Recent trends in incidence, mortality and survival after cancer of the female breast and reproductive organs. Umbria, Italy: 1978-2005

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Summary

This study analyzed the incidence, mortality and survival after cancer of the female breast and reproductive organs in the Umbria region of Italy with the aim of generating hypotheses to explain trends. Mortality data were supplied by ISTAT (1978-1993) and ReNCaM (1994-2005) and incidence (1994-2005) and survival (at 12/31/2007) data by RTUP. Joinpoint regression was applied to evaluate temporal trends of the age-adjusted incidence and mortality rates. Mortality, incidence and relative survival rates were compared with national and international data. The incidence of breast cancer increased up to 2001 and afterwards significantly decreased; mortality rates significantly decreased after 1994. Uterine corpus incidence was practically stable, and decreased over the study period; mortality from all uterine subsites significantly decreased from 1978 onwards. Trends in ovarian cancer incidence and mortality (after 1985) were constant. Trends in occurrence of breast and cervical cancer were linked to population screening of Umbrian women, noting a low compliance by younger females with cervical cancer screening and emphasizing the opportunity of starting breast cancer screening at a younger age. Trends in the incidence of cancer of the uterus and ovary, though unsteady, were probably related to modifications in risk factor exposure. Survival was better for breast and cervical cancers than in the 1978-1982 period and might be due to early diagnosis and progress in therapy.

Key words: Gynecological cancers; Incidence; Mortality; Survival.

Introduction

In 2004 the estimated number of new cases of breast cancer in the European Union was about 275,000, with annual deaths close to 88,000. Gynaecological cancers presented a frequency of about 51,000 incident cases of uterine cancer, 43,000 of ovarian cancer and 30,000 of cervical cancer; deaths were respectively 12, 28 and 13.5 thousand [1].

In Italy the estimated number of new cases of breast cancer was 37,302, constituting about 25% of all female cancers. There were 1.6% uterine cervix cancers, 2.9% ovarian cancers, and 3.9% endometrial cancers [2, 3].

Currently in Umbria, a region in central Italy with about 450,000 resident women, cases of female breast cancer are over 600 annually, with about 35 cases of uterine cervix cancer, over 120 endometrial cancers, and close to 80 ovarian cancers [4].

Cervical cancer screening was offered in the 1980s to Umbrian women aged 25-64 and at present covers most of the targeted female population. Screening for early detection of breast cancer was introduced in the early 1990s on a voluntary basis, and in the late 1990s as active mass screening for females aged 50-69. The procedure was first started in only some local health districts but now covers over 65% of the target population in the region [5].

The Umbrian Population Cancer Registry (RTUP), a regional cancer registry, was established in the early 1990s, therefore data on incidence and survival are available for the period 1994-2005 [5]. Furthermore for the 1978-1982 period, an *ad hoc* survey was carried out in the region to determine the incidence of cancer [6]. The Registry also collects regional mortality data from municipal offices and death certificates from local health districts, and annually publishes general mortality statistics, updated to the previous year.

In this paper we describe findings of cancer incidence, mortality and survival in this region, with the aim of generating hypotheses to explain trends. Explanations will be proposed for trends, focusing on the role of local health service intervention.

Materials and Methods

Mortality data were supplied by the National Institute of Statistics (ISTAT) from 1978 until 1993. For 1994-2005 period, they were supplied by the regional Nominative Causes of Death Registry, (ReNCaM), based on the Registry population Offices of Umbrian municipalities that are linked with death certificates

Revised manuscript accepted for publication May 15, 2009

collected by Local Health Districts and later used for national surveys by ISTAT. No major or systematic difference seemed to appear when ISTAT and ReNCaM-based mortality data were compared. Since ReNCaM data are easier to access than ISTAT mortality data, they allow the inclusion of recent years in the analysis. Causes of death were classified according to the 10th International Classification of Diseases (WHO, 1992) [7]: breast cancer as C50, cervical cancer as C53, endometrial cancer as C54, total uterus cancer as C55 and ovarian cancer as C56.

Incident cases were taken from the Umbrian Population Cancer Registry database from 01/01/1994 to 31/12/2005. All cases were collected, coded, stored and analyzed in accordance with standard methods recommended for cancer registries [8], using the ICD X [7]. Incidence rates referring to 1978-1982 period, are in relation to cases resulting from the ad hoc survey carried out in the 1980s [6].

