

# Epidemiology and cost of cervical cancer care and prevention in Apulia (Italy), 2007/2016

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*Key words: HPV, primary and secondary prevention, costs evaluation.*

*Parole chiave: HPV, prevenzione primaria e secondaria, analisi dei costi*

## Abstract

**Background.** According to recent estimates, cervical cancer is worldwide the second most common cancer in females and the fourth overall. The number of deaths for cervical cancer is around 7.5% of all female cancer deaths. Cervical cancer is the only tumour with a known necessary cause, the HPV infection and, globally, HPV is the most common sexually transmitted infection. Two major approaches for cervical cancer prevention have been designed: primary prevention by HPV vaccination and secondary prevention by screening. The aim of our study is to design an overview of epidemiology, cost of the therapies and cost of prevention measures (screening and vaccines) 9 years after the introduction of anti-HPV vaccination in the Apulia Regional Immunization Program.

**Study design.** retrospective observational study.

**Methods.** To describe the epidemiology of cervical cancer, we analysed data from the Apulia regional archive of hospital discharge forms (SDO). We considered all records referred to cervical cancer using the ICD 9 code 180.xxx both in primary and secondary diagnosis, for the years 2007-2016. Subjects living in Apulia have been considered. Costs of hospitalization were computed considering generated Diagnosis Related Groups (DRG). To describe the Apulian screening program, we analysed data from Regional Screening Data warehouse; the cost of the single test was established according to the Tariff List from the Ministry of Health. Finally, vaccination data were extracted by Regional Immunization Database and official ex-factory price has been used to calculate the costs of immunization program.

**Results.** From 2007 to 2016, an important decrease in the incidence rate of cervical cancer in Apulia has been noted, ranging from 43.7 per 100,000 residents in 2007 to 21.0 per 100,000 residents in 2016. From an economic point of view, a clear reduction (39%) is observed in hospitalization costs over time. Total costs of prevention programs increased over time and globally exceed € 54,000,000, with a decreasing trend for vaccine prophylaxis and an increasing trend for screening.

**Conclusions.** The incidence and costs of cervical cancer in Apulia, although already significantly decreasing, likely will be further reduced since 2027-2032, when we can observe the effects of vaccine prophylaxis on the burden of disease; on this occasion it will be also possible to quantify the actual cost-effectiveness of the vaccine. In our opinion, in the future the Apulia healthcare executives should enhance and improve the active screening test offer, without underestimating the importance of sexual education in young people, especially in those who have not had sexual debut yet.

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## Introduction

According to recent estimates, cervical cancer is worldwide the fourth most common cancer in females and the seventh overall; in 2012, 528,000 new cases have been estimated by WHO. Around 85% of the global burden occurs in the low-income countries, where it accounts for almost 12% of all female cancers (1).

The number of deaths for cervical cancer was around 266,000 in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the low-income countries (1).

Cervical cancer incidence decreases in the developed countries, but the rate remains high in several regions, mostly because of the lack of screening and treatment services (2).

Cervical cancer is the only tumour with a known necessary cause, the HPV infection. Cervical infections related to 15 high-risk human papillomavirus (HPV) genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) accounted virtually all cervical cancers and its immediate precursors worldwide (3).

Globally, HPV is the most common sexually transmitted infection. The majority of HPV infections, including carcinogenic HPV genotypes, are typically transient and self-limiting within 6 to 12 months, occasionally causing mild morphologic changes. Women with persistent carcinogenic HPV infections are at risk of developing pre-cancer lesions, although not all persistent infections may progress. If pre-cancer lesion is not detected and treated in a timely manner, the lesion could evolve in a cancer (4, 5).

Malignant transformation of HPV-infected cells is believed to be mediated by the integration of the viral DNA into the host genome. The virus reproduces separately in most low-grade lesions, but the HPV genome may be integrated into the host's DNA in many advanced precancerous lesions and most cancer cases (6).

