

REGIONAL ESTIMATES OF BREAST CANCER BURDEN IN ITALY

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Aims and background: Breast cancer is the most common cancer and the leading cause of cancer death among women. Knowledge of the present and future burden of the disease at a regional and national scale is a major issue in Italy, where the frequency and coverage of screening programs vary considerably across the country. This study presents estimates and projections of the female breast cancer incidence, prevalence and mortality for Italy and all Italian regions in the period 1970-2010.

Methods: The estimates were obtained by applying the MIAMOD method, a statistical back-calculation approach to derive incidence and prevalence figures from mortality and relative survival data. Published data from the Italian cancer registries were modelled to obtain regional and national estimates of breast cancer survival.

Results: Breast cancer mortality has been declining from the late 1980s in the northern-central regions and from the mid 1990s in the southern regions Puglia, Sicilia and Sardegna. Stable mortality rates are estimated for the other southern re-

gions in the 2000's first decade. The incidence rate in Italy is estimated as increasing until the late 1990s, and stable thereafter (93 per 100,000). The incidence curve is also estimated to flatten in many northern-central regions from the late 1990s or later. Rising incidence trends are estimated in all southern regions, with the exception of Puglia. About 8,500 deaths, 37,000 new diagnoses and 416,000 prevalent cases for breast cancer are estimated among Italian women in 2005. In the same year, the proportion of prevalent cases in the northern area (1,221 per 100,000) is about twice that estimated in the South (685 per 100,000).

Discussion: The geographical variation in female breast cancer burden can be explained by the unequal distribution of screening. A more widespread screening activity in the southern regions would help to bridge the gap between northern-central and southern regions. Continuous monitoring of regional epidemiological indicators for breast cancer is crucial to evaluate the effect of different health measures taken to control breast cancer in Italy.

Key words: breast cancer, cancer registries, incidence, Italy, mortality, population surveillance, prevalence, survival.

Introduction

Breast cancer is the most common cancer and the leading cause of death among women in Italy and worldwide^{1,2}. The number of deaths due to breast cancer in the Italian female population represented about 18% of the total cancer mortality at the end of the 1990s³.

The risk of developing breast cancer is related to a number of factors including the events of reproductive life and lifestyle factors that modify endogenous levels of sex-hormones⁴. Diet has been also found to play an important role in the etiology of breast cancer⁵.

The time trends of the breast cancer incidence have been observed to increase in most European countries including Italy, until the end of the 1990s⁶⁻⁸. Such increase may be explained in part by the implementation of organized screening programs. Conversely, a widespread reduction of mortality rates has been observed in Europe from the early 1990s, which is likely attributable to advancements in medical treatments and to the role of mammography screening in detecting cancers at an earlier stage^{9,10}.

Knowledge of the present and future burden of the disease at a regional and national scale is essential to evaluate the geographical differences within the country and to plan appropriate public health interventions. This is a major issue in Italy, where regional time trends of breast cancer incidence and prevalence are not currently available and there is considerable regional variability in terms of risk factors and screening coverage across the country. The present study is part of a broader program, "I TUMORI IN ITALIA", established by the Istituto Superiore di Sanità in Rome and the Fondazione IRCCS "Istituto Nazionale dei Tumori" in Milan, in collaboration with the Association of Italian Cancer Registries (AIRTum). The aim of the program is to provide up-to-date and systematic cancer statistics at the national and regional level in Italy for the most important cancer sites, including the breast.

The results presented in this paper are the main output from the estimation and projection of female breast cancer incidence, prevalence and mortality in Italy and in all Italian regions for the period 1970-2010. The complete results of this study and of the whole program can be found on the website www.tumori.net.

Acknowledgments: The study was supported by: Foundation "Compagnia di San Paolo" (project "Sperimentazione di un sistema di rilevazione e diffusione dei dati di sopravvivenza per tumore"); Italian Ministry of Health (project "I TUMORI IN ITALIA" promoted by Alleanza Contro il Cancro); European Commission, Health and Consumer Protection Directorate-General (project "EUROCHIP-2: European Cancer Health Indicator Project - The Action").

