adige	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Veneto	45.1	1987-1994	regional	macro-area	regional	macro-area	macro-area	macro-area
Friuli Venezia Giulia	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Emilia Romagna	45.6	1986-1994	regional	regional	regional	macro-area	regional	regional
Center								
Toscana	33.4	1985-1994	regional	regional	regional	macro-area	regional	macro-area
Umbria	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Marche	20.7	1991-1994	regional	macro-area	regional	macro-area	macro-area	macro-area
Lazio	9.4	1983-1994	macro-area	regional	regional	macro-area	macro-area	macro-area
South								
Abruzzo	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Molise	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Campania	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Puglia	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Basilicata	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Calabria	-	-	macro-area	macro-area	macro-area	macro-area	macro-area	macro-area
Sicilia	5.9	1981-1994	regional	regional	regional	macro-area	regional	regional
Sardegna	27.2	1992-1994	regional	macro-area	regional	macro-area[1]	macro-area	macro-area

[1]Only in this case area specific model refers to the pool of CRs in the combined macro-areas of Center and South.

riod trend coefficient, i.e., $\beta_j = \beta_A = \beta \forall j$ in equation [5], we do not need any approximation to obtain directly an exact formula for the only unknown parameter RR_A:

$$RR_A = \ln \left[\sum_{j \in \{NW,NE,C,S\}} w_j e^{RRj} \right] \qquad [7]$$

In all cases, the parameters of the national survival function depend only on the set of parameters P, λ and γ, on the weights w_j and on the parameter β_A and RR_A. The choice between formulas [6] and [7] depends on whether the observed CR data suggest to consider a unique time trend or a geographically specific time trend.

Step 2. MIAMOD method for estimating incidence and prevalence

The incidence and prevalence estimates were derived by the statistical method MIAMOD (Mortality-Incidence Analysis MODel)[9], a back-calculation approach to estimate and project morbidity of chronic irreversible diseases, such as cancers, starting from mortality and survival data. A specific software was developed[16,17] and used to produce estimates. Mortality data by cause of death, age, sex and region are available in Italy by the Italian National Institute of Statistics, ISTAT.

The method is based on the mathematical relationships relating mortality and prevalence to incidence and relative survival probabilities, for a given cancer. For a birth cohort, the age-specific proportion of prevalent cases at age x, P_x, is given by the following recursive formula:

$$P_x = \sum_{i=0}^{x-1} (1-P_i)\,\mu_i S_{i,x} \qquad [8]$$

where the term (1-P_i) represents the probability to be free from cancer at age i, m_i is the probability of being diagnosed with cancer between ages i and i + 1, and $S_{i,x}$

Table 2 - Weights w_j assigned to the four macro-areas specific for sex and cancer site

Macro-area	Lung		Colon-Rectum		Stomach		Prostate	Breast	All cancers	
	M	F	M	F	M	F	M	F	M	F
North-West	0.32	0.36	0.32	0.34	0.30	0.32	0.36	0.33	0.30	0.31
North-East	0.23	0.27	0.23	0.23	0.23	0.25	0.24	0.22	0.22	0.22
Center	0.20	0.18	0.22	0.21	0.26	0.26	0.21	0.22	0.24	0.24
South	0.25	0.19	0.23	0.22	0.20	0.17	0.19	0.23	0.24	0.23

is the relative survival probability up to age x for patients diagnosed at age i. With the assumption $P_0 = 0$, P_x at each age x can be derived as a function of incidence and survival.

For the same birth cohort, the age specific probability to dye (M_x) for a given cancer is expressed as:

$$M_x = \sum_{i=0}^{x} (1-P_i)\, \mu_i\, S_{i,x}\, d_{i,x} \qquad [9]$$

the term $d_{i,x}$ is the probability to dye from cancer at age x for patients diagnosed between ages i and $i + 1$ who survive until age x[9]. By combining equations [8] and [9], we can express expected mortality as a function of incidence and survival, $M = \Phi(\mu, S)$.

