Epidemiology of HPV-related female cancers in the Umbria region of Italy: pre-vaccination period

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Summary

The authors describe the incidence and mortality rates of human papillomavirus (HPV)-related female cancers in Umbria (Italy) in the pre-vaccination period from 1978-2008. Joinpoint regression was applied on age-adjusted incidence and mortality rates to evaluate temporal trends. Mouth and pharynx cancers incidence and mortality trends decreased about three percent per year. For anus and anal canal cancer, incidence and mortality trends presented a non-significant decrease. For malignant neoplasm of vulva, a significant change was found in incidence trend: the annual percentage change decreased from 2001 (- 1.8%). Mortality trend showed a non-significant decrease. Incidence and mortality rates from vaginal cancer were non-significantly decreased. For malignant neoplasm of cervix uteri, incidence rates showed a significant decrease by 2.1% per year. Mortality rates decreased as well, although non-significantly. HPV-related cancers consistently decreased in Umbria. This trend may be a consequence of safer sexual behavior. For cervical cancer, a combination of opportunistic and programmed screening led to a much-reduced disease burden. It is expected that the implementation of vaccination in the future will lead to a further decrease of HPV-related cancer incidence and mortality.

Key words: Incidence; Mortality; HPV-related cancers; Vaccination.

Introduction

Human papillomaviruses (HPVs) are responsible for about 500,000 cases of cervical cancer annually on a global level [1] and ten million further cases of high-grade cervical intraepithelial neoplasia (CIN) [2], pre-invasive lesions are reported. It is estimated that 30 million women and men acquire anogenital warts (condyloma acuminata) or low-grade CIN annually [2] and these data are probably underestimated given the inadequacy of reporting in many countries and the evidence of a rising incidence over time.

HPV infection can be detected from virtually all cervical cancers and CIN II/III [3, 4]. HPV types are also associated with development of squamous cell cancer in sites other than the cervix. HPV is estimated to be responsible for five percent of the global cancer burden [5].

About 40% and 80% of vulvar and vaginal cancers, respectively, are reported to be positive to HPV, supporting the notion of mixed etiology of these cancers [6].

The causal role of the HPV infection in oropharyngeal cancer is currently debated [7-9]. Recent research has highlighted the risk conferred by HPV infection in head and neck cancers [10, 11]. The incidence of head and neck cancers has increased in recent years, particularly among younger age groups, which may be at least partially attributed to HPV infection [12, 13]. Increase of both HPV-positive tonsil and base of tongue cancers has been reported in several recent studies [12, 14-16].

Most HPV-related cancers arise as a consequence of infection with a small subset of HPV types (i.e., HPV 16 and HPV 18) that, as a consequence, earned the definition of high-risk types (HR-HPV). HPV types detected in cervical cancers and in other pre-invasive lesions vary, depending on the geographical region and study sample type (general population vs high-risk population).

HPV 16, the most common HR-HPV, has been reported to be present in 49%-81% of pre-invasive lesions in the cervix. HPV types 16 and 18 have been detected in 52%-64% and 11%-22% of cervical, 27%-58% and 2%-10% of vulvar, and 46%-77% and 3%-27% of vaginal cancers, respectively [3, 4, 6, 17-19]. HPV type 16 has been the most usual type detected from oro-pharyngeal, and penile cancers [20-22].

Cervical cancer is responsible for the main health burden among HPV-associated cancers. Early diagnosis and treatment of cervical disease has proved to be a successful population strategy to decrease morbidity and mortality associated with cervical cancer [23]. Screening introduction in a previously unscreened population leads to a dramatic decrease in the incidence of infiltrating cervical cancer and mortality in the screened cohort [24].

Opportunistic cervical cancer screening has been diffused in Umbria since 1972 when pap testing was offered free of charge. An organized cervical cancer screening program, targeted to all women aged 25-64 years, was begun in 1999. In 2008 the organized screening coverage reached 80% of the target population in all four regional Local Health Units [25]. Screening, however, does not interfere with the circulation of HR-HPV infection.