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Received December 20, 2006; accepted March 5, 2007.

Materials and methods

Mortality data for female breast cancer (ICD-IX revision code 174) and female population data by age, calendar year and geographical region for the period 1970-1999 were obtained from the Italian National Institute of Statistics (ISTAT). A correction coefficient ($K = 0.989$) was applied to the mortality rates for 1970-1994 in order to account for the change in the coding system for the cause of death from manual to automatic; this change was introduced in 1995¹¹.

Relative survival data for female breast cancer in the period of diagnosis 1978-1994 were obtained from the CD-ROM of the EURO CARE-3 study¹² and refer to the populations covered by 13 Italian cancer registries: Torino, Varese, Genova (North-West), Veneto, Modena, Ferrara, Parma, Romagna (North-East), Toscana, Macerata, Latina (Center), Ragusa and Sassari cancer registries (South), jointly covering about 16% of the national population. The distribution of cancer registries by region and geographical area, and the corresponding percentage of the regional population and the time period covered are reported in Table 1. The methodology applied to derive estimates of cancer survival, incidence and prevalence for the 20 Italian regions is extensively described in specific papers^{13,14}.

Incidence and prevalence estimates were derived with the statistical method MIAMOD (Mortality-Inci-

dence Analysis MODEL), a back-calculation approach to estimate and project the morbidity of chronic irreversible diseases starting from the knowledge of mortality and survival data^{15,16}.

The relative survival of breast cancer patients at the national and regional level was estimated from observed cancer registry data by means of parametric cure models of the Weibull type¹⁷. Two categorical covariates (geographical area and age) and one continuous covariate (year of diagnosis) entered the model. Regions were grouped into macro-areas (North-West, North-East, Center, South) to derive survival estimates for all the regions, including those without a cancer registration system in the considered period. In the *Results* section, for reasons of usual Italian data presentation, regions of North-West and North-East macro-areas were grouped into the wider North macro-area. The last column of Table 1 reports the macro-area used for the survival estimation in each region. Note that for the insular region Sardegna survival was estimated combining regions of Center and South macro-areas.

The national survival estimates were obtained as the weighted average of the four macro-area estimates, using the proportion of expected incident cases for each area as weights. Full details of this method have been described elsewhere¹⁸. The survival time trend before 1978 and from 1995 to 2010 was assumed to have the same linear slope as that estimated over the period 1978-1994.

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 (EURO CARE-3 study¹²). Details of the macro-areas used for female breast cancer survival estimates

Macro-area and regions	Regional population*	Cancer Registry (CR)	CR covered area	% of regional population covered by CRs	Reference period	Macro-area for survival estimation
North-West						
Piemonte-Valle d' Aosta	2,254,700	Torino	Town of Torino	21.2	1985-1994	North-West
Lombardia	4,673,900	Varese	Province of Varese	9.0	1978-1994	North-West
Liguria	841,200	Genova	Town of Genova	39.5	1986-1994	North-West
North-East						
Trentino Alto Adige-Friuli Venezia Giulia	1,096,100	-	-	-	-	North-East
Veneto	2,324,500	Veneto	Eleven Health Districts in the Veneto Region	45.1	1987-1994	North-East
Emilia Romagna	2,061,700	Ferrara	Province of Ferrara	9.1	1989-1994	North-East
		Modena	Province of Modena	15.6	1988-1994	
		Parma	Province of Parma	10.0	1978-1994	
		Romagna	Provinces of Forli, Ravenna and Rimini	10.9	1986-1994	
Center						
Toscana	1,826,400	Toscana	Provinces of Firenze and Prato	33.4	1985-1994	Center
Umbria	429,800	-	-	-	-	Center
Marche	755,600	Macerata	Province of Macerata	20.7	1991-1994	Center
Lazio	2,705,700	Latina	Province of Latina	9.4	1983-1994	Center
South						
Abruzzo-Molise	819,700	-	-	-	-	South
Campania	2,943,200	-	-	-	-	South
Puglia	2,082,900	-	-	-	-	South
Basilicata-Calabria	1,338,800	-	-	-	-	South
Sicilia	2,589,000	Ragusa	Province of Ragusa	5.9	1981-1994	South
Sardegna	834,700	Sassari	Province of Sassari	27.2	1992-1994	Center and South

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

Mortality data for the pairs of regions Piemonte-Valle d'Aosta, Trentino Alto Adige-Friuli Venezia Giulia, Abruzzo-Molise and Basilicata-Calabria were pooled to derive more stable estimates. All incidence and prevalence estimates refer to the age class 0-84 years. Age-adjusted rates are based on the standard European population.

