

RESEARCH PAPER



Reduction in the burden of hospital admissions due to cervical disease from 2003–2014 in Spain

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ABSTRACT

Background: Cervix uteri cancer is the 4th most common cancer among women worldwide and the second most frequent cancer in women under 45 years old in Spain. We aimed to describe the burden of hospital admissions by malignant neoplasia (MN) and in situ carcinoma (ISC) of the cervix in Spain from 2003 to 2014, a 12-year period that included the first years after introduction of an HPV vaccination program.

Methods: This epidemiological study reviewed data from the Ministry of Health National Surveillance System, which includes more than 98% of Spanish hospitals. Hospitalization rate, mortality rate, and case fatality rates were calculated per year and age group.

Results: We found 74,933 hospitalizations due to MN and ISC of the cervix. The average age at hospitalization increased significantly during the study period. The average length of hospital stay decreased significantly ($p < 0.001$), while hospitalization costs increased. The mean hospitalization rate was 27.532 cases per 100,000 women (95% CI: 27.335–27.729). This rate decreased significantly during the study period. The mean mortality rate was 1.418 deaths per 100,000 women (95% CI: 1.373–1.463) and the mean case-fatality rate was 5.150% (95% CI: 4.992–5.308).

Conclusion: Our study showed a substantial decrease in the hospitalization burden due to cervical disease. This decrease could be attributable to different causes including cervical cancer prevention measures, and changes in disease management. Further research is needed to confirm the cause. This information could contribute to further evaluations of the impact and cost effectiveness analysis of HPV vaccination in Spain.

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Introduction

Cervix uteri cancer is considered the 4th most common cancer among women worldwide,¹ with 528,000 estimated new cases and 266,000 deaths in 2012.² Human Papillomavirus (HPV) infection is considered a necessary first step to developing cervical cancer.³ At a global level, approximately 70.8% of cervical cancer cases are due to HPV16/18 infection, and 18.5% are due to HPV 31/33/45/52/58 infection.⁴ Estimations from European countries have shown that approximately 33,000 cases of cervical cancer and 15,000 deaths occur each year.⁵

In Spain, cervical cancer is the second most common cancer in women under 45 years old.¹ HPV is so prevalent that it is estimated that nearly 80% of sexually active individuals will become infected at any point in their lifetime.⁶ Data from a prospective study indicated that the age-adjusted prevalence of HPV infection was 14.3% (95% confidence interval (CI): 13.1–15.5), with higher rates observed in women under 25 years old.⁷ Approximately 2,511 cases of cervical cancer and 848 deaths due to cervical cancer occur each year in Spain, with a corresponding crude incidence rate of 10.6 cases per 100,000 women¹ this rate is

one of the lowest in Europe.⁸ However, HPV infection of the cervix accounts for an important burden of disease beyond cervical cancer. According to national studies, approximately 210,046 cases of atypical squamous cells of undetermined significance (ASCUS), 159,352 cases of low-grade squamous intraepithelial lesion (LSIL), 54,087–92,423 cases of high-grade squamous intraepithelial lesion (HSIL), and 6,139 cases of in situ carcinoma (ISC) occur each year in Spain.⁹ Regarding the specific prevalence by HPV type, the abovementioned HPV variants are estimated to be responsible for more than 80% of cervical cancer cases in Spain.⁸

Other co-factors are presumed to be involved in the carcinogenic evolution of HPV infection, including tobacco consumption, concomitant diseases that induce immunosuppression, use of oral contraceptives, co-infection with other sexual transmitted diseases, high parity and certain genetic factors.¹⁰ The adjusted HPV infection prevalence worldwide among women with normal cytology is approximately 11.7% (95% CI: 11.6–11.7%). The highest prevalence occurs a few years after sexual debut, specifically before 25 years of age.¹¹ Although the prevalence tends to decrease

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with age, the 5-year risk of new HPV infection remains significant in women older than 45 years.¹²

Two programs in Spain have been implemented to prevent the occurrence of cervical cancer: screening and HPV vaccination. The Spanish cervical cancer screening program differs by region and is mostly opportunistic and cytology-based.⁹ Although no reliable registries exist, it is estimated that approximately 60% of cervical cancer cases occur in women with no or inadequate screening.⁹ Approximately 72.7% of females have reported receiving a gynecological cervical screening test at least once in the last 3 years.¹ HPV vaccination was introduced in Spain in 2007, targeting girls between 11 and 14 years old. The vaccination schedule was initially based on 3 doses.¹³ Currently, HPV vaccination targets 12-year-old girls with a 2-dose schedule.¹⁴ The latest data show that the coverage rate is approximately 79.2%.¹⁵ Unlike other countries, where HPV vaccination has already shown an impact on reducing the prevalence of HPV infection,¹⁶⁻¹² genital warts,^{16, 21-23} and precancerous cervical lesions,^{16,24-28} limited reports on the effects of HPV vaccination in Spain have been published.

