

REGIONAL ESTIMATES OF ALL CANCER MALIGNANCIES IN ITALY

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Aims and background: The aim of this paper is to present regional and national estimates of mortality, incidence and prevalence for all cancers in Italy over the period 1970-1999, with projections up to 2010.

Methods: The estimates were obtained by applying the MIAMOD method, a statistical back-calculation approach, to derive incidence and prevalence starting from mortality and relative survival data. Published data from the Italian Cancer Registries were modeled in order to estimate regional and national cancer survival.

Results: Cancer time trends resulted more favorable in northern-central regions than in southern regions, both for men and women. Mortality started to decrease in the northern-central area approximately from the mid 1980s, whereas it was expect-

ed to slightly decline only after the year 2000 in the southern area. Incidence was estimated to decrease in men from 1995 in northern and central areas only; no incidence reduction is expected for women during the study period. Overall, 130,000 cancer deaths, 250,000 new cancer cases and 1,700,000 prevalent cancer cases are estimated in Italy in the year 2005.

Conclusions: This up-to-date picture of cancer risk and burden in the Italian regions shows as a relevant epidemiological change is ongoing in Italy. Although a clear geographical variability in mortality and morbidity levels still exists across the country, the historical North-to-South gap appears smaller than in the past. This change is particularly remarkable for men, as a consequence of trends that are favorable in northern-central regions but not yet in southern regions.

Key words: incidence, mortality, neoplasm, population surveillance, prevalence, regional medical programs, registries, regression analysis.

Introduction

Knowledge of the main cancer burden indicators, i.e., mortality, incidence, prevalence and survival, is increasingly used for public health planning and intervention. These tasks require up-to-date estimates and projections to evaluate progresses and possibly define new programs of cancer control. In Italy, continuous monitoring of these indicators on a regional basis is particularly relevant, not only as cancer levels and trends historically strongly vary from North to South, but also as a consequence of the progressive devolution of the public health services to the regional authorities.

Mortality data for the national and regional populations are available in Italy with a delay of 3-5 years¹. The other indicators are generally provided by population-based cancer registries (CRs), which cover a fraction of the national population. At the end of the nineties, cancer registration was established in about 20% of the country², with only 3 (Umbria, Friuli Venezia Giulia and Trentino Alto Adige) out of 20 regions entirely covered, and with a geographical coverage heavily biased toward the northern-central areas of the country. Incidence (and prevalence data) are published 4-6 years after the period to which they refer³,

with a delay that is rather difficult to shorten to less than 3 years.

Statistical models are therefore a useful complement of cancer data collection. Models can be applied to empirical data to produce epidemiological indicators at national and regional scales and to project their estimated values to the near future. A research program, aimed at providing systematic and up-to-date estimates of incidence and prevalence for the major cancers at a regional level, has been established by the Istituto Superiore di Sanità, Rome, and the Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan, in collaboration with the network of Italian Cancer Registries (AIRTum).

The most complete output of the program, named "I TUMORI IN ITALIA", will be a cancer statistics data base accessible on a website (www.tumori.net). This paper, presenting the results for all cancer malignancies, is one of a set of articles aimed at providing the results of this modeling activity for the most important cancer sites in Italy.

Estimated trends for 1970-2010 of mortality and incidence for all cancers combined are illustrated by geographical area. Cancer mortality, incidence and prevalence indicators in Italy and in all Italian regions are presented for the calendar year 2005.

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Materials and methods

Mortality data for all malignant cancers combined (excluding non-melanoma skin cancer: ICD-IX revision 140-172, 174-208) and population data by sex, age, calendar year and geographical region for the period 1970-1999 were obtained from the Italian National Institute of Statistics (ISTAT). A correction coefficient (about -3%) has been applied to the 1970-1994 mortality rates in order to take into account the change from a manual to an automatic coding system for the mortality data, introduced in 1995⁴.