Results

The 5-year relative survival¹² in Italy was observed to increase from 65% in 1978 to 82% in 1994, with an annual percent increase of 1.5%. The proportion of cured patients in the period 1978-1994 was estimated to be about 33%, while the mean survival time for uncured patients was estimated to be around 7 years. Survival was higher in the northern-central area than in the southern area for the whole study period. In 1994, the relative survival for breast cancer varied from 75% in the southern area to 84% in the northern-central area. Detailed results obtained from the survival estimation of breast cancer are extensively reported in a technical document available from the project website www.tumori.net.

The age-standardized mortality and incidence estimated trends of breast cancer for Italian women in the period 1970-2010 are presented in Figure 1. The breast cancer mortality rate in Italy increased until the late 1980s, reaching its maximum value at approximately 27 per 100,000, and started to decline thereafter. The mortality rate is estimated to decline by about 30% during the projection period, dropping to 16 per 100,000 in 2010. The incidence rate is estimated to increase until the end of the 1990s and to remain stable thereafter, at 93 per 100,000.

The regional variation in breast cancer mortality and incidence trends is shown in Figure 2. The mortality is observed to decline from the late 1980s in the northern-central regions and from the mid 1990s in the southern regions of Puglia, Sicilia and Sardegna. Stable rates are

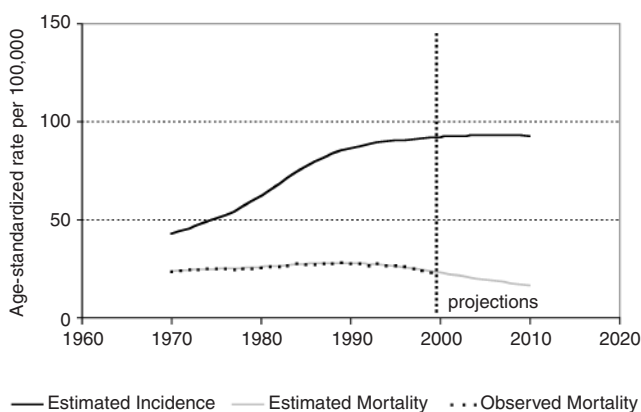


Figure 1 - Mortality and incidence estimates (grey and black continuous lines) for female breast cancer in Italy in the period 1970-2010, compared to the national observed mortality data (dots). Age standardized rates (European population) per 100,000 person years, age 0-84 years.

estimated for the other southern regions in the projection period. The incidence curves are estimated to flatten in many regions, mainly in the northern-central area⁵: stable rates are expected for Lombardia, Liguria, Toscana, Umbria from the end of the 1990s, and for Trentino Alto Adige, Friuli Venezia Giulia, Emilia Romagna, Marche and Lazio in the projection, while only a slackening of the incidence rise at the end of the projection is estimated for Piemonte and Valle d'Aosta and Veneto, where the incidence trends are not stabilizing as yet. Rising incidence trends are estimated in all southern regions except for Puglia, where stable rates are expected from the late 1990s. Among the other southern regions, Abruzzo and Molise, Campania, Basilicata and Calabria present the most critical situation because the rise in incidence is not accompanied by a clear reduction of the mortality.

