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Cancer burden trends in Umbria region using a joinpoint regression

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Abstract

Introduction. The analysis of the epidemiological data on cancer is an important tool to control and evaluate the outcomes of primary and secondary prevention, the effectiveness of health care and, in general, all cancer control activities.

Materials and methods. The aim of the this paper is to analyze the cancer mortality in the Umbria region from 1978 to 2009 and incidence from 1994-2008. Sex and site-specific trends for standardized rates were analyzed by "joinpoint regression", using the surveillance epidemiology and end results (SEER) software.

Results. Applying the jointpoint analyses by sex and cancer site, to incidence spanning from 1994 to 2008 and mortality from 1978 to 2009 for all sites, both in males and females, a significant joinpoint for mortality was found; moreover the trend shape was similar and the joinpoint years were very close. In males standardized rate significantly increased up to 1989 by 1.23% per year and significantly decreased thereafter by -1.31%; among females the mortality rate increased in average of 0.78% (not significant) per year till 1988 and afterward significantly decreased by -0.92% per year. Incidence rate showed different trends among sexes. In males was practically constant over the period studied (not significant increase 0.14% per year), in females significantly increased by 1.49% per year up to 2001 and afterward slowly decreased (-0.71% n.s. estimated annual percent change – EAPC).

Conclusions. For all sites combined trends for mortality decreased since late '80s, both in males and females; such behaviour is in line with national and European Union data. This work shows that, even compared to health systems that invest more resources, the Umbria public health system achieved good health outcomes.

Key words
- cancer
- health system
- evaluation
- outcomes

INTRODUCTION

The analysis of the epidemiological data on cancer is an important tool to control and evaluate the outcomes of primary and secondary prevention, the effectiveness of health care and, in general all cancer control activities [1-4].

Trends in cancer incidence and mortality in Europe are generally going in the right direction in the more wealthy countries starting from the North/North-West countries, showing that the cancer prevention and management activities in Europe and in particular in the European Union, is giving some kind of results [5].

Also in Italy, cancer incidence and mortality show the same trends as the rest of Western Europe. Mortality decreased for the most cancer sites, the incidence increased only for those diagnosed by population screening (*e.g.* colorectal and, in minor extent, female breast cancers) or individual one (*e.g.* thyroid, melanoma) and in females for lung cancer and Hodgkin lymphoma [6].

In the Umbria region of Italy, several studies have been carried-out on geographic distribution and temporal trend of cancer incidence and mortality [2, 7]. Umbria is a small region in the centre of Italy (900 790 inhabitants). Regional health structures, including two main oncology centres (Perugia and Terni), are easy to reach by all residents. Regional population screening interventions were introduced in 1997 for breast cancer, in 1999 for cervical cancer and in 2006 for colorectal cancer [8, 9]. Several years before the start of population screening the regional health system was offering free pap smear test for cervix cancer. Since the late '80s opportunistic screening activities for skin melanoma and prostate cancer have became more and more popular. In particular for prostate cancer, in the late eighties

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digital rectal examination first and prostate specific antigen (PSA) test later began to spread [10].

A regional cancer registry, the Umbrian Population Cancer Registry (RTUP), was established in the early '90, consequently data on incidence, prevalence and survival are available for the period 1994-2009. The registry also collects regional mortality data from municipal offices and death certificates, and publishes official yearly general mortality statistics [11].

The aim of this paper is to analyze the cancer mortality in the Umbria region, from 1978 to 2009 and incidence, from 1994-2008. Possible explanations of observed trends will be proposed with a particular attention to the period 1994-2008.