Because of the nearly absolute etiologic link between carcinogenic HPV and cervical cancer, 2 major approaches for cervical cancer prevention have been designed:

1) primary prevention by HPV vaccination;

2) secondary prevention (screening) with the purpose of identifying and treating women with cervical precancerous lesions and early stage cancers.

Both approaches are highly efficacious when used in their respective target populations (4).

Three effective HPV vaccines are currently available: the bivalent vaccine (HPV2), which protects against HPV types 16 and 18; the tetravalent vaccine (HPV4), which protects against types 16, 18, 6, and 11 (7); the nine-valent vaccine (Gardasil 9<sup>®</sup>), developed with the aim to protect against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58), approved by the Food and Drug Administration in December 2014 and by the European Medicines Agency in June 2015 (8, 9). The three vaccines are indicated for the prevention of premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancers; the indication of the tetravalent vaccine also includes premalignant anal lesions, anal cancers and genital warts, the nine-valent protects against more malignant types in addition to those of bi- and tetra-valent (10).

These vaccines have proved absolute safety and efficacy (7, 11-13) and HPV vaccination programs seem able to reduce the incidence of HPV infections, genital warts, and HPV-attributed precancerous lesions. However, since vaccination program started 10 years ago, studies on the effects of vaccination on cervical cancer rates should be designed in the future, because the lead-time from HPV infection to cervical cancer accounts 15-20 years (7, 14).

The secondary prevention strategies for cervical cancer are based on two screening tests:

- the Pap test identifies precancers, cell changes on the cervix that might become cervical cancer if they are not treated appropriately.

- the HPV test looks for the virus that can cause these cell changes (15).

Cytological screening has reduced the incidence of cervical cancer in countries with organised screening (16-18), causing a reduction in lifetime risk. The universal offer of cytological screening has been demonstrated as high cost-effective (19-21).

In Italy, about 2,918 new cervical cancer cases are diagnosed annually with 1,016 deaths (estimations for 2012) (22).

HPV vaccination has been offered actively and free of charge to girls aged 12 since 2007, using both tetra-valent both bi-valent vaccines, depending on the Region (10); since 2017 nine-valent vaccine is available. Each region is allowed to include additional age cohorts target group in the HPV vaccination program; between 2014 and 2015, nine regions (Veneto, Liguria, Friuli-Venezia Giulia, Apulia, Sicily, Sicilia, Calabria, Molise, Trentino and Sardinia) extended the active vaccination program to 12-year-old boys. The vaccination program was initially based on a three-dose regimen, but was subsequently changed to a 2-dose schedule in 2014 (0 and 6 months) according to official recommendations (10, 23). The National Plan for Vaccine Prevention (PNPV) 2017-2019 confirms the vaccination at 12-years-old girls and provides Universal Mass Vaccination also for 12years-old boys (24).

The most recent Italian HPV vaccine coverage for HPV, on women of 2003 birth cohort, was of 56.3%, with wide variability between regions (25). The values achieved are suboptimal and, however, lower than the targets set out in the National Plan for Vaccine Prevention (PNPV) 2012-2014 (24, 26, 27).

In Italy, a cervical cancer screening program started in 2004; it's based on cytology and recommended every 3 years for women aged 25-64 years. (28). According

to recent evidences, National Prevention Plan encourages the shifting from Pap test to HPV test as screening triage tool (24). According to PASSI study (Italian National Institute of Health), in 2013-2016, 79.6% of Italian women of 25-64 years performed a preventive Pap test in absence of signs and symptoms during the previous three years, as recommended by international and national guidelines. Screening tests mostly take place in the context of programs organized by the Local Health Units (44.6%), while a lower but consistent proportion of women (34.4%) attend preventive measures on personal initiative, outside the programs organized by the National Health System, claiming all or part of the cost of the exam (29).