Age-adjusted mortality and incidence rates were calculated for each site. Site-specific trends for standardized rates were analyzed by "joinpoint regression" [9], using SEER software [10]. 1978-1982 incidence data are reported in figures as observed rates, as the joinpoint analysis was applied only to 1994-2005 rates. Mortality rates were calculated for all combined subsites of uterine cancers, because death certificates frequently do not specify the subsite and only death certificates for recent years can be linked with the cancer Registry, and even then not always.

The Umbria population in the 1991 census was used as the standard in the joinpoint analyses, in an attempt to reduce bias due to the exceeding difference in age structure. Mortality or incidence trend was approximated since it is described by straight segments but was allowed to change over the study period (i.e. segments have different slopes). The grid search method detected segments best describing data. A year when a change in trend was detected over the study period is called a "joinpoint" and significant joinpoints are retained in the final site specific models. The maximum number of joinpoints for each analysis was three. The expected annual percent changes (EAPCs) are reported to describe linear trends by period.

Rates were also age-adjusted by world population for comparison with data reported by Cancer Incidence in Five Continents [11], and other sources of mortality [12].

Relative survival rates were calculated according to the method proposed by Estève *et al*. [13, 14]. Follow-up ended on 12/31/2007. Survival rates were calculated for five separate periods: 1978-1982, 1994-1996, 1997-1999, 2000-2002 and 2003-2005. Five-year age-adjusted relative percent survival for the selected cancer sites for the period 1995-1999 was compared with Italian cancer registries [15].

Results

Table 1 reports incident cases for the different sites and periods, and relative rates per 100,000, age-adjusted by Umbrian and world populations. Table 2 reports the corresponding mortality data. The mortality/incidence ratio was, in the last period, 0.23 for breast cancer, 0.41 for total uterus and 0.66 for ovarian cancer. Clearly breast cancer presented higher incidence and mortality rates. In the last period the 72% rate of deaths from unspecified uterine subsites was still high.

Results of the joinpoint analyses by cancer site, applied to mortality and incidence rates, are reported in Figures 1 and 2.

Table 1. — *Annual number of incident cases and age-adjusted (U=Umbria, W=world population as standard) incidence rates for the selected sites and periods.*

Site	Period	# cases	U-rate *(s.e.)*	W-rate
Breast	1978-82	367	91.2 *(2.1)*	55.8
	1994-96	508	109.0 *(4.9)*	66.3
	1997-99	600	120.3 *(5.1)*	72.5
	2000-02	649	132.2 *(5.5)*	83.0
	2003-05	636	126.1 *(5.1)*	76.7
Uterine cervix	1978-82	55	13.6 *(0.8)*	9.2
	1994-96	39	8.6 *(1.4)*	5.5
	1997-99	39	8.2 *(1.3)*	5.3
	2000-02	39	8.1 *(1.3)*	5.4
	2003-05	37	7.3 *(1.2)*	4.9
Uterine cervix	1978-82	84	20.5 *(1.0)*	12.1
	1994-96	112	23.5 *(2.3)*	12.9
	1997-99	119	24.2 *(2.3)*	13.6
	2000-02	117	24.8 *(2.3)*	13.9
	2003-05	124	24.0 *(2.2)*	13.1
Uterus unsp.	1978-82	15	4.1 *(0.4)*	2.3
	1994-96	2	0.5 *(0.3)*	0.2
	1997-99	5	0.9 *(0.4)*	0.4
	2000-02	4	0.7 *(0.4)*	0.4
	2003-05	2	0.3 *(0.3)*	0.2
Ovary	1978-82	51	12.7 *(0.8)*	8.3
	1994-96	83	17.6 *(2.0)*	10.5
	1997-99	93	19.0 *(2.0)*	11.5
	2000-02	81	17.3 *(1.9)*	10.0
	2003-05	87	16.7 *(1.9)*	9.8

Table 2. — *Annual number of deaths and age-adjusted (U=Umbria, W=world population as standard) mortality rates for the selected sites and periods.*