MATERIALS AND METHODS

Mortality data was supplied by the National Institute of Statistics (ISTAT) until 1993, while, for the following 1994-2009 period, by the Regional Nominative Causes of Death Registry (ReNCaM), based on the Population Register Offices of the Umbrian municipalities linked with the archives of death certificates collected by the Local Health Districts and afterwards used by ISTAT. No major or systematic difference seems to exist comparing ISTAT and ReNCaM based mortality data and, since ReNCaM data are updated earlier than ISTAT mortality data, they allow the inclusion of more recent years in the analysis [12]. Incidence data derived from RTUP and are referred to the 1994-2008 period. Causes were classified according to the X International Classification of Diseases (version 7). Cancer sites examined are listed in *Table 1*. For each site the age-adjusted rates (AADR) have been calculated. Sex and site-specific trends for standardized rates were analyzed by "joinpoint regression", using the Surveillance Epidemiology and End Results (SEER) software [13]. The European population was used as standard for age standard adjustment in the joinpoint analyses. The grid search method allows the detection of segments best describing data. The maximum number of joinpoints allowed for each analysis were three for incidence and four for mortality. The expected annual percent changes (EAPCs) are reported to describe linear trends by period. In this way it is possible to identify for each period a distinct linear, or log-linear trends of rates separated by joinpoints. Within different joint points the EAPC was labelled as statistically significant when its 95% confidence interval did not include zero. The method follows the principle of minimization of the weighted sum of squared errors and the choice of the number of joinpoints is on the basis of permutation tests [14].

Neoplasm of haematopoietic tissue, and other unreported sites, were disregarded because of the very high variability of rates, over the studied period, in relation to the low number of cases. The definition of head and neck cancer is not standard; we included mouth, tongue, and pharynx sites (C01-C06, C10-C13) and reported separately larynx cancer trend among males. Uterus was considered as a total and undefined uterus (C53-C55) both for mortality and incidence, since the inaccuracy of death certifications (leading to the assignment of C55 code) was not constant but decreasing over the study period. A separate analysis of cervix (C53) and uterus (C54) was possible only for incidence.

RESULTS

The estimated annual percent change (EAPC) by jointpoint analyses by sex and cancer site, applied to incidence spanning from 1994 to 2008 and mortality from 1978 to 2009 are reported in *Table 1*.

For all sites, both in males and females, a significant joinpoint for mortality was found *(Figure 1)*; moreover the trend shape was similar and the joinpoint years were very close. In males standardized rate significantly increased up to 1989 by 1.23% per year and significantly decreased thereafter by -1.31%; among females the mortality rate increased in average of 0.78%, not significant (n.s.), per year till 1988 and afterward significantly decreased by-0.92% per year. Incidence rate showed different trends among sexes. In males was practically constant over the period studied (n.s. increase 0.14% per year), in females significantly increased by 1.49% per year up to 2001 and afterward slowly decreased (-0.71% EAPC, n.s.).

Figure 2 reports, only for males, the temporal trends of head and neck, oesophagus, larynx and prostate cancer. The first three cancer sites presented a similar trend, without joinpoints. The rates decreased significantly both in mortality and incidence respectively by -2.36% and -2.92% in head and neck cancer, -2.07% and -6.05% per year in esophagus cancer and -3.17% and -2.93% per year in larynx cancer. Prostate cancer mortality trend is the only one, among these, showing a significant trend with two joinpoints: the rates decreased up to 1989 (-1.99%), then increased up to 1998 (2.66%) and finally decreased (-4.09% EAPC). Incidence showed a constant and significant increase of 3.50% per year.

Gastric cancer showed different mortality trends by gender. In males it was slightly increasing up to 1985 (1.42% n.s.) and significantly decreasing after this year (-3.43% EAPC). It was constantly decreasing among females over the study period and the trend showed a joinpoint in 1994 where the EAPC switched from -1.80% to -4.06%. Incidence constantly decreased in both sexes over the studied period (-3.66% in males and -3.73% in females).

Colon cancer in males showed a significant increase in mortality rate (2.65%) up to 1997 and afterward slightly decreasing (-0.31% n.s.). The incidence significantly increased (1.85%) in the period under investigation. In females both trends in incidence and mortality increased respectively of 0.87% (n.s.) and 0.65%. On the contrary, rectum cancer showed a significant decrease in mortality (-2.25% in males and -2.46% in females); no significant trends for incidence were detected for both females and males (respectively -1.29% and 0.26% n.s.).