Apulia region is located in the South-East of Italy (around 4.000.000 of inhabitants), in Apulia the incidence rate of cervical cancer for the period 2006-2008 was 6.7 per 100,000 inhabitants, with a mortality rate of 1.0 per 100,000 inhabitants; the incidence trend is increasing, while the mortality trend seems to be constant over time (30).

HPV vaccination program, targeting 12-years-old female, started in Apulia in 2008; other targets, such as young women of 16, 18 and 25 years and 12-year-olds males, have been added from 2009 to 2014 by Regional Health Authority. The vaccine coverage achieved is of 69.3% in females and of 52.8% in males for the 2004 birth cohort (31, 32).

Cervical screening program started in 2007 and has been structured according to national guidelines; from 2017, the Apulia Region has introduced the HPV test as the triage test, replacing the Pap test for women aged 30-35 years. Gradually, all women of this age class will be invited to perform the HPV test (33). According to PASSI study (National Institute of Health), in 2013-16, 71% of Apulian women of 25-64 years interviewed performed a preventive Pap test in the absence of signs and symptoms during the previous three years, as recommended

by international and national guidelines. Of these, 28.4% performed it within an organized screening program and 41.9% on personal initiative (29).

The aim of this study is to describe the epidemiology, the analysis of cost of the therapies and of the prevention measures (screening and vaccines) in Apulia 9 years after the introduction of anti-HPV vaccination in the Regional Immunization Program.

## Methods

This is a retrospective observational study.

To describe the epidemiology of cervical cancer, we used the Apulia regional archive of hospital discharge forms (SDO) (34). We considered all records referred to cervical cancer using the ICD 9 code 180.xxx both in primary and secondary diagnosis, for the years 2007-2016. Subjects living in Apulia, discharged both by Apulian hospitals (intra-regional mobility) and by hospitals of other Italian regions (passive mobility) have been considered. From SDOs, we analysed these information: age of patients, age at first hospitalization, length of hospital stay, (excluding Day-hospital admissions); discharge mode.

In case of multiple hospitalizations, only the first admission was considered in the analysis.

Costs of hospitalization were computed considering generated Diagnosis Related Groups (DRG) (35, 36).

To describe the Apulian screening program, we analysed data from Regional Screening Data warehouse; the cost of the single test was established according to the Tariff List from the Ministry of Health (37). Finally, vaccination data were extracted by Regional Immunization Database and official ex-factory price has been used to calculate the costs of immunization program (38, 39).

Data were analysed using Microsoft Office Excel and Stata SE14 softwares.

Continuous variables were expressed as mean, categorical variables as proportions.

To calculate the incidence rate, we considered as denominator the female population of Apulia taken from the ISTAT demographic archives.

## Results

In Apulia, 6,805 cervical cancer hospitalizations were recorded in 2007-2016; 5,375 were in Apulian hospitals (79.0%) and 1,430 in other Italian regions hospitals (11.0%). A decrease of 49.1% in the total number of hospitalizations was observed in the 10 years examined (Figure 1).

The incidence rate of disease per 100,000 Apulian citizens is 33.2 and a decreasing trend is observed in 2007-2016 (Figure 2).

The average age of patients at the time of first hospitalization was 55.9 years, lower among hospitalized in Apulia (mean age = 56.9) than in other Regions (mean age = 52.1); while the average age of subjects in intra-regional mobility decreases over the years (59.6 in 2007, 56.0 in 2016), the age of patients in passive mobility increases (48.2 in 2007, 53.0 in 2016).

The most commonly used discharge method is the planned discharge ( $n = 6,382$ ; 93.7%; table 3); 39 (0.6% patients) died during the hospitalization.

The average length of hospital stay is 6.0 days, same value for patients in intra-regional and passive mobility.

Table 1 describes the distribution of DRGs related to SDOs reporting a diagnosis of cervical cancer in 2007-2016: "chemotherapy not associated with secondary diagnosis of acute leukemia" is the most frequent DRG (20.2%), followed by "radiotherapy" (17.6%) and "malignant neoplasia of the female reproductive system without CC" (14.9%; Table 1).