About 8,500 deaths, 37,000 new diagnoses and 416,000 prevalent cases are estimated for breast cancer among Italian women in the year 2005 (Table 2). Age-standardized mortality rates are lower in the central area (18 per 100,000) than in the northern (22 per 100,000) and southern (20 per 100,000) areas. Some southern regions, such as Campania and Sardegna, are estimated to reach mortality levels similar to those of northern regions. Breast cancer incidence and prevalence present however a marked North-to-South gradient. The incidence rates are 117, 103 and 78 per 100,000 in the northern, central and southern areas, respectively. The regions with the highest incidence are Trentino Alto Adige and Friuli Venezia Giulia (130 per 100,000). Regional differences are marked for the breast cancer prevalence: the proportion of prevalent cases in the northern area is remarkably higher (1,221 per 100,000) than in the central area (1,096 per 100,000) and about twice that estimated in the southern area (685 per 100,000).

Discussion

The estimated breast cancer incidence figures proved to be consistent with the most up-to-date local cancer registry data in all the regions with a cancer registration system. Results of the validation procedure are presented elsewhere¹⁹.

The estimation procedure assumed increasing survival after 1994. This assumption is consistent with the diffusion of the improvement in treatment and, above all, with the beneficial effect of early detection. Organized screening programs, most of which started in Italy at the beginning of the 1990s, and widespread use of mammography as a "spontaneous" practice contributed to an increase in tumors detected at an early stage and with a better prognosis²⁰⁻²³. Furthermore, the increasing number of screening programs and their higher regional coverage than in the past are hypothesized to favorably influence survival also in the next years^{24,25}.

The decrease observed in mortality for the northern-central regions from the late 1980s and for Italy as a whole from the early 1990s may be related to both im-