Liver and pancreas showed heterogeneous trends. Mortality from hepatic cancer in males significantly increased up to 1990 (4.74%) and afterward decreased (-1.63% per year), in females it decreased over all studied period (-1.77%); incidence for both genders was slightly decreasing (-1.04% in males and -1.11% in females, n.s. EAPC). Pancreatic cancer mortality and incidence increased both in males and in females but

Table 1
Joinpoint analysis by sex and selected cancer site in the Umbria region (Italy)*

Site ICD10		Mortality		Confidence interval		Incidence		Confidence interval	
	Sex	Period	EAPC[1]	Lower	Upper	Period	EAPC	Lower	Upper
All sites C00-C97	M	1978-1989	1.23*	0.41	2.04	1994-2008	0.14	-0.24	0.53
	M	1989-2009	-1.31*	-1.60	-1.02				
	F	1978-1988	0.78	-0.11	1.68	1994-2001	1.49*	0.52	2.46
	F	1988-2009	-0.92*	-1.19	-0.65	2001-2008	-0.71	-1.61	0.19
Head and neck C01-C06, C10-C13	M	1978-2009	-2.36*	-3.20	-1.51	1994-2008	-2.92*	-4.46	-1.36
Esophagus C15	M	1978-2009	-2.07*	-3.04	-1.08	1994-2008	-6.05*	-8.93	-3.07
Stomach C16	M	1978-1985	1.42	-1.78	4.73	1994-2008	-3.66*	-4.58	-2.73
	M	1985-2009	-3.43*	-3.94	-2.92				
	F	1978-1994	-1.80*	-2.61	-0.98	1994-2008	-3.73*	-5.06	-2.38
	F	1994-2009	-4.06*	-5.03	-3.09				
Colon C18-C19	M	1978-1997	2.65*	1.80	3.51	1994-2008	1.85*	0.56	3.15
	M	1997-2009	-0.31	-1.55	0.95				
	F	1978-2009	0.65*	0.04	1.25	1994-2008	0.87	-0.32	2.08
Rectum C20-C21	M	1978-2009	-2.25*	-2.91	-1.59	1994-2008	0.26	-1.40	1.94
	F	1978-2009	-2.46*	-3.21	-1.70	1994-2008	-1.29	-2.83	0.28
Liver C22	M	1978-1990	4.74*	1.11	8.50	1994-2008	-1.04	-2.37	0.31
	M	1990-2009	-1.63*	-2.99	-0.26				
	F	1978-2009	-1.77*	-2.38	-1.16	1994-2008	-1.11	-3.81	1.67
Pancreas C25	M	1978-2009	0.38	-0.26	1.02	1994-2008	1.16	-0.58	2.94
	F	1978-2009	1.10*	0.44	1.77	1994-2008	1.57*	0.50	2.66
Larynx C32	M	1978-2009	-3.17*	-3.73	-2.61	1994-2008	-2.93*	-4.86	-0.96
Lung C33-C34	M	1978-1987	3.88*	1.71	6.10	1994-2008	-1.78*	-2.16	-1.41
	M	1987-2009	-1.27*	-1.74	-0.79				
	F	1978-2009	2.49*	1.97	3.00	1994-2008	2.48*	0.94	3.05
Skin melanoma C43	M	1978-2009	2.00*	0.44	3.59	1994-2008	2.59	-0.39	5.65
	F	1978-2009	3.04*	1.65	4.45	1994-2008	1.76	-1.19	4.80
Breast C50	F	1978-1994	0.90	-0.21	2.03	1994-2001	3.62*	1.43	5.85
	F	1994-2009	-1.60*	-2.75	-0.44	2001-2008	-1.79	-3.7	0.17
Uterus C53-C55	F	1978-2006	-3.13*	-3.81	-2.46	1994-2008	-1.10	-2.45	0.26
	F	2006-2009	14.16	-7.79	41.34				
Cervix uteri C53	F	-	-	-	-	1994-2008	-1.84	-4.20	0.57
Body of uterus C54	F	-	-	-	-	1994-2008	-0.69	-1.96	0.59
Ovary C56	F	1978-1985	11.18*	1.68	21.56	1994-2008	-2.06*	-3.69	-0.41
	F	1985-2009	-0.50	-1.58	0.59				
Prostate C61	M	1978-1989	-1.99*	-3.83	-0.12	1994-2008	3.50*	2.22	4.78
	M	1989-1998	2.66*	0.00	5.39				
	M	1998-2009	-4.09*	-5.51	-2.65				
Urinary bladder C67	M	1978-2009	-0.49	-1.08	0.11	1994-2000	0.77	-4.22	6.03
	M					2000-2008	-7.24*	-10.5	-3.85
	F	1978-2009	-0.81*	-1.16	-0.02	1994-2008	-3.83*	-5.09	-2.55
Brain C71	M	1978-2009	1.43*	0.74	2.12	1994-2008	-1.24	-3.42	0.99
	F	1978-2009	1.00*	0.05	1.95	1994-2008	-2.72*	-4.54	-0.86
Thyroid C73	M	1978-2009	1.07	-1.06	3.25	1994-2008	5.09*	1.80	8.50
	F	1978-2009	-2.73*	-4.18	-1.25	1994-1996	55.75	-16.11	189.17
	F					1996-2008	3.65*	1.31	6.03