The burden of cervical cancer in Spanish hospitals was previously investigated.^{29, 30} In 2007, a national retrospective study assessed the hospital burden of cervical cancer in Spain from 1999–2002. According to national scientific guidelines, hospitalization related to cervical disease is mostly driven by surgical treatment, which usually occurs for invasive cervical cancer treatment (i.e. radical hysterectomy and/or pelvic or paraortic lymphadenectomy). Other procedures for precancerous cervical lesions management, such as conizations or colposcopies, do not usually require hospitalization.³¹

In this study, our aim was to complement earlier studies and to describe the burden of hospital admissions by malignant neoplasia (MN) and ISC of the cervix in Spain from 2003 to 2014, a 12-year period that included the first years after implementation of the HPV vaccination program.

Results

MN and ISC of the cervix

During the 12-year study period, we observed 74,933 hospitalizations associated with MN and ISC of the cervix. These

hospitalizations occurred in 49,302 women, corresponding to 1.52 average hospitalizations per woman.

The mean age of hospitalization was 49.99 ± 15.17 years. A significant increase in mean age was observed during the study period ($p < 0.001$), from 49.47 ± 14.91 years in 2003 to 51.67 ± 15.21 years in 2014.

Significant changes in the ALOS and hospitalization costs were observed. During this period, the mean ALOS was 6.67 ± 9.55 days, and this length decreased significantly over the study years ($p < 0.001$). By contrast, hospitalization costs increased significantly ($p < 0.001$) during this period (Figure 1). The mean hospitalization cost over the study period was $4,446 \pm 3,059$ euros. A significant increase in the ALOS and hospitalization cost was also found by age ($p < 0.001$); for ALOS, the highest value occurred in the group of women aged more than 75 years old, and women between 60 and 74 years old had the highest costs (Table 1).

During this period, the mean hospitalization rate was 27.532 cases per 100,000 women (95% CI: 27.335-27.729), and this rate tended to increase significantly by age ($p < 0.001$). However, a significant decrease in mean hospitalization rate occurred during the study period ($p < 0.001$), and the decrease was more evident from 2011 onwards (Figure 2).

In total, 3,859 deaths recorded as MN and ISC of the cervix were registered in the hospital setting during the study period, which correspond to a mortality rate of 1.418 deaths per 100,000 women (95% CI: 1.373-1.463) and a CFR of 5.150% (CI 95%: 4.992-5.308). An increase with age ($p < 0.001$) and a decrease over time ($p < 0.0401$ for mortality and $p < 0.001$ for CFR) were observed for both rates during the study period.

Different patterns for MN and ISC of the cervix were identified in terms of frequency, age, costs, hospitalization, mortality and CFR; these results are described separately below.

MN of the cervix

A total of 48,375 hospitalizations associated with MN of the cervix were documented, 29,425 of which recorded MN of the cervix as the first cause of discharge. The mean hospitalization rate during this period was 17.774 cases per 100,000 women