Site	Period	# deaths	U-rate *(s.e.)*	W-rate
Breast	1978-82	124	31.0 *(1.2)*	16.7
	1994-96	170	34.6 *(2.7)*	18.6
	1997-99	170	31.8 *(2.5)*	16.3
	2000-02	180	32.5 *(2.5)*	16.7
	2003-05	164	28.4 *(2.3)*	14.6
Uterine cervix	1978-82	6	1.3 *(0.2)*	0.7
	1994-96	8	1.7 *(0.6)*	0.9
	1997-99	14	2.5 *(0.7)*	1.2
	2000-02	8	1.4 *(0.5)*	0.9
	2003-05	7	1.1 *(0.4)*	0.5
Uterine cervix	1978-82	4	1.0 *(0.2)*	0.5
	1994-96	8	1.6 *(0.6)*	0.6
	1997-99	10	1.7 *(0.6)*	0.7
	2000-02	10	1.7 *(0.6)*	0.8
	2003-05	5	0.9 *(0.4)*	0.5
Uterus unsp.	1978-82	16	11.9 *(0.7)*	5.5
	1994-96	26	5.1 *(1.0)*	2.5
	1997-99	24	4.0 *(0.9)*	1.7
	2000-02	18	2.9 *(0.7)*	1.3
	2003-05	31	4.8 *(0.9)*	2.3
Ovary	1978-82	22	5.4 *(0.5)*	3.1
	1994-96	49	9.4 *(1.4)*	5.0
	1997-99	52	9.4 *(1.4)*	4.6
	2000-02	46	8.5 *(1.3)*	4.3
	2003-05	62	10.8 *(1.4)*	5.1

For breast cancer, significant joinpoints were found in incidence and mortality (Figure 1). Mortality rates increased up to 1994 (0.93% per year, n.s.) and signifi-

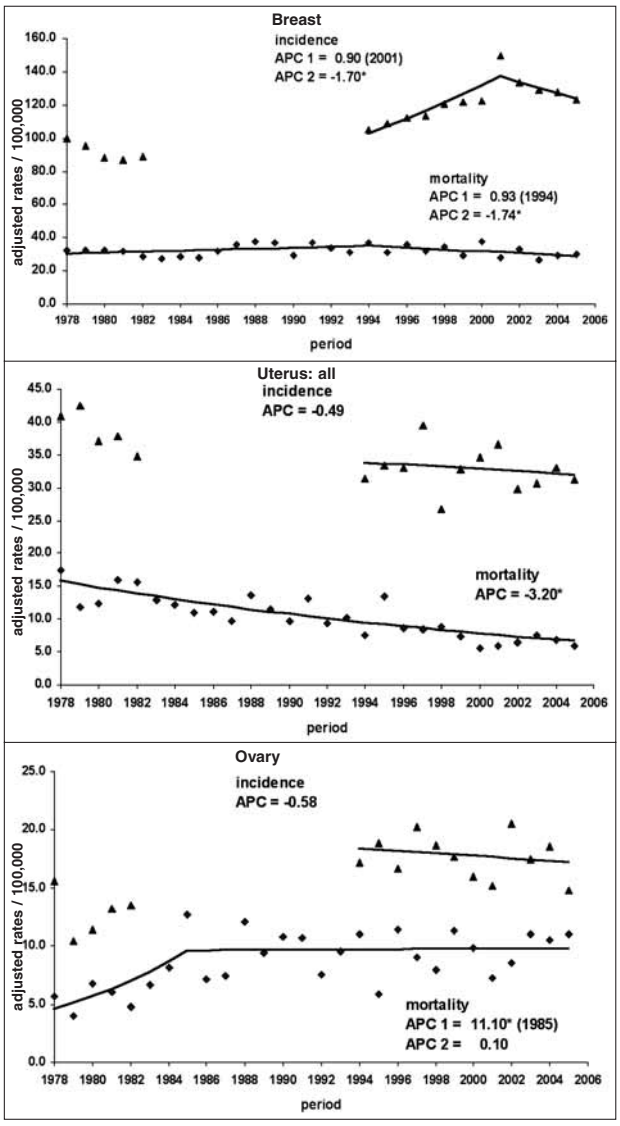

Figure 1. — Observed standardized rates per 100,000 inhabitants (▲ incidence, ◆ mortality) and "best" joinpoint model estimates (solid lines) for breast, total uterus and ovary cancers (note: the adjusted rate scales in the graphs are different).