[1]EAPC: estimated annual percent change.
*Significant change ($p < 0.05$). Only significant joinpoints ($p < 0.05$) were retained in final models for each site.

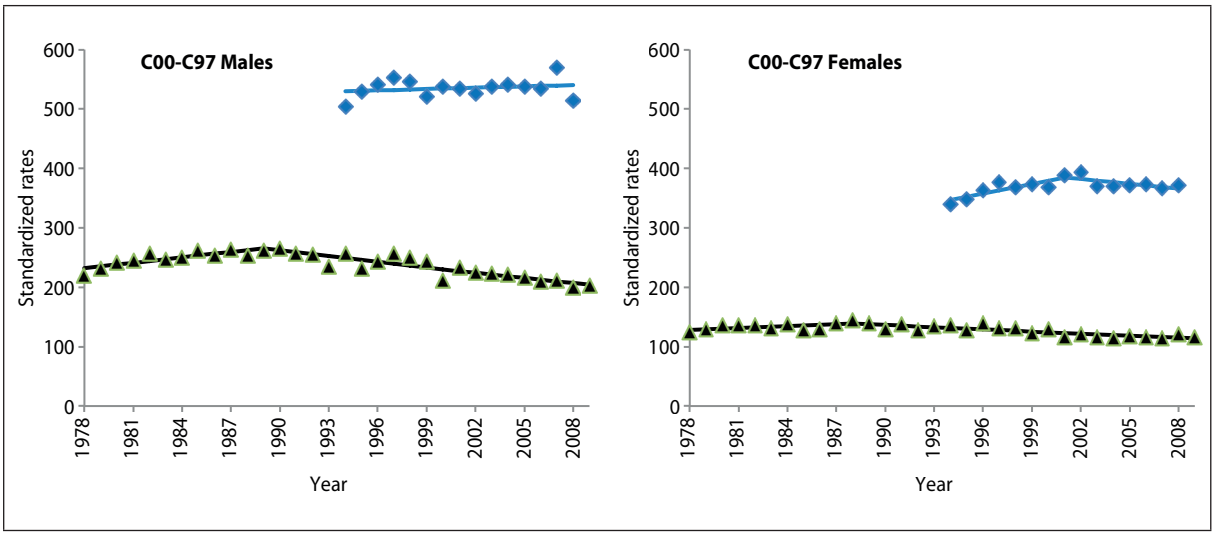

Figure 1
Observed standardized rates per 100 000 inhabitants of incidence (diamond marker) and mortality (triangle marker) and "best" joinpoint model estimates (solid line) for all sire cancers.