Revised manuscript accepted for publication October 18, 2012

Prophylactic vaccines against HR-HPV are now available. The quadrivalent HPV vaccine, for instance, has the potential to prevent about 70% of cervical cancers and over 90% of condylomas, by targeting HPV types 16 and 18 and types 6 and 11, respectively, according to available evidence [26-28]. Efficacy against vulvar and vaginal intraepithelial neoplasia grade 1, 2 was 100% (72% to 100%) [29]. High-efficacy against condyloma was also demonstrated (92% to 100%) [30]. A bivalent vaccine is also available and is targeted at HR-HPV types 16 and 18 only.

Duration of protection so far has been shown to be at least nine years with the prototype HPV 16 vaccine, and immune memory has also been documented. Some cross-protections have been shown against closely-related HPV types (31 and 45) with bivalent and quadrivalent vaccines [31-33].

A vaccination strategy based on active invitation of all 12-year-old girls and using the bivalent anti-HPV vaccine was adopted at a national level and introduced in Umbria in 2008. Moreover, vaccination was offered for free to 13-year-old girls and at a reduced price to older women.

The aim of this paper is to describe the current epidemiological trends of HPV-related female cancers in the Umbria region in the pre-vaccination period. This study may be used as a baseline for future comparisons and to evaluate the effectiveness of vaccination.

Materials and Methods

Incident data were collected from the Umbrian Population Cancer Registry (RTUP), established in the early 1990s, from 1994 to 2008 [34]. Furthermore, for the 1978-1982 period, an *ad hoc* survey was carried out in the region to determine the incidence of cancer [35]. Mortality data 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 collected by Local Health Districts and later used for national survey by the National Institute of Statistics (ISTAT). Incidence and mortality data are classified according to the 10th International Classification of Diseases (ICD X): cancers of the mouth and oro-pharynx (C00-C06, C09-C10, and C13-C14), anus and anal canal cancer (C21), cancer of the vulva (C51), vaginal cancer (C52), and cervix uteri cancer (C53) [36]. All cases were collected, coded, stored, and analyzed in accordance with standard methods recommended for cancer registries [37], using the ICD X classification [36].

Age-adjusted incidence and mortality rates (using Umbrian, Italian, and world population standards) were calculated for each site. Site-specific trends for standardized rates were analyzed by "joinpoint regression" [38], using the SEER software [39]. The aim of the approach is to identify possible "joinpoints" where a significant change in the log-linear trend occurs. For each linear segment the average annual percentage change (APC), its significance, and corresponding 95% confidence intervals were calculated [39]. The Umbrian population in the 2001 census was used as the standard in the "joinpoint analysis" to reduce bias due to differences in age structure.

Results

The annual number of incident cases for the different sites and incidence rates per 100,000 inhabitants throughout the period 1978-2008 are presented in Table 1. Mortality data are shown in Table 2. Mortality rates for C21 and C52 are not present for the 1978-1982 period, because of classification problems (i.e., tumors of anus and anal canal were classified within the "rectum" three digit category according to the IX version of the ICD in use. Similarly, vaginal cancers were included among malignant neoplasm of vulvar cancer category. These cancer sites were identified by the fourth digit of the ICD IX classification and this resulted in lower accuracy). The curves by age for incidence and mortality, in the four periods taken into account, are shown in Figure 1.

Incidence of mouth and oropharynx cancers begins increasing in the 55-59 age group. The increase is less-pronounced in the most recent study period, thus the incidence in the elderly is lower in the 2004-08 period than in previous periods. Mortality is shifted toward older ages with respect to incidence; age-specific mortality rates are increasing for the age-classes 60-64 years and older.

The anus and anal canal cancer incidence rates by age showed a rapid increase in the 69-74 age group; this increase was more marked in the 1994-1998 period. A decrease in the anus and anal canal cancer incidence was observed in the oldest age group, except for the 1999-2003 interval. The anus and anal canal cancer mortality rates showed an increase with age. The age-specific incidence and mortality curves for vulval cancer increased with age and remained constant over the study period. Vaginal cancer incidence in the 75-85 age group was higher in the 1999-2003 time period than in the other study periods. Mortality from vaginal cancer was low and showed some variability; however, it increased among women over 80 years of age. The cervix uteri cancer incidence rates by age resulted different by period. The age-specific incidence curve for cervical cancer showed a steady increase among women 35-39 years of age and then remained stable or increased slowly. The age distribution was quite different in the 1978-82 period, when the curve steadily increasing among the age groups over 35-39 years until it reached a peak at 60-64 years. Moreover, a slow but progressively decreasing incidence was observed by period among middle-aged women. Results of the joinpoint analysis by cancer site, applied to incidence and mortality rates, are reported in Figure 2.