Incidence probability m is modeled in the logistic scale as a regular polynomial function of age (x), period (t) and cohort (c = t-x) covariates:

$$\operatorname{logit}\left(\mu_{x,t}(\alpha)\right) = \alpha_0 + \sum_{i=0}^{A} \alpha_i (x)^i + \sum_{i=1}^{P} \alpha_{A+i}(t)^i + d_{i,x} \sum_{i=1}^{C} \alpha_{A+P+i}(c)^i \qquad [10]$$

where coefficients α are estimated by regressing the expected mortality on the observed mortality by calendar year and annual age. The regression coefficients are obtained through the maximum likelihood method, assuming a Poisson distribution for cancer deaths.

To avoid co-linearity problems, the linear period coefficient, α_{A+1}, is excluded from equation [10] when polynomial degrees A,P,C are all different from 0. The polynomial degrees and the parameter values α are determined by fitting several nested models in a stepwise-like procedure. Once the incidence function has been estimated, prevalence is derived from equation [8].

Incidence is projected in the future by model [10], assuming that age and cohort coefficients will persist in the next years, whereas the period polynomial is substituted by the linear drift. Mortality and prevalence are forward projected through equations [8] and [9]. The population is also projected by MIAMOD assuming that the number of newborns and the mortality rates for causes other than cancer will remain constant and equal to the last year of observation (1999).

All the estimates refer to the age class 0-84 years, as mortality data for the population older than 85 are too sparse to be modeled.

Results

As incidence and prevalence estimates produced by MIAMOD (step 2 of the methods) are presented elsewhere[2-7], we present herein the results of modeling and projecting cancer patient survival figures (step 1 of the methods) that were used as input by MIAMOD.

Table 1 shows the list of the Italian regions, the percentage coverage by cancer registration with respect to the regional population, the incidence period of the survival cases available, and the details on the survival model used.

Figure 1 shows the estimated trends of 5-year relative survival for men by cancer site and macro-area. Relative survival dramatically improved for all the cancer types, including lung and stomach cancers, which are traditionally considered big killers. Relative survival in the southern area was generally worse, particularly for prostate cancer and all cancers combined.

Figure 2 shows the estimated trends of 5-year relative survival for women by cancer site and macro-area. Relative survival in the southern area was in this case markedly worse than in the other areas.

Table 3 reports the proportion cured (P) and the mean survival time for uncured (T) and the corresponding standard errors by cancer site, sex, and age class in Italy. The fraction cured was 30-50% for colorectal and breast cancers, and for all cancers combined, whereas it was lower for stomach, lung, and prostate cancers. The fraction cured was generally higher for women than men. The mean survival time for uncured was very short, 1-1.5 years, thus indicating that the death hazard was usually concentrated at a short time, with the exceptions of prostate and breast cancers, with a mean survival time for uncured variable from 4-12 years.

Age is a strong predictor of outcome for cancer. The fraction cured and the mean survival time for uncured declined with age. Figure 3 shows for all cancers combined how the fraction cured P and the mean survival time for uncured T change with age class. Young women had the top P and T. Both P and T declined with increasing age. For men, the mean survival time for uncured T remained almost steady by age whereas the proportion cured declined from 50% for young men to 15% for the elderly.

Discussion

Within the project "I TUMORI IN ITALIA", we derived estimates of cancer burden in Italy, at a regional level, by combining the MIAMOD method and the cure parametric mixture survival models in a unique framework. Such an approach allows us to take advantage of all information available with the aim of obtaining the most reliable estimates. Cancer survival and incidence estimates were validated by using cancer registry data where available. Results of validation of estimated incidence are reported in a specific paper[10]. Modeled survival is confirmed within the incidence validation, since to obtain validated incidence estimates we need a proper and unbiased survival estimate.

The value of producing regional estimates of cancer burden indicators was motivated by the lack of this information systematically on the Italian national territory. Cancer registration is expanding in Italy and today has reached a coverage of about 26% of the whole national population[18], although the distribution of local CRs is still not representative of the Italian population and only 14 regions have partial coverage.