Relative survival data for all malignant cancers were derived from the CD-ROM of the EURO CARE-3 study⁵ and refer to the incident cases collected by 13 Italian CRs (Table 1) during the period of diagnosis 1978-1994 and followed until 1999: Torino, Varese, Genova, Veneto, Modena, Ferrara, Parma, Romagna, Toscana, Macerata, Latina, Ragusa and Sassari CRs, all together covering about 16% of the national population. Each registry has a specific geographic coverage (health district, town or province) and a different percentage of population covered in the region.

Incidence and prevalence estimates have been derived by the statistical method MIAMOD (Mortality-Incidence Analysis MODel)^{6,7}, a back-calculation approach to estimate and project morbidity of chronic irreversible diseases, starting from the knowledge of mortality and survival data. The method is based on the mathematical relationships relating mortality and prevalence, for a given disease, to incidence and survival probabilities. Incidence is modeled as a polynomial function of age, period, and birth cohort (APC) covariates. The incidence model parameters are back-calculated through a Poisson maximum likelihood regression on the observed mortality data. Prevalence is then computed by convolution of incidence and survival over time. Incidence, and all the related quantities, are projected beyond the last year of observed data (1999) on the basis of the estimated APC coefficients.

To estimate relative survival of cancer patients for each Italian region, the locally observed data were modeled by means of parametric cure models of a Weibull type⁸. A categorical covariate for age at diagnosis (15-44, 45-54, 55-64, 65-74, 75+) and one continuous covariate for year of diagnosis were included in the model, which was separately estimated for each sex and geographical area.

A regional geographic area was used when long-term local CR data were available, i.e., Lombardia (Varese CR), Emilia Romagna (Parma CR*), and Sicilia (Ragusa CR), respectively. A wider geographic area (North-Center, South) was considered to derive stable survival estimates in the regions with more recently established CRs or without any cancer registration system at all.

The northern-central area included the cancer registries of Torino, Varese, Genova, Veneto, Modena, Ferrara, Par-

ma, Romagna, Toscana, Macerata and Latina. The survival estimate obtained for this area was attributed to the regions of Piemonte, Valle d'Aosta, Liguria, Trentino Alto Adige, Veneto, Friuli Venezia Giulia (northern Italy), Toscana, Umbria, Marche, and Lazio (central Italy). The southern area included data from the registries of Ragusa, Sassari and Latina** and was used to derive survival estimates for the regions Abruzzo, Molise, Campania, Puglia, Basilicata, Calabria, and Sardegna.

The survival estimate for Italy was obtained as the geometric weighted average of northern, central and southern areas estimates, using the proportions of expected incident cases in each area as weights. A full description of the modeling approach used to derive national survival estimates has been reported in a recently published paper⁹.

For projections up to 2010, cancer survival is assumed to increase during the projection period 1995-2010 at the same rate as that observed during the 1978-1994 time window. All mortality, incidence and prevalence estimates refer to the age class 0-84 years. Age-adjusted rates are based on the standard European population.

Results

The results obtained from the survival analysis⁵ are not reported in detail in this paper, since they can be considered as a by-product for the true objective of the program, i.e., incidence and prevalence estimation. However, they are extensively reported in a technical document available from the project website www.tumori.net. In brief, all cancers survival in Italy showed relevant improvements during the study period and a certain degree of geographic variability, especially in men. Male patients' 5-year survival increased from 25% in the period 1978-82 to 42% in 1992-94 in the northern-central area, with an annual rate of about 3%. In the southern area, the annual growth was about 2% and survival increased to 36% in 1992-94. Women's survival increased at the same rate (2%) both in northern-central and southern areas, growing from 42% to 56% and from 38% to 52%, respectively.

Figures 1 and 2 report mortality and incidence trends for all cancers in Italy by geographic area, in the period 1970-2010 for men and women, respectively. The official mortality for 1970-1999, used as input in the estimation procedure, is also reported to show the estimated mortality fit to observed data.