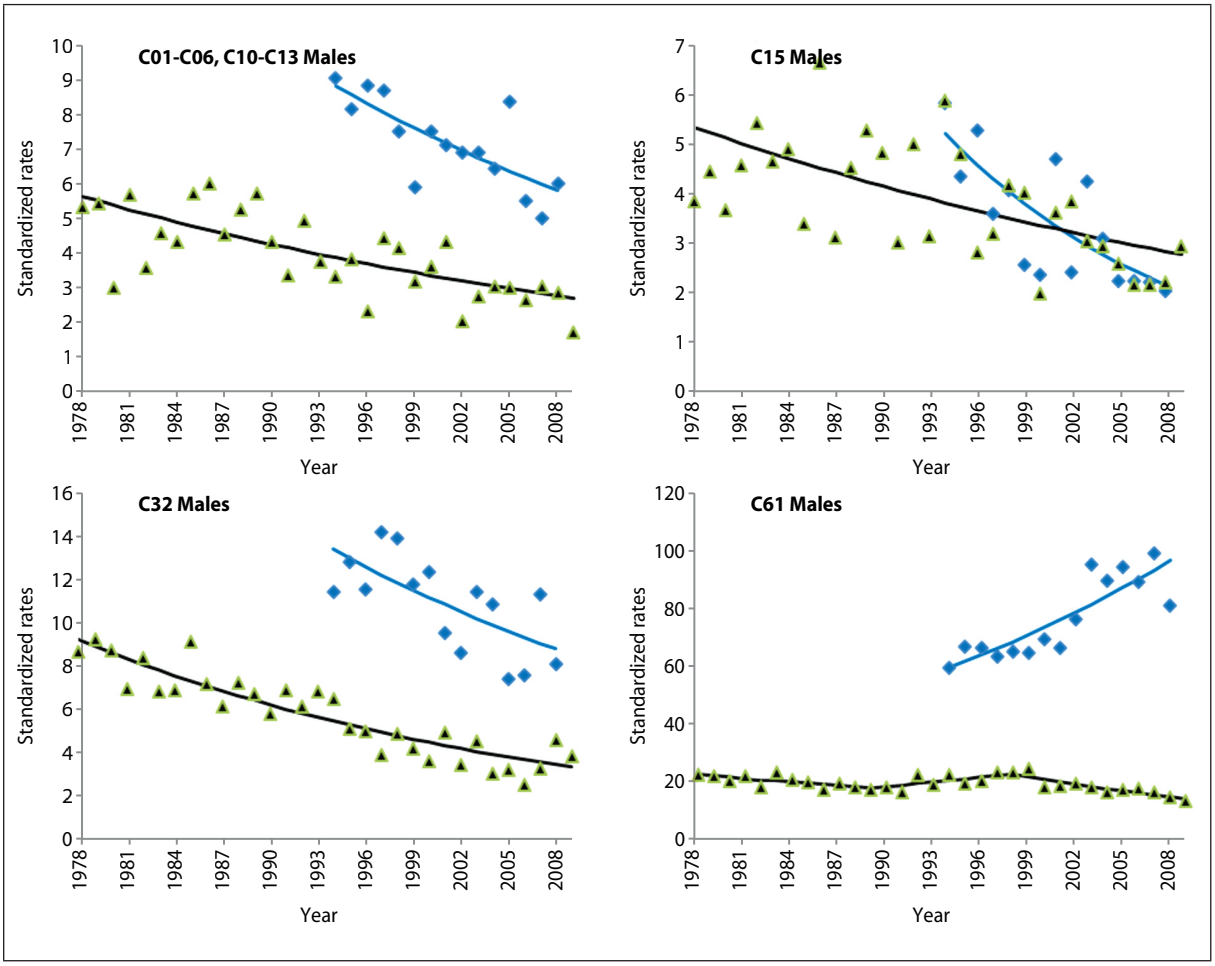

Figure 2
Observed standardized rates per 100 000 inhabitants of incidence (diamond marker) and mortality (triangle marker) and "best" joinpoint model estimates (solid line) for head and neck (C01-C06, C10-C13), esophagus (C15), larynx (C32) and prostate (C61) cancers.

no significant in males (0.38% mortality and 1.16% incidence EAPC) while in females increases were significant (1.10% and 1.57% respectively).

Lung cancer mortality rates in males significantly increased (3.88%) up to 1987 and decreased after (-1.27%); the incidence for the overall period decreased significantly (-1.78%). In females, both mortality and incidence increased by 2.49% and 2.48% (significant EAPC) respectively.

The trends relative to skin melanoma were always increasing, significantly in mortality (2.00% in males and 3.04% in females) and not significantly in incidence (2.59% in males and 1.76% in females).

Trends in female breast cancer presented a joinpoint both in mortality and in incidence *(Figure 3)*. Mortality increased (0.90% n.s.) up to 1994 and after significantly decreased (-1.60%); incidence significantly increased in rates (3.62%) up to 2001 and then decreased (-1.79% n.s.).

The rates relative to ovary cancer *(Figure 3)* present a significant increase trend up to 1985 (11.18%), while afterward the trend slowly decrease (-0.50% n.s.); the incidence decreased over the study period by -2.06% per year, statistically significant.