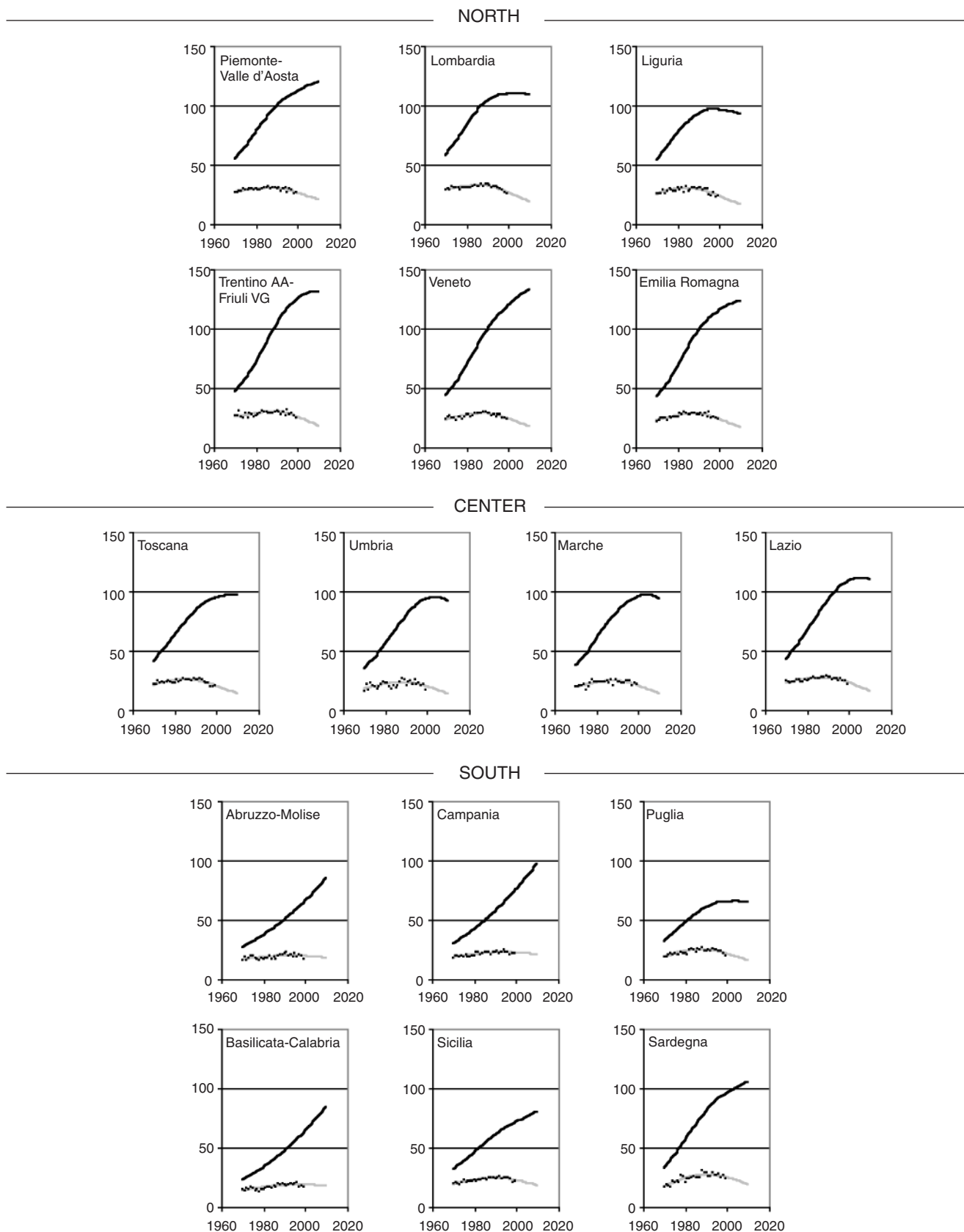


Figure 2 - Regional mortality and incidence estimates (grey and black continuous lines) for female breast cancer in Italy in the period 1970-2010, compared to the regional observed mortality data (dots). Age-standardized rates (European population) per 100,000 person years, age 0-84 years. Trentino AA, Trentino Alto Adige; Friuli VG, Friuli Venezia Giulia.

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

Macro-area and regions	Mortality			Incidence			Prevalence		
	no. of cases	crude rates	age-std rates	no. of cases	crude rates	age-std rates	no. of cases	crude proportions	age-std proportions
North	4648	37	22	22087	175	117	245720	1952	1221
Piemonte	837	40	24	3797	182	119	41415	1989	1222
Valle d' Aosta	23	40	24	107	182	119	1162	1989	1222
Lombardia	1667	37	23	7256	162	110	83705	1865	1200
Liguria	305	39	20	1263	162	95	15494	1984	1075
Trentino Alto Adige	172	37	22	882	189	130	9718	2079	1314
Veneto	743	33	21	4086	184	127	42305	1902	1260
Friuli Venezia Giulia	211	37	22	1080	189	130	11890	2079	1314
Emilia Romagna	690	36	20	3617	189	121	40029	2090	1254
Center	1659	30	18	8274	151	103	94760	1729	1096
Toscana	511	30	17	2550	149	97	29722	1735	1050
Umbria	122	30	17	589	146	95	6872	1699	1006
Marche	211	30	17	1027	145	97	12089	1702	1046
Lazio	815	31	20	4108	155	111	46077	1738	1162
South	2817	27	20	10269	97	78	91379	865	685
Abruzzo	182	29	19	661	105	75	5604	892	616
Molise	46	29	19	168	105	75	1428	892	616
Campania	786	26	22	2953	99	86	24225	816	696
Puglia	515	25	19	1708	82	65	16943	816	642
Basilicata	73	24	18	275	91	74	2270	756	599
Calabria	251	24	18	939	91	74	7766	756	599
Sicilia	713	28	21	2481	96	76	22508	872	677
Sardegna	250	31	22	1084	132	101	10635	1300	972
Italy*	8505	30	19	37302	130	93	415910	1453	989

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

proved treatment and early detection diffusion. The improvements in breast cancer care, including the more widespread use of adjuvant hormonal therapy (tamoxifen) and chemotherapy, and the progress in radiotherapy and surgery, are likely to be the major determinants of the mortality reduction in the late 1980s and early 1990s, i.e., before organized screening could have produced its effect^{6,9}. Also spontaneous early detection before the beginning of screening programs can be supposed to have had some favorable effect on mortality²⁶, especially in northern-central regions. Possible explanations for the delay in the mortality decline in the southern regions are the limited coverage areas (or even absence) of screening programs and the lesser participation in mammography screening with respect to northern-central regions²⁴.