Both incidence (annual percentage of change (APC) -3.0, 95% confidence interval (CI) from -6.1 to + 0.3) and mortality (APC - 3.3, 95% CI from -7.3 to + 0.9) for mouth and oro-pharyngeal cancer non-significantly decreased over the study period. Again, for anus and anal canal cancer, incidence and mortality trends presented a non-significant decrease over the study periods. For malignant neoplasm of vulva, a significantly decreasing trend was found for incidence rates (APC -1.8% 95% CI: from -3.4 to - 0.3). The mortality trend had a similar but non-significant APC (- 1.8 CI: from - 5.2 to 1.6). Incidence and mortality rates from vaginal cancer decreased non-significantly. For malignant neoplasm of cervix uteri, incidence rates showed a significant decrease by 2.1% per year (95% CI: - 4.1 to - 0.1), and mortality rates presented a non-significant decrement by 4.6% per year.

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

Cancer site (ICD-X)	Period	Cases	Crude rates	U-rates (s.e.)	I-rates (s.e.)	W-rates (s.e.)
Mouth and pharynx (C00-C14.9)*	1978-1982	44	2.1	2.5 (0.4)	2.2 (0.3)	1.3 (0.2)
	1994-1998	87	4.1	4.1 (0.4)	3.5 (0.4)	1.7 (0.2)
	1999-2003	89	4.2	3.9 (0.4)	3.4 (0.4)	1.7 (0.2)
	2004-2008	71	3.2	2.8 (0.3)	2.5 (0.3)	1.2 (0.2)
Anus and anal canal (C21)	1978-1982	1	0.0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	1994-1998	45	2.1	2.2 (0.3)	1.8 (0.3)	0.8 (0.1)
	1999-2003	48	2.2	2.1 (0.3)	1.9 (0.3)	1.1 (0.2)
	2004-2008	39	1.7	1.6 (0.3)	1.4 (0.2)	0.8 (0.1)
Vulva (C51)	1978-1982	100	4.9	6.1 (0.6)	5.2 (0.5)	2.5 (0.3)
	1994-1998	101	4.8	4.7 (0.5)	3.9 (0.4)	1.6 (0.2)
	1999-2003	110	5.1	4.7 (0.4)	3.9 (0.4)	1.7 (0.2)
	2004-2008	103	4.6	4.0 (0.4)	3.3 (0.3)	1.4 (0.2)
Vagina (C52)	1978-1982	20	1.0	1.1 (0.2)	1.0 (0.2)	0.6 (0.2)
	1994-1998	25	1.2	1.2 (0.2)	1.0 (0.2)	0.6 (0.1)
	1999-2003	21	1.0	0.9 (0.2)	0.7 (0.2)	0.3 (0.1)
	2004-2008	14	0.6	0.5 (0.1)	0.5 (0.1)	0.2 (0.1)
Cervix uteri (C53)	1978-1982	264	12.8	13.9 (0.9)	13.1 (0.8)	8.7 (0.6)
	1994-1998	195	9.3	9.4 (0.7)	8.8 (0.6)	5.5 (0.4)
	1999-2003	180	8.4	8.3 (0.6)	7.8 (0.6)	5.3 (0.4)
	2004-2008	177	7.9	7.5 (0.6)	7.1 (0.5)	4.7 (0.4)

*Excluding nasopharynx and salivary glands. s.e.: standard error.