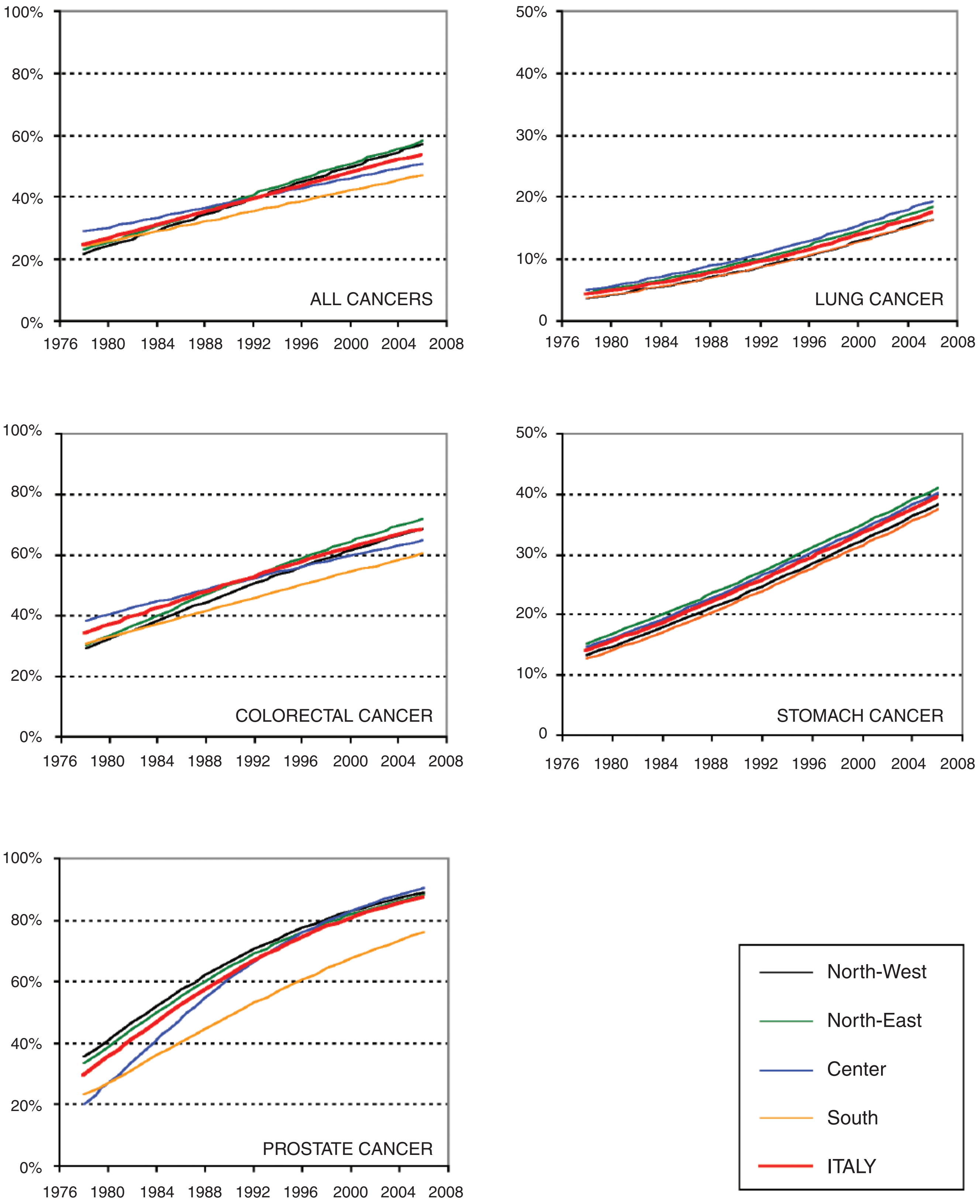

Figure 1 - 5-year modeled relative survival trends by cancer site and geographical area. Men.