The widespread rise in breast cancer incidence during the 1990s may be explained by the effect of screening, especially in the northern-central area of Italy, where the number of organized programs and their coverage are considerably higher than in the southern area^{8,24}. It has been shown that the introduction of screening mainly increases the incidence of early-stage cancers, but this also involves women in age groups not targeted by screening programs, thus supporting the role of a spontaneous early-detection activity²⁰⁻²³. This study produced also results by birth cohort (data not shown). The analysis of the incidence age profile at the national level for birth cohorts from 1920 to 1950 showed an increased risk for the recent cohorts and a peak in the incidence rate approximately at ages 50 and 60 for cohorts born in 1940 and

1930, attributable to screening activity. The stabilization of incidence rates estimated at the national level and for many northern-central regions from the late 1990s could be explained by the exhaustion of the initial screening effect. Such a situation cannot yet be hypothesized for southern regions because screening is just starting there and the screening coverage is lower. The only southern region expected to have a stable incidence trend is Puglia.

The current gap in the breast cancer prevalence between northern-central and southern regions is mainly attributable to the pronounced differences in past incidence levels, which were much higher in the northern and central areas than in the South. The greater aging of the population and the higher survival rates for northern-central regions are the other factors contributing to the geographical variability of the prevalence in Italy.

In conclusion, the geographical variation in female breast cancer burden can be partially explained by the different distribution of screening. Expansion of the screening activity is expected to produce an increase in breast cancer survival and, probably, a stabilization of the incidence of advanced tumors, mainly in northern-central regions. A more widespread screening activity in the South would help to close the gap between northern-central and southern regions. Continuous monitoring of regional epidemiological indicators for breast cancer is crucial in evaluating the effect of different health measures taken to control breast cancer in Italy.