Table 2. — *Annual number of incident cases and age-adjusted (U = Umbria, I = Italy, W = World population as standard) incidence rates for the selected sites and periods.*

Cancer site (ICD-X)	Period	Deaths	Crude rates	U-rates (s.e.)	I-rates (s.e.)	W-rates (s.e.)
Mouth and pharynx (C00-C14.9)*	1978-1982	21	1.0	1.4 (0.3)	1.2 (0.3)	0.5 (0.1)
	1994-1998	44	2.1	2.0 (0.3)	1.7 (0.3)	0.8 (0.1)
	1999-2003	37	1.7	1.6 (0.3)	1.4 (0.2)	0.6 (0.1)
	2004-2008	34	1.5	1.3 (0.2)	1.1 (0.2)	0.5 (0.1)
Anus and anal canal (C21)	1978-1982					
	1994-1998	8	0.4	0.4 (0.1)	0.3 (0.1)	0.1 (0.0)
	1999-2003	11	0.5	0.4 (0.1)	0.3 (0.1)	0.1 (0.0)
	2004-2008	7	0.3	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)
Vulva (C51)	1978-1982	36	1.7	2.4 (0.4)	1.9 (0.3)	0.8 (0.1)
	1994-1998	49	2.3	2.3 (0.3)	1.8 (0.3)	0.6 (0.1)
	1999-2003	43	2.0	1.7 (0.3)	1.4 (0.2)	0.5 (0.1)
	2004-2008	46	2.0	1.7 (0.2)	1.4 (0.2)	0.6 (0.2)
Vagina (C52)	1978-1982					
	1994-1998	10	0.5	0.5 (0.1)	0.4 (0.1)	0.1 (0.0)
	1999-2003	8	0.4	0.3 (0.1)	0.3 (0.1)	0.1 (0.0)
	2004-2008	8	0.4	0.3 (0.1)	0.2 (0.1)	0.1 (0.0)
Cervix uteri (C53)	1978-1982	28	1.4	1.6 (0.3)	1.4 (0.3)	0.8 (0.2)
	1994-1998	54	2.6	2.6 (0.3)	2.3 (0.3)	1.2 (0.2)
	1999-2003	38	1.8	1.6 (0.3)	1.4 (0.2)	0.7 (0.1)
	2004-2008	41	1.8	1.6 (0.3)	1.4 (0.2)	0.7 (0.1)

*Excluding nasopharynx and salivary glands. s.e.: standard error.

Discussion

Invasive cervical cancer is an infrequent disease in Western countries. It represents a long-term consequence of a subset of lasting HPV infections that are otherwise transient and common. To control cervical cancer, screening is effective [24]. However, there are drawbacks to this strategy. The main limitation of screening is that it does not interfere with circulation of HR-HPV infection and, thus, there is the need to indefinitely maintain the intervention and high-level of adherence to avoid progression of premalignant lesions. Moreover, cervical cancer screening contributes minimally to overall control of all other HPV-related diseases.

The availability of a prophylactic vaccine, a primary prevention tool, therefore opens alternatives to prevention of cervical and other HPV-related cancers by eliminating their widespread cause, i.e., infection with HR-HPV strains. Pro-