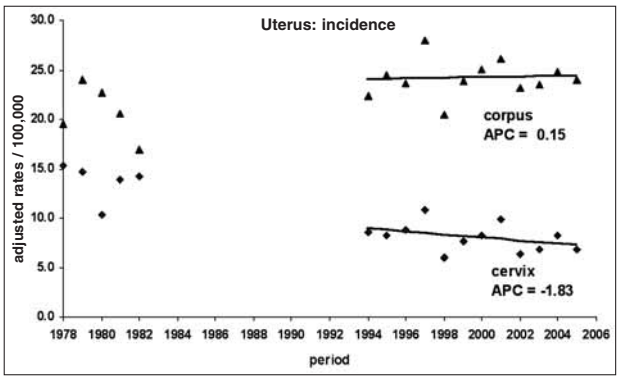

Figure 2. — Observed standardized incidence rates per 100,000 inhabitants (▲ uterine corpus, ◆ uterine cervix) and "best" joinpoint model estimates (solid lines).

cantly decreased thereafter by 1.70%; incidence rates, from 1994 to 2005, increased on average by 0.90 (n.s.) each year till 2001 and afterwards significantly decreased by 1.74%. The increase in incidence rates in the initial period seemed to start from 1982.

For cancer of the total uterus, incidence and mortality decreased over the study periods. For incidence the decrement was 0.49 (n.s.), and the mortality rates significantly dropped by 3.20 per year. In this site, the decrease in incidence seemed to start from 1979.

Incidence rates from ovarian cancer showed a small, non-significant decrease of 0.58; the mortality trend, from 1978 to 2005, presented a significant joinpoint. Rates sharply increased (up to 1985 by 11.10% per year) and afterwards remained constant (0.10%, n.s.) (Figure 2). In the 1978-1982 period incidence rates were lower than in the most recent period.

Figure 2 also shows non-significant trends in the incidence rates of cervical and uterine cancers. The former slightly increased by 0.15%, the latter non-significantly decreased by 1.83% and this trend seemed to start in the 1980s.

Relative survival trends are different for the selected cancer sites. A constant improvement in survival was found for breast and cervical cancers, while no clear modifications emerged for uterine cancers. Survival improvement was rather modest for ovarian cancer (Figure 3).

A comparison with Italian registry incidence rates is reported in Figure 4. The breast cancer ranking shows a north-south gradient: the rate in the Ferrara Province was nearly double the rate in the Salerno Province. The Umbrian register is ranked sixteenth in the 22 registries. Incidence rates of cervical and uterine cancers presented the same variability. The Umbrian registry is twentieth in the rank of cervical cancer rates, and ninth in uterine cancer rates. The variability of ovarian cancer rates is less wide, ranging from 11.9 per 100,000 inhabitants in the Modena Province to 7.6 in Naples; the Umbrian rate is sixth.

The comparison with European cancer mortality rates, referred to the year 2000 is reported in Table 3. Adjusted mortality rates for the Umbria region were quite similar to the Italian for ovarian cancer and lower for breast and total uterine cancers. Compared with several European countries, the Italian rates were among the lowest for all examined sites.

Five-year adjusted relative survival rates in Umbria, compared with other Italian cancer registries, were very similar to the Italian average (Table 4). As in the rest of Italy, the highest survival rate was found for breast cancer (83%) and the lowest for ovarian cancer which was 38%. in the Umbria region. The highest rate of 60% was found in the Trento Province.