Male mortality rates (Figure 1) in northern and central areas started to decrease approximately from the mid 1980s, whereas in the southern area they remained almost stable throughout the 1990s and started to decline just thereafter. A relevant reduction of male incidence rates was estimated for both northern and central areas after 1995. This decline was stronger in the northern area, where the incidence rate was expected to decrease from 430 to 350 per 100,000 person years (py) in 2010. A rate of 350 per 100,000 py in 2010 was also predicted

*Parma is the first-established CR but also the data of Romagna, Ferrara and Modena CRs contributed to the estimation of survival for the region Emilia Romagna.

**Latina cancer registry located on the border between Center and South has been considered for the estimation of survival in both areas.

Table 1 - Regional distribution of the Italian Cancer Registries (CRs) included in the study. Percentage of regional population coverage in the reference period of CR's survival data of all cancers (EUROCARE-3 study⁵)

Macro-area and regions	Regional population*	Cancer Registry (CR)	CR covered area	% of regional population covered by CRs	Reference period
North-West					
Piemonte	4,251,500	Torino	Town of Torino	21.8	1985-1994
Lombardia	9,077,700	Varese	Province of Varese	9.0	1978-1994
Liguria	1,595,500	Genova	Town of Genova	39.5	1986-1994
North-East					
Veneto	4,535,300	Veneto	Eleven Health Districts in the Veneto Region	45.1	1987-1994
Emilia Romagna	3,996,600	Ferrara	Province of Ferrara	9.1	1989-1994
		Modena	Province of Modena	15.6	1988-1994
		Parma	Province of Parma	10.0	1978-1994
		Romagna	Provinces of Forlì, Ravenna and Rimini	10.9	1986-1994
Center					
Toscana	3,522,300	Toscana	Provinces of Firenze and Prato	33.4	1985-1994
Marche	1,470,200	Macerata	Province of Macerata	20.7	1991-1994
Lazio	5,209,700	Latina	Province of Latina	9.4	1983-1994
South					
Sicilia	5,021,200	Ragusa	Province of Ragusa	5.9	1981-1994
Sardegna	1,639,400	Sassari	Province of Sassari	27.2	1992-1994

*Regional population from Census 2001 (men and women). Source: Health for all database.