Brain cancer showed a steady and significant increase in mortality (1.43% in males and 1.00% in females), and decrease in incidence (-1.24% and -2.72% in two sexes respectively) significantly also in females.

The trends relative to cervix and body of uterus are described only for incidence; the relative decrease is not significant for both (cervix -1.84% and body -0.69%). The analysis for total uterus cancer confirmed for incidence a no significant decrease; on the contrary mortality trend was significantly decreasing up to 2006 (-3.13%), while the following increase (14.16%) is not significant.

Regressions relative to urinary bladder, brain and thyroid cancer are documented. For urinary bladder cancer, a joinpoint was detected only for incidence in males: it increased till year 2000 (0.77% n.s.) and then significantly decreased (-7.24% EAPC). For mortality no significant trends were detected (-0.49% EAPC n.s.). In females both mortality and incidence decreased significantly over the study period.

Mortality rate in male is quite constant (+1.07% n.s.) and decreased in females by -2.73% per year (statistically significant) for thyroid cancer. The trend analysis of this site is affected by the low number of cases: incidence constantly increased for males (5.09%), for females increased up to 1996 (55.75% n.s., probably due to the low number of cases) and afterward increased significantly by 3.65% per year till the period considered.

CONCLUSIONS

The present study shows for most cancer sites a reduction trend for mortality and incidence in the Umbria region. For all sites combined trends for mortality decreased since late '80s, both in males and females; such behaviour is in line with national and European Union data [3-5]. The global burden of cancer remains high in developed countries and is growing in those developing [15, 16]. This is due to an increase in the average expected life span and to a high prevalence of environmental and behavioural risk factors that in the past were present almost exclusively in western societies, such as air pollution, smoking, alcohol consumption, high-fat diet and physical inactivity [15]. Approximately 30% of all deaths from cancer are attributable to tobacco smoking and unhealthy diets and physical inactivity [17].

During the period considered the Umbria region shows a decrease in incidence of upper aero digestive tract cancer [7]. This trend was also observed for mortality rates, for the same cancer, among males and females. This favourable regional pattern is in line with the trends in the rest of Southern Europe [18]. In Italy, as in France and in Spain, the observed trends largely reflect two major changes in individual behaviours: the fall of tobacco smoking habit among males and the decline in alcohol consumption [4, 19]. It was estimated that at least three quarters of oral cavity cancers are pre-

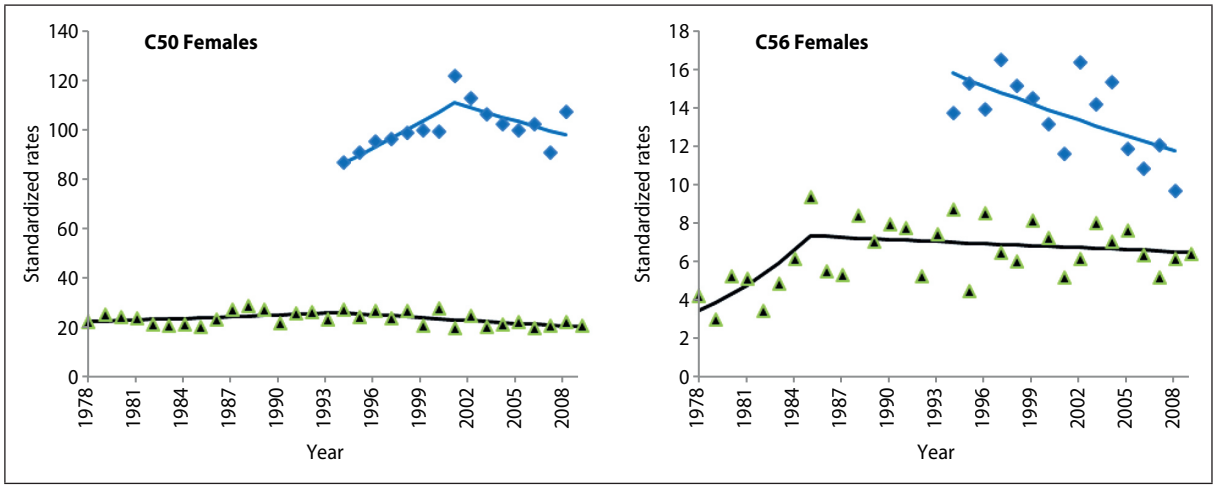

Figure 3
Observed standardized rates per 100 000 inhabitants of incidence (diamond marker) and mortality (triangle marker) and "best" joinpoint model estimates (solid line) for female breast (C50), and ovary (C56) cancers.