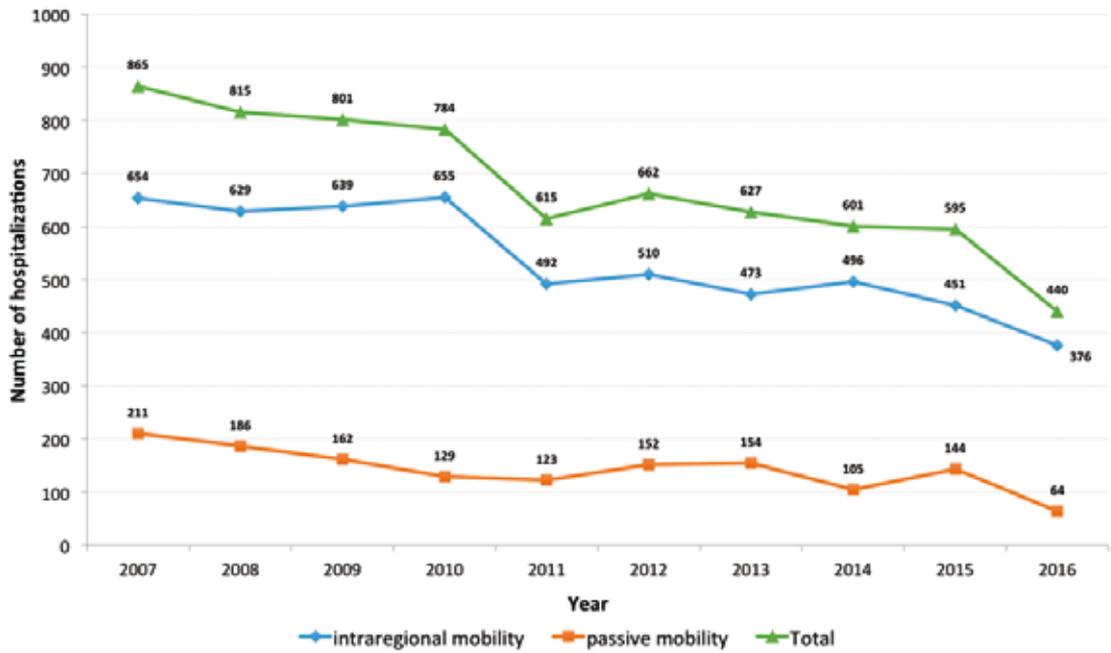


Figure 1 - Number of hospitalization for cervical cancer per category of hospitalization (intraregional, passive). Apulia, years 2007-2016.