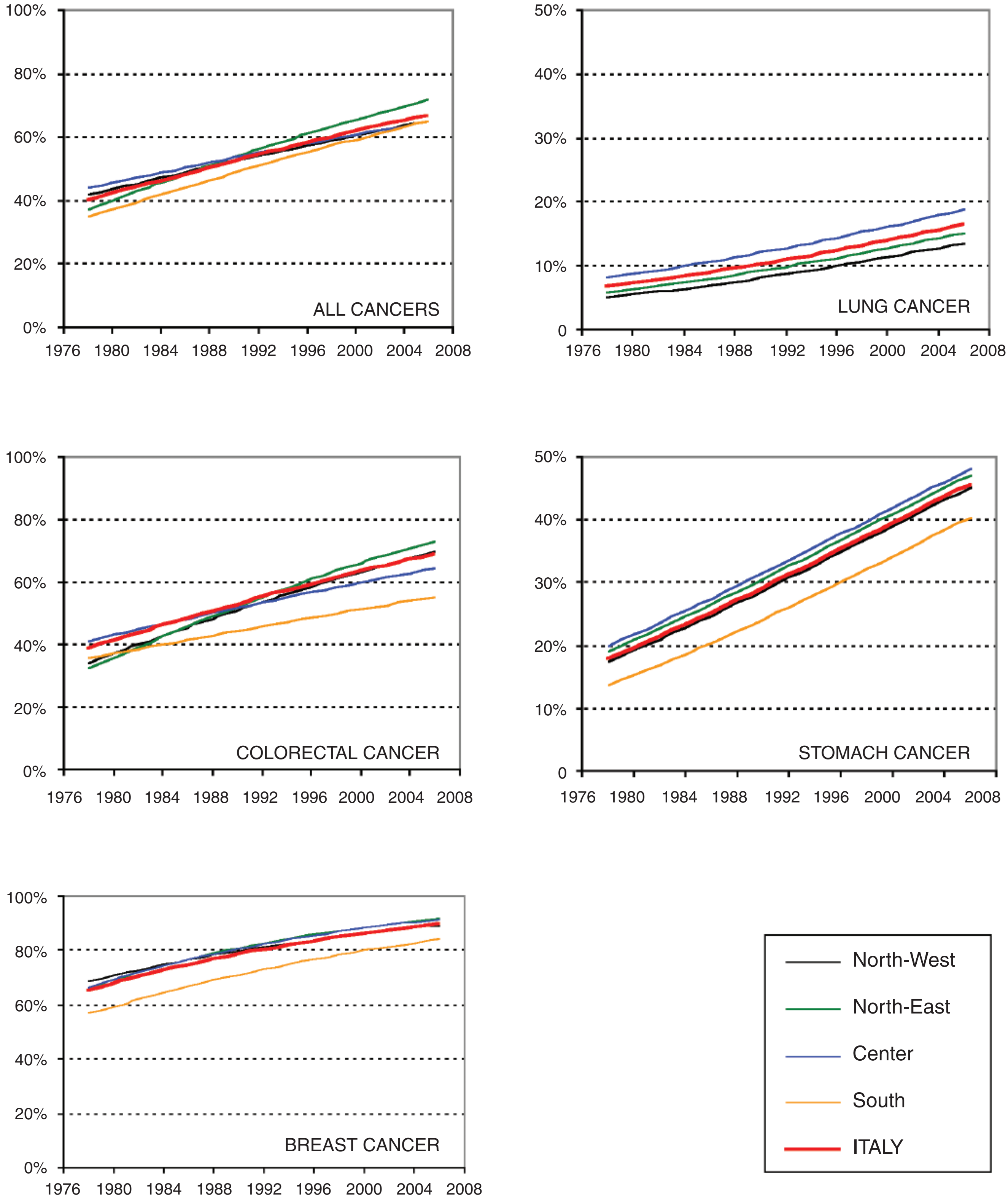

Figure 2 - 5-year modeled relative survival trends by cancer site and geographical area. Women. (Female lung cancer is a rare disease in southern regions and leads to lack of convergence of the modeling procedure. Female lung cancer survival for the southern regions was obtained from the pool of the Italian cancer registries and not presented in the chart.)