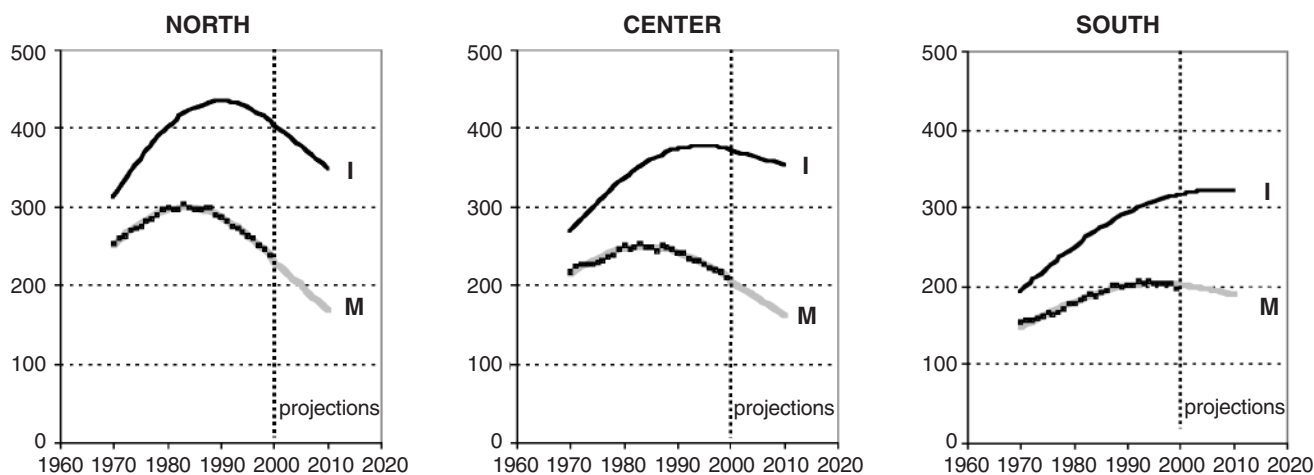


Figure 1 - Mortality (M) and incidence (I) estimates (grey and black continuous lines) for all cancer malignancies in Italy by geographical area in the period 1970-2010, compared to the national observed mortality data (dots). Age-standardized rates (European population) per 100,000 person years, age 0-84 years, men. North is the combination between North-West and North-East.

for central Italy. Conversely, in the South incidence was estimated to increase throughout the study period, with just a flattening in projections around the value of 320 per 100,000 py. As a result, the historical gap between northern-central and southern regions will diminish markedly in the near future.

Female cancer mortality (Figure 2) decreased in northern and central areas from the second half of the 1980s. Mortality rates were rather stable in the South until the late 1990s and were expected to be weakly declining only in the projection period. According to these forecasts, in the next years mortality in women will uniformly reach the value of 100 per 100,000 py across the country. Incidence was estimated to increase in all areas

throughout the entire study period for women. Very similar patterns were estimated for northern and central regions, with rates increasing from about 200 per 100,000 py in 1970 to 300 per 100,000 py in 2010. In the southern area, incidence was expected to rise from 145 to 225 per 100,000 py.

Projections of regional cancer mortality, incidence and prevalence in Italy for the year 2005 are presented in Tables 2, 3 and 4, respectively. The estimated number of total cancer deaths in Italy (Table 2) is about 130,000, with a higher proportion in men (60%). Age-adjusted mortality rates were uniform across the country (from 184 to 199 per 100,000 py in men, from 99 to 110 per 100,000 py in women). A gap between North and South was still

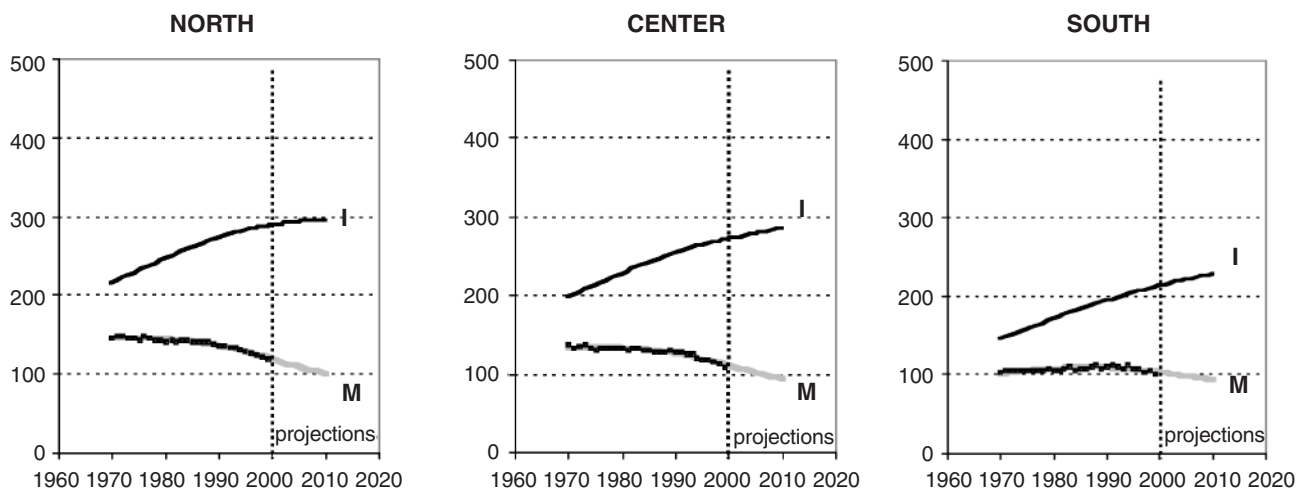


Figure 2 - Mortality (M) and incidence (I) estimates (grey and black continuous lines) for all cancer malignancies in Italy by geographical area in the period 1970-2010, compared to the national observed mortality data (dots). Age-standardized rates (European population) per 100,000 person years, age 0-84 years, women. North is the combination between North-West and North-East.