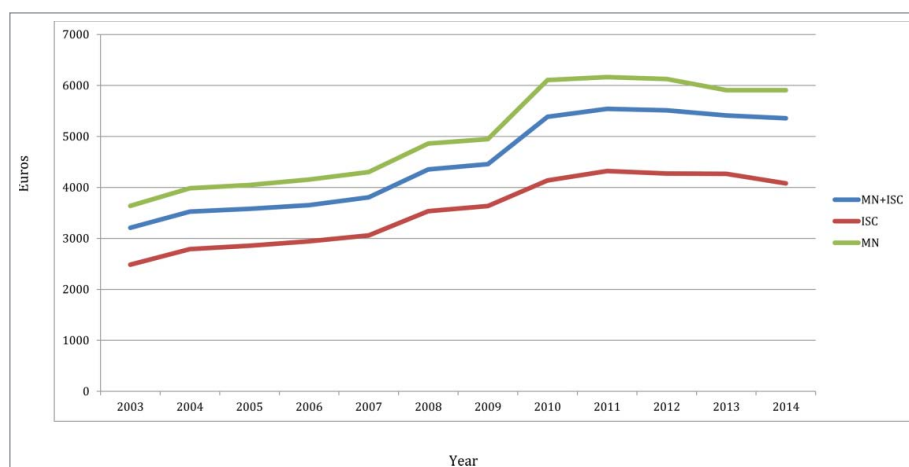


Figure 1. Median hospitalization cost due to malignant neoplasia (MN) + in situ carcinoma (ISC) of cervix, malignant neoplasia (MN) of cervix and in situ carcinoma (ISC) of cervix per year of the study period.

Table 1. Average length of hospital stay (ALOS), hospitalization cost, hospitalization rate, mortality rate and case fatality rate of hospitalizations related to malignant neoplasia (MN) and in situ carcinoma (ISC) of cervix over the period (2003-2014).

Age	NM+ISC						
	Number N	ALOS Mean (SD) (days)	Mean cost Mean (SD) (euros)	Hospitalization rate per 100,000 women (CI95%)	Number of deaths N	Mortality rate per 100,000 women (CI95%)	Case fatality rate % (CI95%)
0-19	175	2.89 (2.84)	3,011 (1,755)	0.342 (0.291-0.392)	0	0.000	0.000
20-29	4,437	3.17 (5.24)	3,242 (2,013)	12.300 (11.938-12.662)	30	0.083 (0.053-0.113)	0.676 (0.435-0.917)
30-44	26,599	5.41 (7.80)	4,190 (2,633)	40.471 (39.985-40.957)	675	1.027 (0.950-1.105)	2.538 (2.349-2.727)
45-59	24,510	7.20 (10.21)	4,739 (3,111)	46.726 (46.141-47.311)	1,221	2.328 (2.197-2.458)	4.982 (4.709-5.254)
60-74	12,879	8.29 (10.99)	4,792 (3,798)	33.217 (32.643-33.790)	968	2.497 (2.339-2.654)	7.516 (7.061-7.971)
> = 75	6,333	9.21 (11.20)	4,567 (3,161)	22.693 (22.134-23.252)	965	3.458 (3.240-3.676)	15.238 (14.353-16.123)
TOTAL	74,933	6.67 (9.55)	4,446 (3,059)	27.532 (27.335-27.729)	3,859	1.418 (1.373-1.463)	5,150 (4.992-5.398)

(95% CI: 17.616-17.933) and differed significantly by age ($p < 0.001$); women aged between 45 and 59 years old had the highest mean rate. Additionally, this rate decreased significantly during the study period ($p < 0.001$), reaching the highest value in 2003, at 19.394 cases per 100,000 women (95% CI: 18.802-19.986), and the lowest in 2014, at 16.066 cases per 100,000 women (95% CI: 15.552-16.581) (Figure 3).

The mean age of hospitalization was 54.56 ± 14.83 years; the highest mean age was observed in 2013 and 2014, at 55.21 ± 14.78 years and 55.14 ± 14.90 years, respectively. The mean ALOS was 8.46 ± 11.02 days, and the mean hospitalization costs were $5,013 \pm 3,301$ euros. As in the combined MN and ISC analysis, the ALOS decreased significantly during the study period ($p < 0.001$), and the hospitalization costs increased ($p < 0.001$). For both variables, a significant increase with age was found ($p < 0.001$) (Table 2).

The most common comorbidities associated with MN of the cervix were as follows: essential hypertension not specified ($n = 8,148$), irradiation ($n = 4,743$) and tobacco use disorder ($n = 4,572$). The highest number of comorbidities was observed in females aged more than 75 years old (mean: 5.63 ± 3.52).