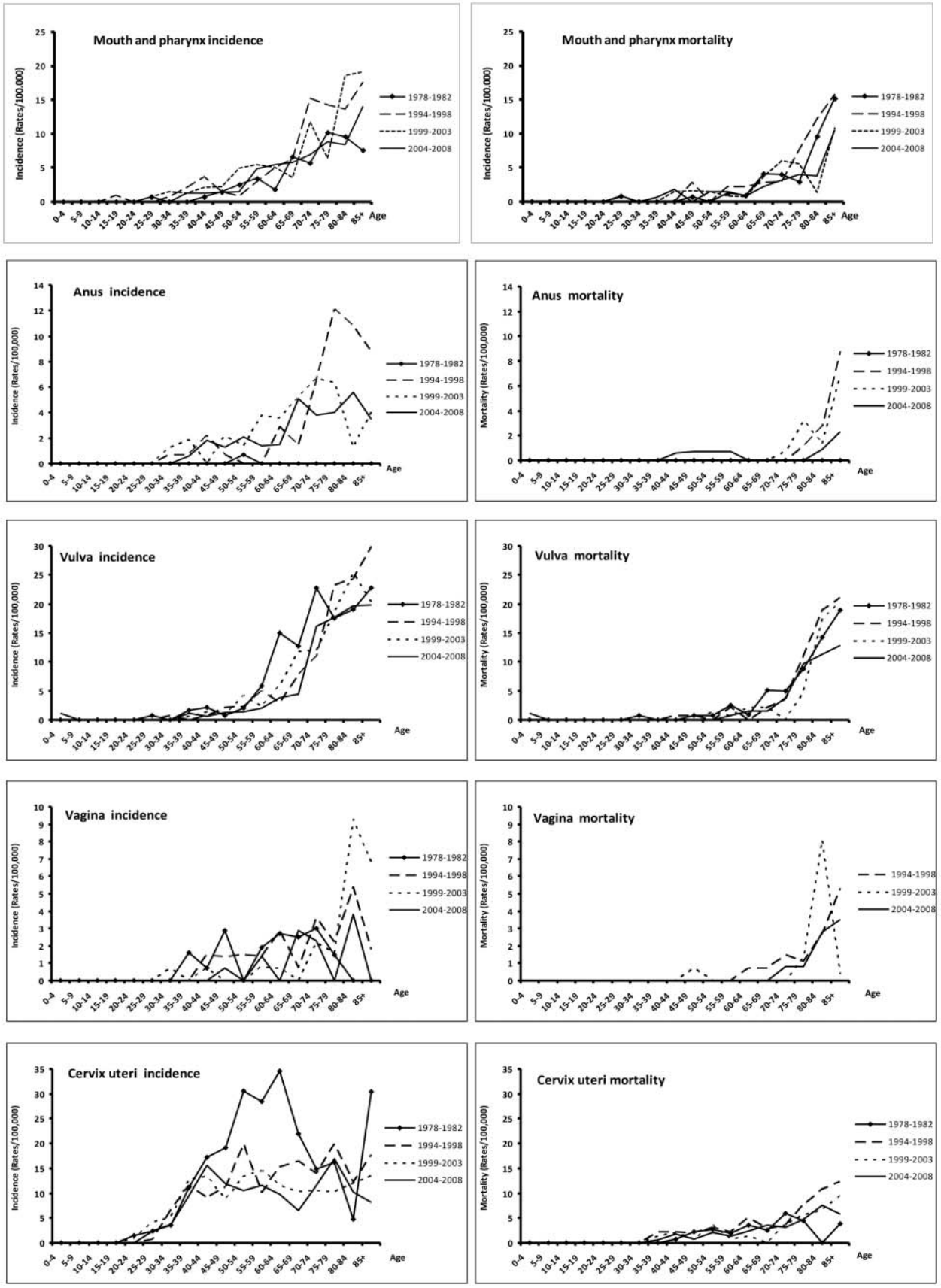

Figure 1. — Incidence and mortality rates for the selected sites, by age and period.