References

1. AIRT Working Group: Italian cancer figures, Report 2006: Incidence, mortality and estimates. *Epidemiol Prev*, 30 (Suppl 2), 2006.
2. Parkin M, Bray F, Ferlay B, Pisani P: Estimating the world cancer burden: Globocan 2000. *Int J Cancer*, 94: 153-156, 2001.
3. Istituto Nazionale di Statistica: Nuove evidenze nell'evoluzione della mortalità per tumori in Italia, anni 1970-1999. ISTAT, Rome, 2005.
4. Key T, Appleby P, Barnes I, Reeves G, Endogenous Hormones and Breast Cancer Collaborative Group: Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*, 94: 606-616, 2002.
5. Linos E, Holmes MD, Willett WC: Diet and breast cancer. *Curr Oncol Rep*, 9(1): 31-41, 2007.
6. Botha JL, Bray F, Sankila R, Parkin DM: Breast cancer incidence and mortality trends in 16 European countries. *Eur J Cancer*, 39: 1718-1729, 2003.
7. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA: Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*, 34: 405-412, 2005.
8. Crocetti E, Capocaccia R, Casella C, Ferretti S, Guzzinati S, Rosso S, Pacchettini C, Spitale A, Stracci F, Tumino R (Eds): Cancer trends in Italy: figures from the cancer registries (1986-1997). *Epidemiol Prev*, 28 (Suppl 2), 2004.
9. Levi F, Bosetti C, Lucchini F, Negri E, La Vecchia C: Monitoring the decrease in breast cancer mortality in Europe. *Eur J Cancer Prev*, 14: 497-502, 2005.
10. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C: Cancer mortality in Europe, 1995-1999, and an overview of trends since 1960. *Int J Cancer*, 110: 155-169, 2004.
11. Istituto Nazionale di Statistica: La nuova indagine sulle cause di morte. ISTAT, Rome, 2001.
12. Roazzi P, Capocaccia R, Santaquilani M, Carrani E and the EURO CARE Working Group: Electronic availability of EURO CARE-3 data: a tool for further analysis. *Ann Oncol*, 14 (Suppl 5): 150-155, 2003.
13. Grande E, Inghelmann R, Francisci S, Verdecchia A, Micheli A, Capocaccia R, De Angelis R: Estimating regional cancer burden in countries with partial registration coverage: An application to all malignant neoplasms in Italy over the period 1970-2010. *Eur J Cancer*, 42: 3236-3245, 2006.
14. Verdecchia A, De Angelis R, Francisci S, Grande E: Methodology for estimation of cancer incidence, survival and prevalence in Italian regions. *Tumori*, 93: 337-344, 2007.
15. Verdecchia A, Capocaccia R, Egidi V, Golini A: A method for the estimation of chronic disease morbidity and trends from mortality data. *Stat Med*, 8: 201-206, 1989.
16. De Angelis G, De Angelis R, Frova L, Verdecchia A: MIAMOD: a computer package to estimate chronic disease morbidity using mortality and survival data. *Comput Programs Biomed*, 44: 99-107, 1994.
17. De Angelis R, Capocaccia R, Hakulinen T, Soderman B, Verdecchia A: Mixture models for cancer survival analysis: application to population-based data with covariates. *Stat Med*, 18: 441-454, 1999.
18. Inghelmann R, Grande E, Francisci S, De Angelis R, Micheli A, Verdecchia A, Ferretti S, Vercelli M, Ramazzotti V, Pannelli F, Federico M, De Lisi V, Tumino R, Falcini F, Budroni M, Zanetti R, Paci E, Crosignani P, Zambon P, Capocaccia R: National estimates of cancer patients survival in Italy: a model-based method. *Tumori*, 91: 109-115, 2005.
19. Capocaccia R, Buzzoni C, Grande E, Inghelmann R, Bellù F, Cassetti T, de Dottori M, Donato A, De Lisi V, Falcini F, Federico M, Ferretti S, Fusco M, Giacomini A, Guzzinati S, Mangone L, Piffer S, Rosso S, Sechi O, Tagliabue G, Tumino R, Vercelli M, Vitarelli S: Estimated and observed cancer incidence in Italy: a validation study. *Tumori*, 93: 387-391, 2007.
20. Barchielli A, Paci E: Trends in breast cancer mortality, incidence, and survival, and mammographic screening in Tuscany, Italy. *Cancer Causes Control*, 12: 249-255, 2001.
21. Turchetti D, Mangone L, Negri R, Rossi G, Cortesi L, Vinceti M, Maiorana A, Gallo E, Federico M: Changes in breast cancer incidence and stage distribution in Modena, Italy: the effect of a mammographic screening program. *Cancer Causes Control*, 13: 729-734, 2002.
22. Barchielli A, Federico M, De Lisi V, Bucchi L, Ferretti S, Paci E, Ponti A, Buiatti E, for the SCREENREG Working Group: In situ breast cancer: incidence trend and organised screening programmes in Italy. *Eur J Cancer*, 41: 1045-1050, 2005.
23. Buiatti E, Barchielli A, Bertolacci S, Federico M, De Lisi V, Bucchi L, Ferretti S, Paci E, Segnan N, Tumino R, the SCREENREG Working Group: The impact of organised screening programmes on the stage-specific incidence of breast cancer in some Italian areas. *Eur J Cancer*, 39: 1776-1782, 2003.
24. Giorgi D, Giordano L, Ventura L, Puliti D, Piccinni P, Paci E: Lo screening mammografico in Italia: survey 2003-2004. In: Osservatorio Nazionale Screening. Quarto Rapporto, pp 16-27, 2005.
25. Giordano L, Giorgi D, Piccinni P, Stefanini V, Castagno R, Senore C: Trend temporali di alcuni indicatori dei programmi di screening mammografico in Italia: 1996-2003. In: Osservatorio Nazionale Screening. Quarto Rapporto, pp 28-41, 2005.
26. Buiatti E, Barchielli A, Bertolacci S, Bucchi L, De Lisi V, Federico M, Ferretti S, Paci E, Vettorazzi M, Zanetti R, the SCREENREG Working Group: Stage-specific incidence of breast cancer before the beginning of organized screening programs in Italy. *Cancer Cause Control*, 13: 65-71, 2002.