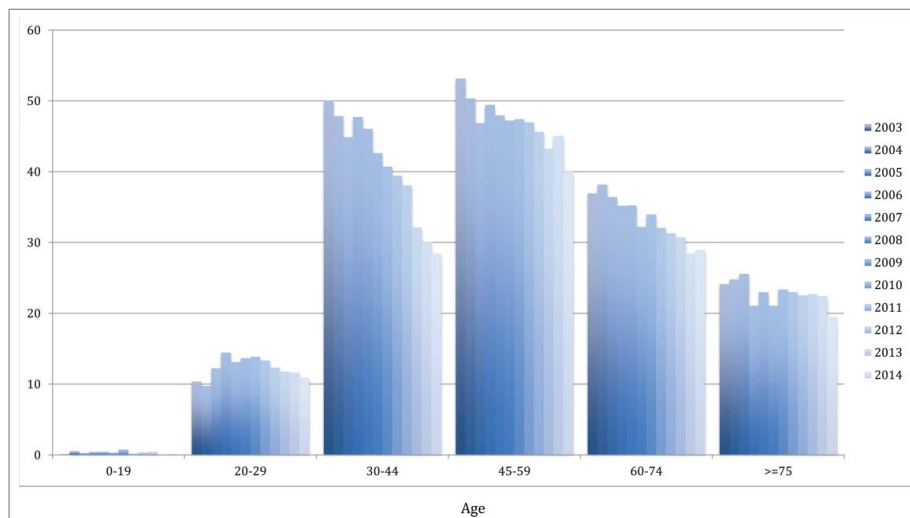
Regarding procedures, the most frequent procedures associated with MN of the cervix were transfusion of hematite concentrate ($n = 5,759$), implantation or insertion of radioactive elements ($n = 5,422$) and computed tomography of the abdomen ($n = 5,231$).

Females aged between 45 and 59 years old had the highest number of documented procedures (mean: 2.84 ± 2.45).

In total, 3,802 deaths were documented during this period, corresponding to a mortality rate of 1.397 deaths per 100,000 women (95% CI: 1.353-1.441) and a CFR of 7.859% (95% CI 7.620-8.099). Both rates increased significantly with age ($p < 0.001$). The mortality rate decreased during this period ($p = 0.0443$), but the CFR remained relatively constant ($p = 0.0292$).

ISC of the cervix

We identified 27,124 hospitalizations associated with ISC of the cervix, and in most, 23,833, ISC was the first diagnosis. The mean hospitalization rate was 9.966 cases per 100,000 women (95% CI: 9.874-10.085). This rate increased significantly with age ($p < 0.001$) but significantly decreased during the study period ($p < 0.001$), from 11.384 cases per 100,000 females in 2003 to 6.838 cases per 100,000 females in 2014 (Figure 4). The mean age of hospitalization was 41.80 ± 11.96 years, and this age was lowest in 2006 (41.03 ± 11.59 years) and highest in 2014 (43.47 ± 12.52 years). The mean ALOS was 3.49 ± 4.46 days, and the mean hospitalization cost was $3,459 \pm 2,247$ euros. The ALOS decreased significantly during the study years ($p < 0.001$) and increased by age ($p < 0.001$). By contrast,

**Figure 2.** Hospitalization rate due to malignant neoplasia (MN) and in situ carcinoma (ISC) of cervix per year and per age group.

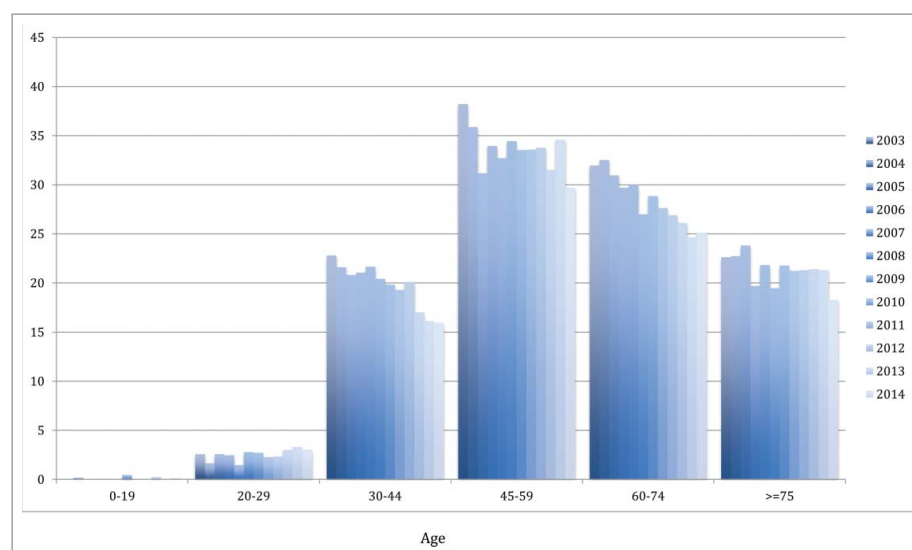


Figure 3. Hospitalization rate due to malignant neoplasia (MN) of cervix per year and per age group.

hospitalization costs increased both by age and during the study period ($p < 0.001$).