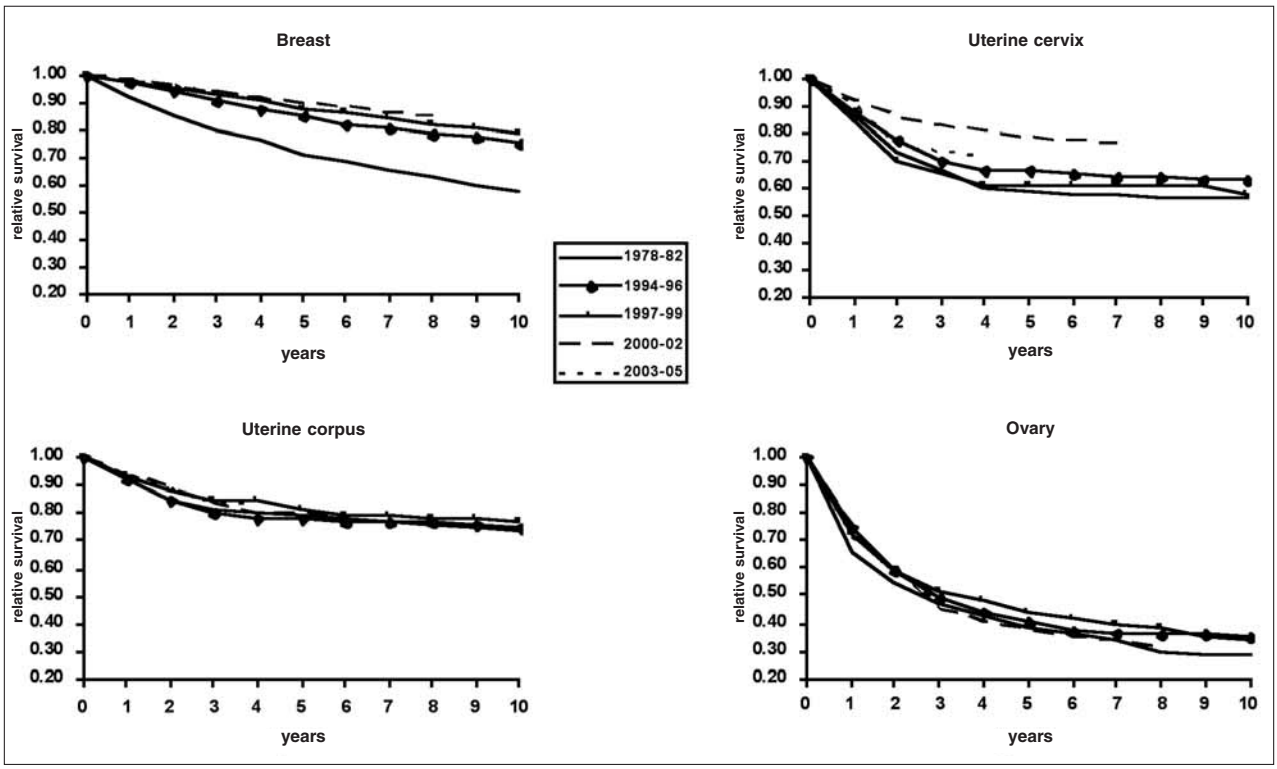

Figure 3. — Relative survival trends for the selected cancer sites.

Table 3. — *Age-adjusted mortality (world population) for the selected cancer sites in the European Union, 2000, and in the Umbria region, 2000-2002*.

Country	Breast	Uterus	Ovary
Austria	18.9	5.5	5.7
Belgium	25.3	4.8	7.4
Czech Rep.	18.7	9.5	7.4
Denmark	25.8	7.2	9.4
Estonia	22.3	9.6	7.9
Finland	16.0	4.1	5.4
France	19.8	4.7	5.3
Germany	19.5	4.8	6.2
Greece	14.7	3.6	4.2
Hungary	22.6	9.3	6.2
Ireland	25.0	4.7	8.4
Latvia	18.0	10.3	6.2
Lithuania	17.7	13.2	9.1
Luxemburg	21.7	4.4	4.3
Malta	31.8	3.7	6.0
Poland	15.0	10.2	6.7
Portugal	16.0	6.1	3.4
Slovakia	18.3	10.8	6.6
Slovenia	18.2	7.5	5.7
Spain	14.3	4.8	4.1
Sweden	16.5	4.5	7.4
The Netherlands	23.1	4.1	6
United Kingdom	21.4	4.6	7.7
Italy	17.8	3.9	4.2
Umbria Region	*16.7*	*3.0*	*4.3*

Table 4. — *Five-year age-adjusted relative percent survival for the selected cancer sites in the Italian registries (1995-1999).*