Table 2 - Estimated all cancer mortality in Italy and in Italian regions for the year 2005 by gender. Number of cases, crude and European age-standardized (age-std) rates per 100,000 person years. Age 0-84 years

Macro-area and regions	Men			Women			Men and Women		
	no. of cases	crude rates	age-std rates	no. of cases	crude rates	age-std rates	no. of cases	crude rates	age-std rates
North	37370	307	199	26310	209	110	63680	257	149
Piemonte	6570	326	189	4320	207	106	10890	266	148
Valle d'Aosta	180	312	199	120	199	110	300	258	155
Lombardia	13170	304	210	9480	211	116	22650	257	157
Liguria	2640	362	191	1780	228	102	4420	293	141
Trentino Alto Adige	1200	262	196	820	176	105	2020	218	145
Veneto	5930	274	194	4240	190	106	10170	232	146
Friuli Venezia Giulia	1820	333	204	1420	248	122	3240	290	158
Emilia Romagna	5860	317	181	4130	216	106	9990	266	139
Center	15310	294	184	10330	188	102	25640	240	138
Toscana	5290	324	185	3480	203	101	8770	262	138
Umbria	1230	316	179	830	204	100	2060	260	136
Marche	2080	302	178	1280	181	94	3360	241	131
Lazio	6710	268	185	4740	179	105	11450	222	140
South	25090	246	197	15460	146	99	40550	195	142
Abruzzo	1630	269	173	1030	164	89	2660	216	127
Molise	430	277	180	240	147	83	670	212	127
Campania	7370	258	236	4290	145	108	11660	200	164
Puglia	4760	238	188	2930	141	95	7690	189	136
Basilicata	790	267	188	450	150	94	1240	208	136
Calabria	2150	215	165	1320	129	86	3470	171	121
Sicilia	5850	237	185	3890	151	100	9740	193	137
Sardegna	2110	264	205	1310	160	103	3420	212	149
Italy*	76420	277	191	52450	183	105	128870	229	143

*National estimate was obtained by applying a specific model and not as the sum of regional estimates.

evident in crude mortality rates, with almost all northern and central regions above (on the average, 307 and 294 per 100,000 py in men, 209 and 188 per 100,000 py in women), and the southern regions below the national level (246 per 100,000 py for men, 146 for women).

More than 250,000 new cancer cases (Table 3) were estimated to be in Italy in the year 2005 and about 53% of those related to men. The crude incidence rates at a

national level were 482 and 417 per 100,000 py, in men and women, respectively. A North to South gradient in incidence was observed, with crude rates ranging from 555 to 388 per 100,000 py in men and from 484 to 302 per 100,000 py in women. For men, the highest crude incidence rate was expected in the Liguria region (652 per 100,000 py); the top level among women was estimated for Friuli Venezia Giulia (564 per 100,000 py).

Table 3 - Estimated all cancer incidence in Italy and in Italian regions for the year 2005 by gender. Number of cases, crude and European age-standardized (age-std) rates per 100,000 person years. Age 0-84 years