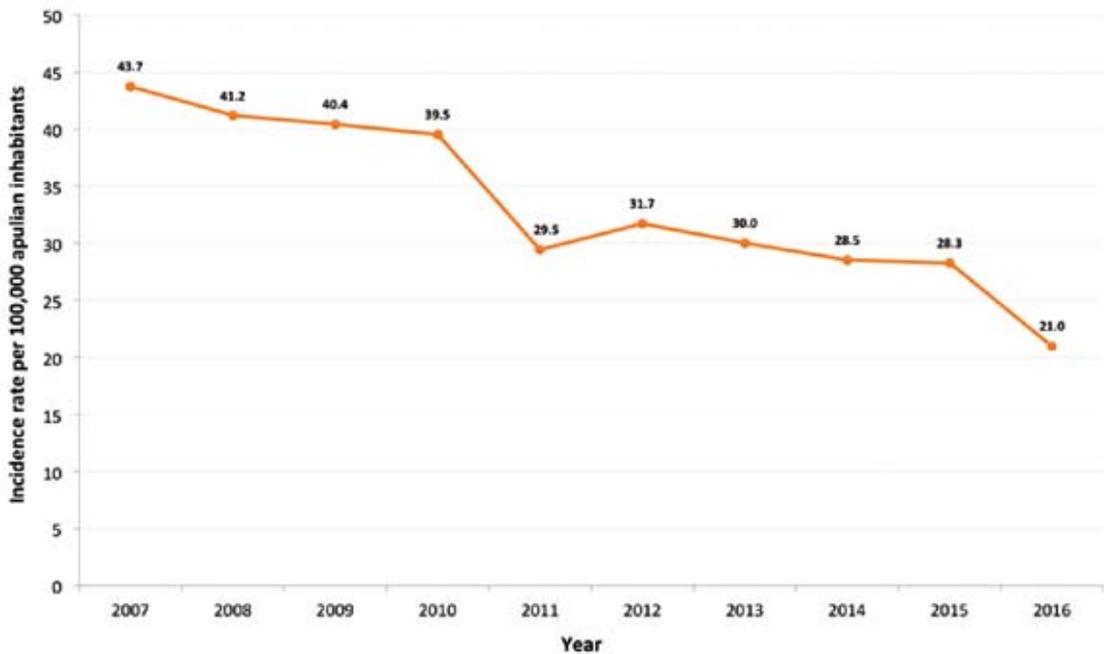


Figure 2 - Incidence rate of cervical cancer per 100,000 Apulian citizens. Apulia, years 2007-2016.

Table 1 - Distribution of DRGs related to SDOs reporting a diagnosis of cervical cancer. Apulia, years 2007-2016.

DRG	n	%
Chemotherapy not associated with secondary diagnosis of acute leukemia	1,365	20.2
Radiotherapy	1,189	17.6
Malignant neoplasia of the female reproductive system without CC	1,006	14.9
Dilation and scraping, combining and planting radioactive material for malignant neoplasia	811	11.9
Pelvic evisceration, radical hysterectomy and radical vulvectomy	714	10.6
Malignant neoplasia of the female reproductive system with CC	423	6.3
Surgical interventions on the uterus and on the annexes for not ovarian and not annexes malignant neoplasia without CC	193	2.9
Surgical interventions on vagina, cervix and vulva	91	1.4
Myeloproliferative disorders or little differentiated tumors with other surgical interventions	87	1.4
Other	926	12.8
Total	6,805	100.0

In 2007-2016, the hospitalization costs for cervical cancer amounted to € 17,281,629.8, of which € 12,993,959.2 in intraregional mobility (75.2%) and € 4,287,670.5 in passive mobility (24.8%). A decrease of 39.3% of the expenses in the analysis period is observed, a trend that is confirmed by the costs of intraregional and passive hospitalizations (Figure 3).

In 2007/2016, 494,259 doses of anti-HPV vaccine were administered; table 2 describes the number of doses administered per year and type of vaccine.

In 2007-2016, the cost of administered vaccine amounted to an estimate of € 47,947,831.5, of which € 34,002,875.0 for HPV2 (70.9%), € 8,775,832.0 for HPV4 (18.3%) and € 5,169,124.5 for unknown anti-HPV vaccine (a mean cost has been applied to calculate this cost). The maximum expenditure is observed in 2011 and decreases by 55.3% in 2016, a trend that is confirmed for all type of vaccine.

In the examined period, 564,126 Apulian women participated to the first level of the organized screening program organized

Table 2 - Number of doses of anti-HPV vaccine administered, per type of vaccine (HPV2/HPV4/Unknown). Apulia, years 2007-2016.