Registry	Breast	Cervix	Corpus	Ovary
Alto-Adige Region	82	58	81	38
Biella Province	84	61	66	36
Ferrara Province	83	78	79	40
Firenze Province	86	67	75	34
Friuli V.G. Region	79	66	75	40
Genoa	82	61	75	32
Macerata Province	84	71	77	38
Modena Province	86	67	77	36
Naples	81	40	69	31
Parma Province	84	65	72	38
Ragusa Province	79	58	–	29
Reggio Emilia Province	85	67	80	43
Romagna Region	85	66	75	31
Salerno Province	72	56	66	29
Sassari Province	80	58	74	32
Trento Province	80	61	81	60
Turin	83	55	73	34
Varese Province	84	70	80	37
Veneto Region	82	68	76	33
Italian pool	83	65	76	36
Umbria Region	*83*	*62*	*77*	*38*

Discussion

The analysis of incidence, mortality and survival trends is an important tool for monitoring cancer control and assessing primary or secondary prevention interventions.

The decrease in breast cancer mortality in recent years confirms the observed trend in the Umbria region of Italy

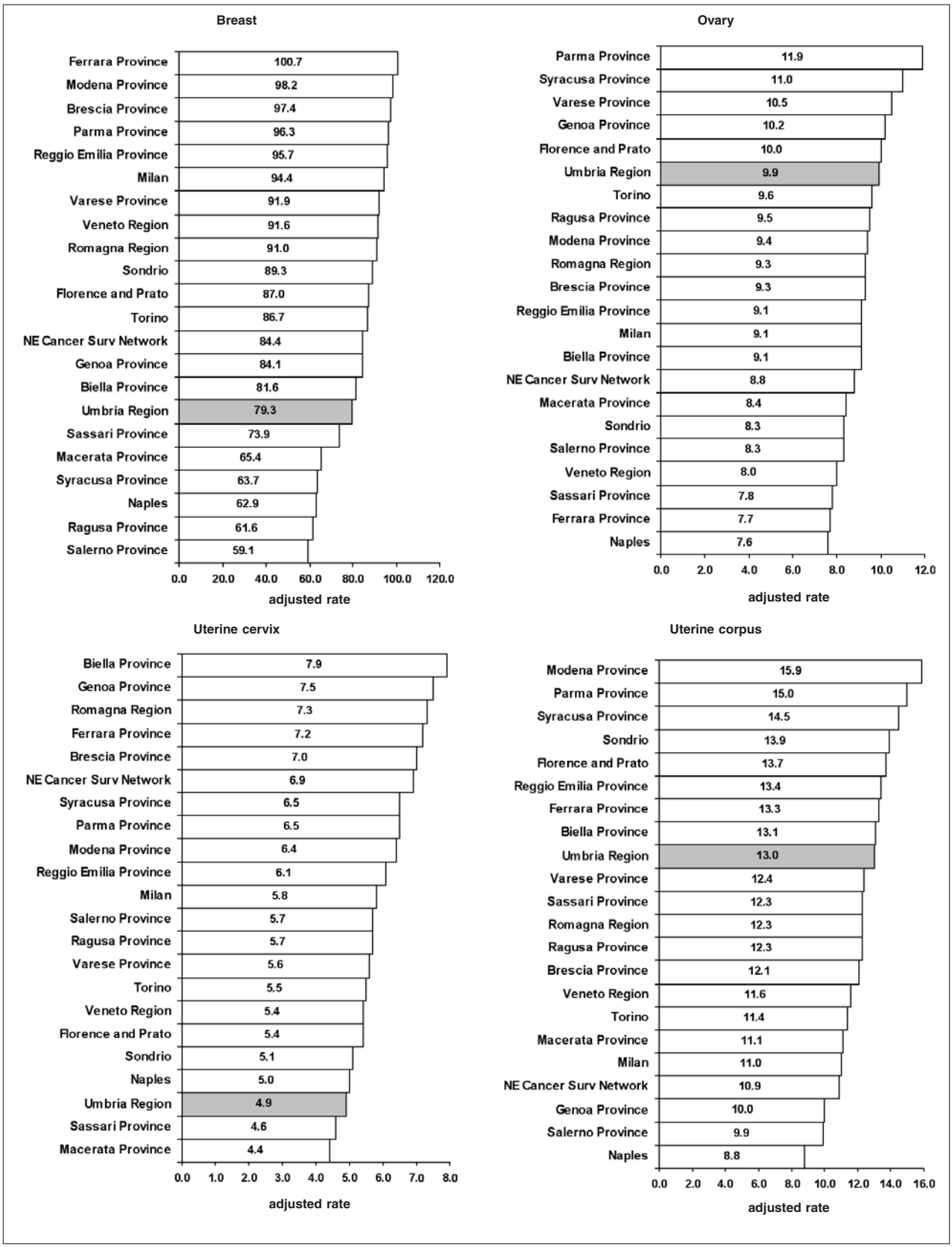

Figure 4. — Age-adjusted incidence (world population) for the selected cancer sites in Italy, 1998-2002 (note: the incidence rate scales in the graphs are different).