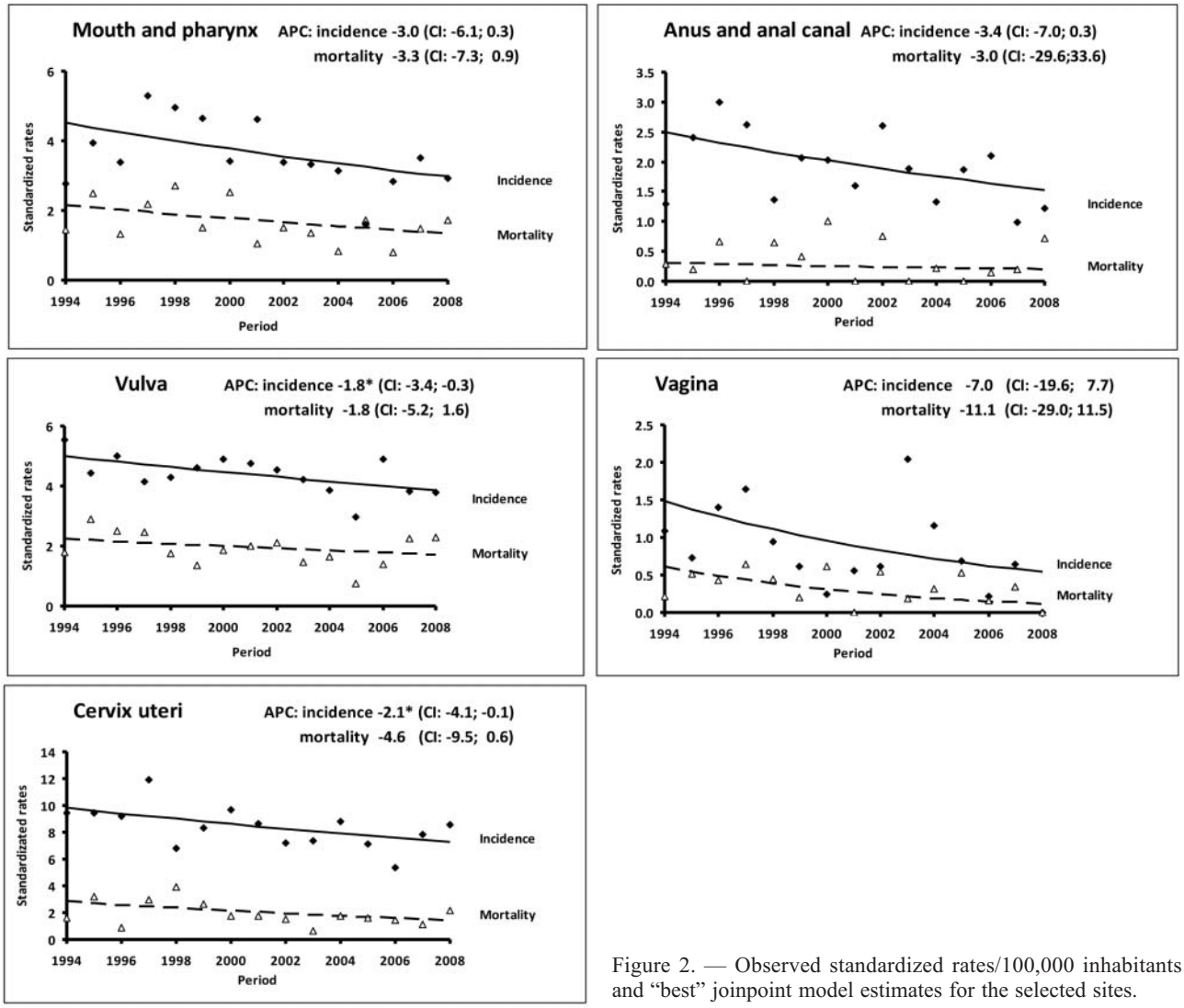

Figure 2. — Observed standardized rates/100,000 inhabitants and "best" joinpoint model estimates for the selected sites.

viding vaccination both to males and females is justified by the goal to prevent HPV related cancers, including cervical cancer. Theoretically, vaccinating both girls and boys against HPV would be a radical and powerful approach, which would lead to a rapid decrease in HPV infections [40].

Justifying the cost of vaccination of both sexes has proven to be difficult, and, thus, an anti-HPV vaccination strategy targeted mainly at 12-year-old girls was begun in 2008 in Umbria. The bivalent vaccine, protecting against HPV 16 and 18 was used in the Umbria vaccination program as in the rest of Italy [41]. This strategy does not aim to eliminate relevant HR-HPV types nor is it aimed to protect from HPV-related diseases occurring in males.

Vaccination coverage for the birth cohort of 1997 was 79% for the first dose, 77.5% for the second dose and 73.3% for the third dose to 30 June 2010 [42]. However, it will take decades before the benefits of this preventive intervention will become apparent. An early indirect evaluation of vaccination results could be obtained through the surveillance of HPV-related cellular abnormalities in young women participating in the screening. In general, cervical cancer screening will allow some evaluation of the vaccination effectiveness and will ensure cervical cancer prevention for non-vaccinated women. How to combine in the future primary and secondary prevention of cervical cancer effectively remains to be determined [43].

While HPV is a proximal cause of cancers, sexual behavior determines exposure to HPV. Sexual behaviour is associated with cancer risk of head and neck subsites previously associated with HPV infection [44]. The epidemiologic pattern of HPV infection in the population is a reflection of sexual behavior in given socio-cultural circumstances, and is both socially conditioned as well as depending on personal choices.