ventable with the eradication of smoking and alcohol habit [20, 21]. The decrease of the above-mentioned risk factors does not fully justify the fall of esophageal cancer. This decline in incidence that occurred can also be explained by early detection of precancerous lesions and subsequent early treatment of the lesion; although the evidence is not yet sufficient.

Historically the Umbrian region is a high risk area for gastric cancer [7]. The reason of this high incidence can find its explanation in the local dietary pattern [22]. In the period observed, incidence rates decreased in both sexes. Mortality trend is constantly decreasing among Umbrian females, while in Umbrian males there's a slight increase up to 1985 and a decrease after. The trends observed in the Umbrian region are quite similar to those observed in the rest of Italy [6]. The decrease in mortality rates in Umbria is closely linked to the reduction in the number of new cases and also to the implementation of the Umbrian oncology health care system [23]. Despite the favourable trends during the last decades, the gastric cancer still ranks fourth in Umbrian males and fifth for the females [24, 25]. The same of Italy where this cancer is the fifth in frequency in both sexes and the fourth leading cause of cancer death in males and the fifth in females [23].

The incidence rate of liver cancer in the Umbria region shows a moderate decreasing trend in both sexes. Downward trends in mortality were observed among females over all period and in males since 1990. For the same period in Italy no large incidence and mortality changes were reported in liver cancer but rather a slight steady downward trend since the mid-nineties [6]. Across Europe, indeed, liver cancer shows a large heterogeneity with the presence of three main different risk geographical areas [26]. Incidence and mortality data on liver cancer in Umbria is difficult to interpret and subject to large uncertainties and errors [27]. Furthermore, improvements in liver cirrhosis surveillance led to an increase in liver cancer diagnosis and in countries where mortality for cirrhosis is relatively frequent, the exchange of cirrhosis with liver cancer on death certification, even if in a few cases, may have an important effect [27]. Even with these limitations, we can state that the downward trend in Umbria is, at least in part, real. Indeed, declined prevalence of hepatotropic viruses infections and alcohol consumption may have contributed to the observed trend [28]. Regarding the different frequencies of liver cancer by gender, it is in line with the worldwide trend.

Lung cancer among Umbrian females shows an increase both in incidence and in mortality. The corresponding incidence rates in Umbrian males decreases for the same period, constituting third cancer in frequency [24]. The same trends are observed in the rest of Italy [6]. This is perfectly in line with the international data [29, 30]. Gender differences in rates of lung cancer observed in Umbria and in the rest of Italy are also due to different trends in the prevalence of smoking [31]. In the last decade most of the prevention activities carried out in Italy have been dedicated against smoking habit [32]. Lung cancer mortality trends are quite similar to incidence trends because the prognosis continues to be very poor [6]. Indeed the survival for patients with lung cancer is only three years in advanced stage cases [30].

In many studies a decreasing trend for breast cancer was observed since the beginning of the twenty-first century for Italy as well as for many industrialized countries (*e.g.* USA 2001-2004 [33], Germany 2002-2005 and France 2003-2006 [34-37]). Breast cancer trend for Umbria is consistent with these findings. Due to the poor diffusion of the hormone replace therapy (HRT) in Italy [37], the incidence trends in different age cohorts for invasive and intraductal breast cancer in the period 1994-2008 have been studied. Different age cohorts were analyzed: 40-49, 50-69and 70-79 years old. The organized breast cancer screening started in 1998. The data underlines a significant increase of invasive cancer only in the screening cohort (50-69) till 2001. This result is consistent with the first organized screening program in 1997. Furthermore it can be assumed that the health promotion campaign induced a higher participation to breast opportunistic screening. The following decreasing trend maybe partially due to two consequences of the screening program: the saturation and the diagnostic anticipation. In effect the data shows for the same period an increase in the number of diagnosis of intraductal neoplasm. The increasing trends in the pre-screening cohort during the overall study period could be related to the implementation of the opportunistic screening. Moreover, in the over 70 cohort the trend of infiltrating neoplasm shows a slight decrease in rate (n.s.), which could be related to diagnostic anticipation.