and in the European Union [3, 16, 17]. In Italy, data from cancer registries did not show a decrease until 2002 [3], while the present data, which cover a more recent period, indicated a significant decrease. The forecast variation in breast cancer incidence in Italy indicated a steady trend in the 2000-2010 period [18].

Relative survival rates increased constantly and in the most recent period rose to 90% at 5-year follow-up.

The increasing incidence trend until 2001 followed by a significant decrease, a drop in mortality and improvement in survival, were clearly typical consequences of early diagnosis and then of mass screening; treatment improvements also contributed to reduce mortality and improve survival [19]. The comparison with Italian registry data suggests that despite widespread screening, the incidence is very low. However in Umbria, the incidence increased in women aged up to 50 which might suggest starting screening at a younger age.

The difficulty in considering the different uterus sites separately when analyzing mortality, hinders interpretation of trends [20, 21]. An attempt to specify the subsite using incidence data from the Umbrian Cancer Registry yielded unreliable results because of the small proportion of linked cases.

Although diffusion of Pap testing for cervical cancer may have led to some improvements in stage at diagnosis, it mostly reduced incidence by removing premalignant lesions before progression [22, 23]. In Umbria the incidence of cervical cancer increased in women aged from 25 to 44, it decreased until 59, and then increased up to 74 years of age. The all-age annual number of cases was under 40. Mortality rates showed the same trend with a delay of ten years. These observations seem to indicate that screening compliance, in the first target years of the female population, was probably low enough.

As for breast cancer, the relative survival increase for the uterine cervix could also be due to population screening throughout the Umbria region, as also results from the very small annual number of incident cases which, on the other hand, make survival rates unstable.

The incidence of uterine cancers doubled in women aged from 50 to 55 years, showing a peak at 64-69 years, confirming the common pattern in European countries which shows the disease is less common in premenopausal women than in those aged over 50-55. This is also linked, on one hand, to the increasing number of women reproducing at a late age and to the long-lasting protective effect of estrogen-progestin oral contraceptives, and, on the other, to use of exogenous hormones that increase the risk of endometrial cancer [24, 25].

In the Umbria region mortality from uterine cancer was very unsteady while mortality from total uterine cancer constantly increased until 1984 [4].

Relative survival rates remained practically constant over the study period and, in the Umbria region, this seemed to be the effect of improvements in therapy.

Ovarian cancer mortality rates showed a very high variability. Improvements in the diagnostic definition of abdominal cancers probably contributed to the increasing trend from 1985 onward [16]. This fact seems to be confirmed by the evident increase in incidence rates starting from the 1980s that were practically constant in the 1994-2005 period. It will be interesting to evaluate this trend considering prescriptions in the Umbria region of menopausal hormone therapy, even if its relationship with ovarian cancer is still not clear [26-28]. At present these data are unavailable. Furthermore the number of gynecologists who prescribe alternative therapeutic approaches for menopausal symptoms seems to be on the increase [29-31]. Modifications of personal and behavioral risk factors like consumption of beverages such as coffee and black tea or smoking [32, 33] are difficult to evaluate in a population study.

The relative ovarian cancer survival rates also slightly increased from 1978 to 2005, which could depend, among other things, on different criteria for classifying borderline cystoadenal carcinomas that, if considered malignant, increase survival rates.

In conclusion, it seems that in the Umbria region widespread population screening for breast and cervical cancers, together with advances in therapy, has led to a constant increase in survival, while survival for uterine and ovarian cancers has not improved much.

Acknowledgements

This work was supported by the Department of Health, Regional Government of Umbria. The authors thank the operators of the Municipal Offices and the ReNCaM referents of the four Local Health Districts of Umbria.

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