The analysis of incidence and mortality trends is an important tool for monitoring cancer control and assessing primary or secondary prevention interventions. In Western countries, the incidence of HPV-related cancers is generally low. Recently, an increase of HPV-related oro-pharyn-

geal cancers has been documented in many countries [45-47].

In Italy, data from cancer registries show a regular incidence and mortality decrease of HPV-related cancers over the last two decades [48]. Similarly, in Umbria, incidence of HPV-related cancers consistently decreased and a shift towards older age of incidence was also evident in the data. This pattern may be a consequence of the adoption of safer sexual behavior (e.g., use of protection devices, avoiding multiple sexual partners) perhaps following anti-AIDS awareness campaigns.

Certainly, HPV infection is not responsible for all HPV-related cancers. The etiologic fraction is highest for cervical cancer and lowest and perhaps variable for cancer of the mouth and pharynx, which recognize alcohol consumption and tobacco smoking as the main risk factors [5]. Thus the observed incidence trends may not be interpreted directly and unequivocally as a result of the changing exposure to HPV infection. Cervical cancer epidemiologic data showed some peculiarities, largely due to the ongoing screening.

Studies from other European countries showed that the incidence and mortality rates of HPV-related cervical cancer varied greatly throughout Europe [49]. All recent trends analyses confirm the dramatic contrast in the burden of cervical cancer between the 15 original and most of the ten new EU member states and between Western and Eastern Europe in general [50, 24].

With regards to age, incidence of cervical cancers was about two times higher in women 50 to 55 years of age with respect to 45-49-year-olds, and peaked at 64-69 years. This incidence pattern is similar to the one reported for many European countries, characterized by a lower incidence of the disease in pre-menopausal women [51].

Several European countries have nationally adopted organized cervical screening programs but others continue with opportunistic screening. There is limited but consistent evidence that organized screening is an improvement over opportunistic screening [52].

Generally, organized screening has greater potential ability to reduce cancer mortality and in some instances cancer incidence due to higher achievable levels of population coverage, follow-up, and quality control of the screening and treatment process. In the absence of organized call and recall systems, opportunistic screening tends to be less efficient, contributing to health inequalities and achieving lower coverage [53].

In Umbria, opportunistic screening has been present since 1972 and a regional organized cervical cancer screening program was introduced in 1999 for women 25-64 years of age. Presently screening participation in Umbria is among the highest in Italy (85%). However, opportunistic screening is not yet diffused among women and accounts for only 28% of screening tests according to a recent national health survey [54].

Cervical cancer screening has undergone some variations over the study period. In addition to liquid-based cytology and computer-assisted image analysis that were implemented to various extents by the four regional screening services, molecular testing was introduced. In Umbria, in accordance with the GISCI (Gruppo Italiano Screening del Cervicocarcinoma, that is the cervical cancer screening Italian study group) recommendations, a pilot program to evaluate HPV-DNA testing in primary screening of women in the 35-64 age group, and to test the diagnostic utility of p16INK4 as marker of progression to cervical dysplasias and carcinomas was started in 2010.

Effective integration of HPV vaccination, molecular testing, and cervical cytology will be a critical and evolving challenge. The cancer registry database has been linked to screening services and expanded to include pre-malignant cervical lesions in order to provide a more refined tool for HPV-related disease surveillance and evaluation of the effectiveness of cervical cancer screening, and the anti-HPV vaccination campaign in the near future.

Conclusion

The authors observed a consistent decrease of HPV-related cancer incidence and mortality in women. A mix of opportunistic and organized screening has certainly contributed to improving incidence and mortality trends for cervical cancer. Safer sexual behavior is likely involved in the reduced health burden from all HPV related cancers. The implementation of vaccination will lead to a further reduction of cases of cervical and other HPV-related cancers.

Acknowledgements

This work was supported by the Department of Health, Regional Government of Umbria. The authors thank the Municipal Offices and the ReNCaM referents of the four Local Health Districts of Umbria. They would also like to give special thanks to Katherine Brandt for English reviewing.

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