The mortality for rectal cancer is decreasing in both sexes while this is not true for colon carcinoma (only lightly decreasing since 1997 in males and steady in women). These results reinforce the need to promote screening activities that will allow not only to achieve the reduction of mortality, but also a strong improvement of the quality of life.

The trends in incidence and mortality for this cancer vary in the world and in the EU. This heterogeneity can be largely interpreted by analyzing the coverage and quality of screening, the changes in exposure to risk factors that are mainly related to sexual habits and persistent infection of human papilloma-virus [38]. Countries with organized screening programs in the last decades have witnessed a significant decrease in incidence and mortality [38]. In Umbria the organized screening started in 1999 (although preceded by an opportunistic one). The incidence of cervical cancer shows a decrease trend, probably due to the program: about 85% of women aged 25-64 years reported having a preventive Pap test (57% within an organized screening program, 28% as individual prevention). Such explanation is supported by the sharp increase in severe dysplasia, APC 6.75 (CI 4.98-8.55).

Incidence and mortality trends for prostate cancer in Umbria agree with Italian trends and Western countries. The decrease of mortality can deal with the improvements of the surgery and radio therapeutic treatments and to the role of opportunistic screening through PSA. PSA screening has spread spontaneously mainly to its simplicity [39].

Skin melanoma mortality trends in Umbria grow for the overall study period, incidence presents an

unstable trend. Such differences could be due to the low number of cases and also to the effects of information campaigns. It is well known that eighty percent of melanoma is due to damages from ultraviolet on very sensible skin, particularly dangerous are episodic exposure during the childhood [40]. Primary prevention of melanoma is therefore based on the use of protective measures [41]. Anyway some studies demonstrated that the only sunscreen use was even associated with increased risk of cutaneous melanoma [42]. Screening for skin melanoma is based on a specialist visit. The evaluation of a pilot project in Germany demonstrated that an organized population based skin cancer screening is useful to detect more cases of early stage melanomas. Comparing to the average melanoma mortality in Germany a reduction of about 50% could be detected in the screened population [43]. These promising results suggest that combining secondary prevention with primary prevention interventions could be effective to fight skin melanoma incidence and mortality.

The analysis of trends for thyroid cancer could have been associated to the cancers which benefit of primary prevention interventions; this is because the risk factors are largely known and sometimes modifiable [42, 44]. Nevertheless the problem needs to be analyzed separately because many authors highlighted for thyroid carcinoma the role of so-called "incidental screening". In Europe as well as all over the world many studies have documented an increase in thyroid cancer incidence in the last two or three decades while for mortality the trend is stable [45]. For Italy the increasing trend for incidence was confirmed especially in women, while mortality for both genders was characterized by a no significant decrease [6]. Time trend in Umbria, even if affected by the poor number of cases, seems to be in line with the Italian epidemiologic frame; the only difference is the significant decrease in mortality for females. As already mentioned, many authors addressed the increasing incidence to the improvement of the diagnostic techniques which could be a consequence of un opportunistic screening intervention. Particularly some studies stressed how the increase in thyroid cancer incidence affected only small nodules while other authors showed significant increases of differentiated thyroid cancers of all sizes formulating the hypothesis that other factors could have contributed to the incidence rate [46-48].

In the US Cancer Statistic report, 2011, the authors confirmed what already stressed in the 2008 report: "Cancer replaced heart disease as the leading cause of death among men and women aged younger than 85" [17]. The World Health Organization (WHO) estimates that about 40% of all cancer deaths can be prevented [49]. Starting from these last points it is important to assess trends of incidence and mortality cancer in relation to primary and secondary prevention interventions.

This works shows how a public health system funded with only 9.5% of GDP [50], with still some several inefficiencies (esp. insufficient standardized protocols) and low investment in primary prevention (less 1% of GDP) presents numbers much better than other countries ranking always in the first ten of WHO [51, 52]. The data reassures the public health experts from this point of view, considering also that the trends are comparable with other European countries with a global funding much higher as: The Netherlands, France and Germany [53].

Conflict of interest statement

None.

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