Year	HPV2		HPV4		Unknown		Total
	n	%	n	%	n	%	n
2007	8	11.4	33	47.1	29	41.5	70
2008	21,340	72.3	284	1.0	7,909	26.7	29,533
2009	43,339	82.0	610	1.2	8,920	16.8	52,869
2010	47,549	70.0	11,221	16.5	9,150	13.5	67,920
2011	61,375	69.3	15,808	17.8	11,392	12.9	88,575
2012	55,506	68.5	15,400	19.0	10,123	12.5	81,029
2013	42,764	71.3	12,426	21.1	3,798	6.4	58,988
2014	27,792	71.1	10,910	27.9	387	1.0	39,089
2015	26,395	72.4	9,854	27.0	184	0.6	36,433
2016	31,857	80.1	7,837	19.8	59	0.1	39,753
Total	357,925	72.4	84,383	17.1	51,951	10.5	494,259

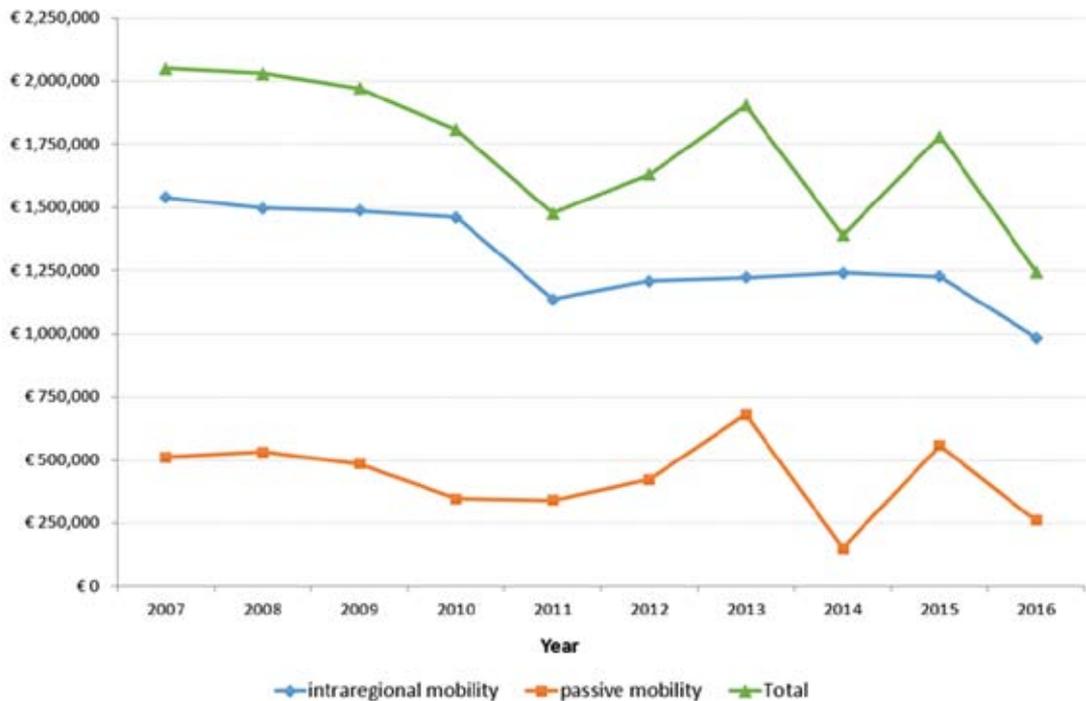


Figure 3 - Estimated cost of hospitalization for cervical cancer, per category of hospitalization (intraregional, passive). Apulia, years 2007-2016.

by the Regional Health Authority, with an estimated cost of € 6,259,646.2. Over the years, we observe an increasing trend in the number of women screened and in the related costs (Table 3).

## Discussion and Conclusions

From 2007 to 2016, an important decrease in the incidence rate of cervical cancer in Apulia has been noted, ranging from 43.7

Table 3 - Number of women who participated to the first level of the organized screening program and cost of the screening. Apulia, years 2007-2016.