Macro-area and regions	Men			Women			Men and Women		
	no. of cases	crude rates	age-std rates	no. of cases	crude rates	age-std rates	no. of cases	crude rates	age-std rates
North	67460	555	377	60980	484	293	128440	519	329
Piemonte	12100	602	364	10000	480	284	22100	540	328
Valle d'Aosta	330	572	378	280	475	302	610	524	346
Lombardia	23590	544	389	21800	486	305	45390	514	339
Liguria	4740	652	374	3990	511	271	8730	579	313
Trentino Alto Adige	2200	480	375	1920	411	278	4120	445	320
Veneto	10700	494	367	9900	445	281	20600	469	320
Friuli Venezia Giulia	3210	587	380	3230	564	324	6440	576	346
Emilia Romagna	10590	574	352	9860	515	294	20450	544	318
Center	28500	547	363	24330	444	279	52830	494	314
Toscana	9650	591	361	8040	469	272	17690	529	310
Umbria	2300	592	361	1920	476	275	4220	532	312
Marche	3880	566	355	3020	425	261	6900	494	301
Lazio	12670	506	366	11350	428	285	24020	466	320
South	39510	388	321	31890	302	220	71400	344	265
Abruzzo	2550	421	284	2150	342	207	4700	381	241
Molise	690	442	305	490	307	196	1180	374	245
Campania	11930	417	389	9390	316	254	21320	366	312
Puglia	7510	376	308	6270	302	220	13780	338	258
Basilicata	1270	431	318	980	326	225	2250	378	266
Calabria	3470	346	275	2870	279	202	6340	312	234
Sicilia	8750	354	287	6890	267	191	15640	310	234
Sardegna	3340	418	333	2850	348	241	6190	383	282
Italy*	132930	482	348	119260	417	271	252190	449	303

*National estimate was obtained by applying a specific model and not as the sum of regional estimates.

The overall number of prevalent cases in Italy (Table 4) was predicted to be about 1,700,000 in 2005 (56% women). More than half of the overall cancer patients

(53%) were expected in the North, as a consequence of the past incidence levels. Crude cancer prevalence proportion in Italy was estimated to be higher in women

Table 4 - Estimated all cancer prevalence in Italy and in Italian regions for the year 2005 by gender. Number of cases, crude and European age-standardized (age-std) proportions per 100,000 persons. Age 0-84 years

Macro-area and regions	Men			Women			Men and Women		
	no. of cases	crude proportions	age-std proportions	no. of cases	crude proportions	age-std proportions	no. of cases	crude proportions	age-std proportions
North	404860	3332	2266	509160	4044	2490	914020	3694	2361
Piemonte	68870	3424	2141	83990	4033	2424	152860	3734	2301
Valle d'Aosta	1990	3437	2336	2310	3950	2543	4300	3697	2452
Lombardia	141400	3260	2338	186610	4157	2643	328010	3716	2472
Liguria	27310	3752	2125	34370	4402	2374	61680	4088	2245
Trentino Alto Adige	12870	2806	2188	15440	3303	2281	28310	3057	2212
Veneto	68650	3172	2337	80770	3629	2353	149420	3404	2327
Friuli Venezia Giulia	20010	3662	2360	26580	4647	2700	46590	4166	2512
Emilia Romagna	63760	3453	2131	79090	4128	2412	142850	3797	2259
Center	159780	3066	2052	203230	3709	2359	363010	3395	2194
Toscana	55180	3378	2081	67390	3934	2321	122570	3663	2187
Umbria	12480	3215	1983	15370	3800	2253	27850	3514	2107
Marche	21330	3109	1984	25160	3541	2213	46490	3328	2083
Lazio	70790	2827	2061	95310	3594	2421	166100	3221	2243
South	180380	1771	1479	219680	2080	1568	400060	1928	1515
Abruzzo	12130	2004	1387	14610	2324	1481	26740	2168	1427
Molise	3190	2053	1441	3600	2245	1453	6790	2152	1439
Campania	53790	1880	1756	64840	2184	1791	118630	2035	1757
Puglia	35210	1763	1459	44330	2134	1611	79540	1952	1528
Basilicata	5500	1868	1402	6570	2187	1568	12070	2029	1473
Calabria	16230	1617	1305	19990	1947	1456	36220	1784	1376
Sicilia	38250	1549	1276	46880	1816	1343	85130	1686	1305
Sardegna	16080	2013	1614	18860	2307	1646	34940	2162	1620
Italy*	750040	2722	1976	958730	3349	2233	1708770	3042	2092

*National estimate was obtained by applying a specific model and not as the sum of regional estimates.