The most common comorbidities associated with ISC hospitalization were HPV infection ($n = 3,976$), tobacco use disorder ($n = 3,224$), and essential hypertension not specified ($n = 1,578$). Women aged more than 75 years old had a higher mean number of associated comorbidities: 3.78 ± 3.13 . Cervical conization ($n = 9,114$), cauterization of the cervix lesion ($n = 6,027$) and dilatation/curettage ($n = 2,623$) were the more commonly documented procedures. The mean number of procedures was higher in females aged 45–59 years old (2.16 ± 1.62), 60–74 years old (2.41 ± 1.80) and more than 75 years old (2.46 ± 1.94) than in younger women.

Finally, 59 deaths due to ISC of the cervix were documented in the hospital environment from 2003 to 2014, corresponding to a mortality rate of 0.022 cases per 100,000 females (95% CI: 0.016–0.027) and a CFR of 0.218% (95% CI: 0.162–1.273). The mortality rate remained quite stable with age ($p = 0.1736$) and throughout the study period ($p = 0.7429$); the CFR increased significantly by age ($P < 0.001$), but no significant changes in CFR during the study period were observed ($p = 0.7852$).

Some important differences between MN and ISC were found. The number of hospitalizations for MN was 1.78-fold higher than that of ISC, leading to a higher hospitalization rate in MN. The mean age of hospitalization was 54.46 years for MN and 41.80 years for ISC, and the mean ALOS and costs

were also higher for MN than for ISC. Finally, the CFR was 7.859% for MN and 0.218% for ISC.

Discussion

In this study, we assessed the hospital burden of cervical disease in Spain during the last 12 years. We found a total of 74,933 hospitalizations related to MN and ISC of the cervix uteri. We have observed a decrease of 25.69% in the annual hospital burden of cervical disease during this period, from 6,503 discharges in 2003 to 5,301 in 2014. This reduction was even stronger, 39.93%, when restricted to ISC of the cervix. Additionally, an absolute reduction of 1.27 days in ALOS was observed, although the hospitalization costs increased by more than 2,149 euros per hospitalization during the study period, representing an increase of 66.97% from the initial cost. Finally, the mean age of hospitalized females increased during the study period, from 49.47 years old in 2003 to 51.67 years old in 2014. The age groups with the highest hospitalization rates were women aged between 30–44, and 45–59 years old. This is consistent with the fact that cervical cancer is the second most frequent cancer in women under 45 years old.¹ Comparing our results with those from published data on a previous period, 1999–2002,³⁰ there is an important decrease in the hospitalization rate due to MN and ISC from 25.5 and 17.0 cases per 100,000 women in 1997–2002 to 17.8 and 9.9 cases per 100,000 women in 2003–2014, respectively.

Table 2. Average length of hospital stay (ALOS), hospitalization cost, hospitalization rate, mortality rate and case fatality rate of hospitalizations related to malignant neoplasia (MN) of cervix over the period (2003–2014).

Age	MN						
	Number N	ALOS Mean (SD) (days)	Mean cost Mean (SD) (euros)	Hospitalization rate per 100,000 women (CI95%)	Number of deaths N	Mortality rate per 100,000 women (CI95%)	Case fatality rate % (CI95%)
0-19	56	4.07 (3.87)	3,709 (2,070)	0.109 (0.081-0.138)	0	0.000	0.000
20-29	897	7.31 (9.57)	4,928 (2,983)	2.487 (2.324-2.649)	29	0.080 (0.051-1.110)	3.233 (2.076-4.390)
30-44	12,926	7.82 (9.92)	5,155 (2,908)	19.677 (19.328-20.006)	658	1.001 (0.925-1.078)	5.091 (4.712-5.469)
45-59	17,570	8.45 (11.50)	5,111 (3,212)	33.496 (33.000-33.991)	1,206	2.299 (2.169-2.429)	6.864 (6.490-7.238)
60-74	11,002	8.82 (11.35)	4,928 (3,879)	28.376 (27.846-28.906)	956	2.466 (2.309-2.622)	8.689 (8.163-9.216)
> = 75	5,924	9.42 (11.38)	4,598 (3,212)	21.228 (20.687-21.768)	953	3.415 (3.198-3.632)	16.087 (15.151-17.023)
TOTAL	48,375	8.46 (11.02)	5,013 (3,301)	17.774 (17.616-17.933)	3,802	1.397 (1.353-1.441)	7.859 (7.620-8.099)