Year	Number of female screened	Cost of screening [€]
2007	14,664	163,650.2
2008	38,247	426,836.6
2009	60,216	672,010.7
2010	50,063	558,703.1
2011	49,124	548,223.8
2012	62,009	692,020.4
2013	58,424	652,011.8
2014	77,347	863,192.5
2015	78,467	875,691.7
2016	75,565	843,305.4
Total	564,126	6,295,646.2

per 100,000 residents in 2007 to 21.0 per 100,000 residents in 2016. The higher proportion of cancer regarded females of 40-59 years and the average age of hospitalization tends to decrease over time, a sign of improved instrumental techniques and effectiveness of early diagnosis; we noted that patients in passive mobility have an average age lower than intraregional mobility, and this difference seems to show that younger patients presumably prefer to be cured in other regions.

The number of screened women increased over the years, due to the adoption of Regional Plan for Oncological Screening.

The number of vaccine doses increased until 2011, then decreases; probably this peculiar trend is due to the fact that in the first years of introduction of HPV vaccine the administered doses were three (then reduced to two) and that women of other ages have been vaccinated too, especially at the start of vaccination campaign. It is plausible that the last years in our analysis are more truthful of the situation of doses administered to the 12-year-old cohort.

Moreover, the decrease of the number of HPV vaccine doses administered happened in a general scenario of vaccination crisis related to the vaccine hesitancy and lack of knowledge about vaccine safety and effectiveness in the general population and in particular among physicians, as reported in some recent surveys (40, 41).

From an economic point of view, a clear reduction (39%) is observed in hospitalization costs over time, but more than € 4,000,000 of costs are related to passive mobility (23% of total spending). Total costs of prevention programs increased over time and globally exceed € 54,000,000, with a decreasing trend for vaccine prophylaxis and an increasing trend for screening.

Several studies in literature are consistent with our findings: Bray F et al. in a 2008 study asserted that well-organized screening

programs have been highly effective in reducing the incidence of cervical cancer in Europe (17); a 2010 review concludes that HPV vaccine is highly efficacious and potentially lifesaving if administered to females naive or unexposed to vaccine HPV types and can be cost-effective with an ICER of \$100,000 or less per QALY gained if administered to females aged 12 years in the context of cervical screening intervals typically greater than 1 year (42). A Belgian 2003 study concludes that extending HPV vaccination also to females post-sexual debut could lead to a substantial reduction in CC-related burden and would be cost-effective (43).

The strength of our study is the sample size and the long period of investigation time (10 years). The major limit is that the SDO Regional Archive is built for administrative and non-epidemiological purposes, so there is a theoretical risk of underestimating the phenomenon. This risk is low, because the type of disease in consideration requires hospitalization in around all cases. In addition, we underline that the decrease (49%) of cases of cervical cancer is due to the effect of screening rather than the impact of vaccination, phenomenon described by other recent studies in literature (23); premature diagnosis of precancerous lesions, in fact, results in timely interventions and non-evolution towards cancer. The effects of vaccine prophylaxis may be visible from 20-25 years after the vaccination of the 12-year-old belonging to birth cohort 2007.

Another important limitation is the impossibility of linking different archives (for privacy laws) and the lack of data about circulating HPV in Apulian women affected by cervical lesions.

It will be desirable for the future to repeat the study expanding the time span and including cohorts of different ages to assess the vaccination status of the subjects analysed, performing the data linking of hospitalization database and immunization

register. In addition, in order to better estimate the phenomenon, it would be advisable to extract the data of interest from other sources and integrate them with the regional SDO archive (cancer registries, etc). It would be interesting to include in our analysis the epidemiology and costs associated of pre-cancerous lesions and genital warts, to have a general picture and make a better estimate of public spending. Furthermore, it would be advisable to improve the services offered by the Regional Immunization Database, in order to be able to calculate a better estimate of vaccine prophylaxis costs.