Table 3 - Proportion cured (P) and mean survival time for uncured (T) by cancer site in Italy

Cancer site	Age class	Men				Women			
		Proportion of cured cases		Mean survival time (years)		Proportion of cured cases		Mean survival time (years)	
		estimate	std. error	estimate	std. error	estimate	std. error	estimate	std. error
Colon-Rectum	15-44	0.445	0.008	2.050	0.094	0.458	0.008	2.149	0.101
	45-54	0.413	0.005	2.043	0.056	0.475	0.004	1.952	0.055
	55-64	0.384	0.005	2.221	0.044	0.438	0.005	2.367	0.052
	65-74	0.322	0.007	2.373	0.041	0.404	0.005	1.846	0.035
	75-99	0.224	0.010	1.890	0.032	0.307	0.005	1.267	0.023
Stomach	15-44	0.299	0.024	3.431	0.151	0.336	0.012	1.574	0.119
	45-54	0.279	0.006	1.524	0.055	0.290	0.011	2.021	0.094
	55-64	0.189	0.004	1.363	0.031	0.240	0.008	1.714	0.054
	65-74	0.147	0.004	1.164	0.023	0.214	0.005	1.224	0.035
	75-99	0.098	0.004	0.819	0.020	0.142	0.004	0.821	0.022
Lung	15-44	0.156	0.004	0.853	0.041	0.219	0.009	0.947	0.082
	45-54	0.092	0.002	1.029	0.024	0.121	0.004	0.882	0.038
	55-64	0.074	0.001	1.003	0.014	0.086	0.003	0.910	0.027
	65-74	0.046	0.001	0.931	0.013	0.046	0.002	0.823	0.023
	75-99	0.018	0.001	0.650	0.650	0.030	0.002	0.590	0.022
Breast	15-44					0.482	0.007	5.124	0.116
	45-54					0.503	0.007	5.163	0.115
	55-64					0.410	0.009	5.412	0.130
	65-74					0.291	0.023	7.669	0.399
	75-99					0.000	0.000	12.425	0.170
Prostate	15-54	0.259	0.048	4.316	0.450				
	55-64	0.332	0.018	4.830	0.227				
	65-74	0.271	0.018	5.578	0.236				
	75-84	0.000	0.000	7.743	0.086				
	85-99	0.000	0.000	3.411	0.095				
All cancers	15-44	0.506	0.004	2.145	0.045	0.568	0.008	5.289	0.155
	45-54	0.328	0.003	1.583	0.022	0.520	0.006	4.345	0.083
	55-64	0.259	0.002	1.655	0.013	0.433	0.004	3.349	0.039
	65-74	0.210	0.003	1.846	0.011	0.341	0.005	2.868	0.023
	75-99	0.147	0.005	1.819	0.010	0.258	0.004	1.431	0.011

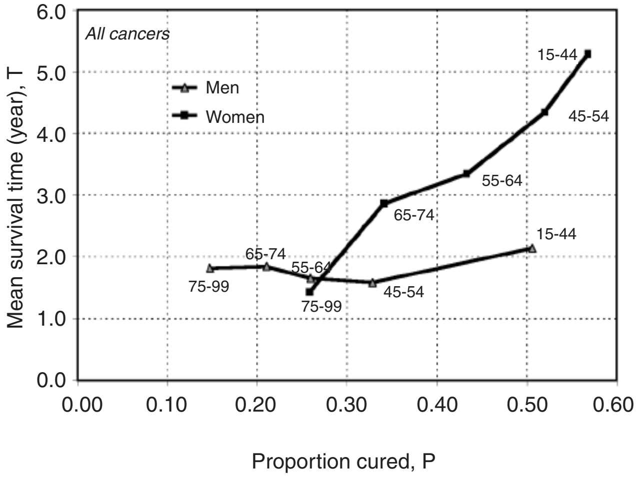

Figure 3 - Fraction of cured and mean survival time for uncured by sex and age class. All cancer survival in Italy. Confidence limits on both axis were very small (see standard errors in Table 3) and not reported on the plot.

Differently, mortality data are routinely collected and available for the whole country. With appropriate modeling of patient survival figures available by local CRs, we derived estimates of relative survival by region in Italy as a first step, and the results are presented herein. Combining together information of cancer mortality and patient survival, the MIAMOD method allowed us to obtain useful information on trends in incidence, mortality, and prevalence by single region and nationally with projections to 2010.

The methodology here illustrated has been proved to represent a flexible and valid procedure to systematically provide incidence and prevalence estimates and projections, for the main cancer sites, for both sexes and all regions. The procedure developed for deriving regional and national incidence and prevalence estimates in Italy has the potential to be a model for other European countries with no national cancer registration.

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