(3,349 per 100,000) than in men (2,722 per 100,000), due to the predominance of better prognosis cancers and the higher life expectancy in the female population. Prevalence levels in the southern area was significantly below the Italian average, at about 2,100 (women) and 1,700 (men) per 100,000.

Discussion

The estimates were derived with a common methodology taking into account the time trends 1970-1999 of the official regional mortality data and the variations by time of diagnosis and geographic area of cancer survival. A more detailed description of the methodology is presented in a specific paper¹⁰.

The adaptation of the cure-models to the observed survival data was satisfactory, as survival rates leveled off after 5-6 years from the diagnosis for all cancer malignancies. The goodness of fit to the regional mortality data was very high in all regions, as shown in Figures 1 and 2. Thus, we are confident that the incidence APC parameters, estimated on the basis of a 30-year-long mortality time series, are well established.

Whenever data were available, the regional estimates were validated against the CR incidence and mortality observations. Direct and full comparisons were not possible as the regional population was often not completely covered by the CRs, the registration period was in several occasions limited, and multiple tumors were included, unlike MIAMOD estimates, in CRs statistics. Given these limitations, the regional estimated levels and trends were consistent with the locally collected data. The results of the validation procedure are widely illustrated in an ad-hoc paper¹¹.

The published regional incidence estimates in Italy 2001, based on the incidence-mortality ratio observed in 1993-1998¹², gave higher values than those obtained in this study. The differences are due partly to data selections (our estimates did not include all ages and multiple tumors) and partly to the different methodology adopted.

Projections were mainly based on the assumption that survival for all malignancies will continue to increase at the same rate as observed from the empirical data until 1994. This assumption seems reasonable if we consider the diagnostic and therapeutic progressive advances from the half of the nineties up to now.

This study gives a wide picture of cancer trends variability by sex and geographical area in Italy. Differences between men and women are mainly due to the gender-specific case-mix of sites in all cancers. In particular, among men the reduction in incidence and mortality in northern and central Italy can be explained mostly by the downward trends of stomach and lung cancer³; among women the increase in incidence accompanied by the decrease in mortality reflects mostly breast cancer trends and the relatively high survival for female cancers.

A recent study¹³ showed that the reduction in cancer mortality over the last years also concerned the whole European Union and confirmed that the trend was largely due to the decline in mortality for tobacco-related cancers in men, breast and uterine cancers in women, and gastric and intestinal cancers in both sexes. Over the same period, a less marked decrease in cancer mortality rates was observed in the United States¹⁴, especially for women, partly as a consequence of the higher proportion of smokers among the US female population with respect to Italy.

The decline in age-standardized cancer incidence estimated for men mainly in the northern area from the mid 1990s, if confirmed by empirical data, would represent a very important epidemiological change for our country.

Regional analysis revealed that mortality and morbidity levels varied considerably from northern-central to southern Italy. However, these differences seemed to be smaller than in the past, as observed both in mortality (for men and women) and incidence (for men), due to the combination of favorable downward trends for northern-central regions and upward or at most flat trends for southern regions. This would mean that progresses against cancer achieved in northern and central areas, particularly remarkable in the male population, are spreading with a certain delay to southern Italy.

Estimates and projections of epidemiological indicators at a regional scale in Italy are a basic information for planning and improving strategies and resources in public health. From this point of view, this study shows that a clear geographic variability in cancer risk and burden exists across the country and that specific interventions are required in each region. In particular, we believe that future effort should be made particularly in southern regions, where spread of prevention programs and access to optimal care facilities are lower than in northern and central regions.

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