The incidence and costs of cervical cancer in Apulia, although already significantly decreasing, likely will be further reduced since 2027-2032, when we will observe the first effects of vaccine prophylaxis on the burden of disease; on this occasion it will be also possible to quantify the actual cost-effectiveness of the vaccine. In addition, the availability of 9valent vaccine at the end of 2017 will further reduce the incidence of disease that a recent Italian study estimates to be 17% (22), as well as the introduction of the HPV test as the main test of screening. We certainly look at the critical: many Apulian people (11.0%) who prefer to be treated in other regions should be a cause of alarm and reflection for Apulia healthcare executives, in this contest it is necessary to enhance and improve the active screening test offer, without underestimating the importance of sexual education in young people, especially in those who have not had sexual debut yet.

## Riassunto

*Epidemiologia del cancro della cervice e costi correlati alla cura e prevenzione della patologia in Puglia (Italia), 2007/2016*

**Background.** Secondo stime recenti, a livello globale il cancro della cervice uterina è il secondo tumore per frequenza nelle donne e il quarto complessivamente. Il numero di decessi per cancro della cervice uterina corrisponde a

circa il 7,5% di tutte le morti per cancro nelle donne. Tale cancro è l'unico tumore con causa nota conosciuta, ossia l'infezione da HPV, che rappresenta, a livello globale, la più comune infezione a trasmissione sessuale. Sono stati progettati due principali approcci per la prevenzione del cancro della cervice uterina: prevenzione primaria mediante la vaccinazione anti-HPV e prevenzione secondaria mediante il test di screening. L'obiettivo del nostro studio è quello di descrivere una panoramica della epidemiologia del cancro della cervice uterina, costo delle terapie e costi delle misure di prevenzione (screening e vaccini) a 9 anni dall'introduzione della vaccinazione anti-HPV nel Calendario Vaccinale della regione Puglia.

**Disegno dello studio.** Studio osservazionale retrospettivo.

**Metodi.** Per descrivere l'epidemiologia del cancro della cervice uterina, è stato utilizzato l'archivio regionale pugliese delle Schede di Dimissione Ospedaliera (SDO). Sono stati considerati tutti i record relativi al cancro della cervice per gli anni 2007-2016, utilizzando il codice ICD 9 180.xxx sia nella diagnosi primaria che secondaria. Sono stati reclutati solo i soggetti residenti in Puglia. I costi di ospedalizzazione sono stati calcolati considerando i gruppi correlati alla diagnosi (DRG) generati. Per descrivere il programma di screening, abbiamo analizzato i dati dall'archivio dati dello screening regionale pugliese; il costo del singolo test è stato stabilito secondo l'elenco delle tariffe del Ministero della Salute. Infine, i dati di vaccinazione sono stati estratti dal Sistema informativo delle vaccinazioni (Giava) e il prezzo ufficiale *ex-factory* è stato utilizzato per calcolare i costi del programma di immunizzazione.

**Risultati.** Nel periodo 2007-2016 è stata rilevata un'importante diminuzione del tasso di incidenza del cancro della cervice uterina in Puglia, che passa da 43,7 per 100.000 residenti nel 2007 a 21,0 per 100.000 residenti nel 2016. Da un punto di vista economico, nel periodo in analisi si osserva una netta riduzione (39%) nei costi di ospedalizzazione. I costi totali dei programmi di prevenzione sono aumentati nel tempo e hanno superato i 54.000.000 di euro, con una trend in diminuzione per la profilassi vaccinale e una trend crescente per i test di screening.

**Conclusioni.** L'incidenza e i costi correlati al cancro della cervice uterina nella regione Puglia, anche se già in significativa diminuzione, probabilmente subiranno un ulteriore decremento a partire dal 2027-2032, quando si osserveranno i primi effetti della profilassi vaccinale sulla epidemiologia della patologia; in questa occasione sarà anche possibile quantificare l'effettivo rapporto costo-efficacia del vaccino. A nostro avviso, in futuro i dirigenti sanitari della regione Puglia dovrebbero migliorare e implementare l'offerta attiva dei test di screening, senza sottovalutare l'importanza dell'educazione sessuale nei giovani, specialmente in coloro che non hanno ancora avuto le prime esperienze sessuali.

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