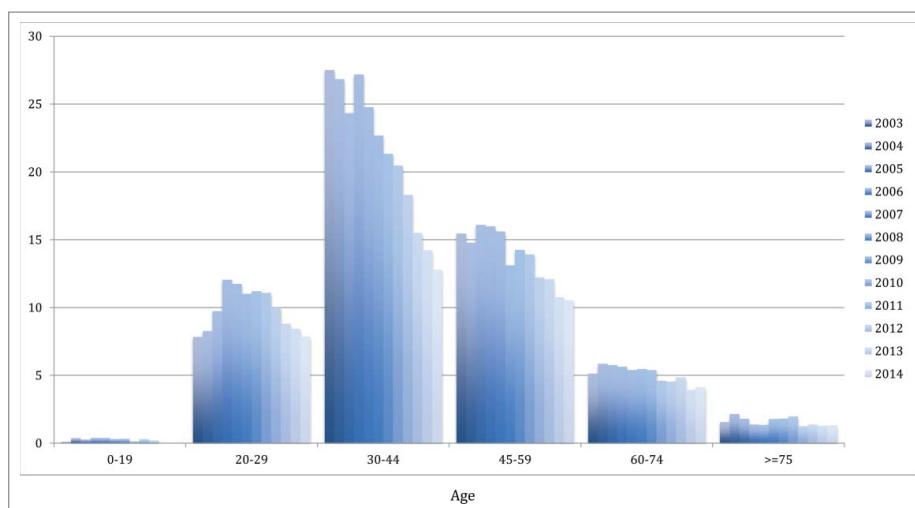


Figure 4. Hospitalization rate due to in situ carcinoma (ISC) of cervix per year and per age group.

The reduction in hospitalization rate could be attributable to several factors: first, cervical screening programs are well known to reduce the incidence and mortality of cervical cancer, and in Spain, these programs are widely implemented.¹ Cervical screening is managed and implemented by the regional Health Authorities of the 19 regions in which Spain is divided. Nowadays, most of cervical screening programs are opportunistic and cytology-based although it is expected that HPV test will be introduced progressively. The Spanish Society of Cervical Pathology and Colposcopy recommends an age specific screening schedule: between 25 and 30 years: cervical cytology every three years; between 30 and 65 years: HPV test every five years; and from 65 years onwards: end of screening if negative on prior screening tests for at least 10 years and no cervical cancer lesions for at least 20 years.⁹

Another potential explanation for this reduction is the substantial changes in the management of cervical disease. In general, hospitalization is mostly needed when surgical treatment of cervical disease is required. Surgical treatment occurs mainly for invasive cervical cancer; as women suffering from this disease usually undergo a radical hysterectomy and/or pelvic or paraortic lymphadenectomy. Other types of treatment such as colposcopy or even conization are usually managed outpatient, without hospitalization; so it is less likely that these hospitalizations refer to precancerous cervical lesions. This also affected ISC which is now usually treated outside the hospital setting, as stated in national medical guidelines.³¹ Additionally, some clinical improvements have emerged during the study period. Some techniques as the sentinel lymph node biopsy, may have a critical role to prevent the execution of surgical procedures of great magnitude for an initial disease, avoiding the morbidity associated with them.³¹ This type of progresses may help to explain the decrease of ALOS and the increase of hospitalization costs described in our paper.

Finally, the early impact of HPV vaccination on cervical precancerous lesions could be another factor related to this reduction. As mentioned previously, HPV vaccination was introduced in Spain in 2007/2008¹³, and clinical trials have shown that HPV vaccines are effective against high-grade precancerous lesions due to certain types of HPV³²⁻³⁴; more recently, the effectiveness and impact of these vaccines have been proven at the population level.^{16, 24-28}

Further research is necessary to confirm the reasons for this reduction; however, the main decreases in this study were found in women aged between 30 and 44 years old. This age group is not included in the Spanish national vaccination program, and the vaccination coverage rate in the private sector is low, approximately 1%,³⁵ which means that this reduction is less likely to be due to vaccination impact and it is more likely to be related to new advances in cervical cancer therapies³¹; new procedures and treatments, that have led to a most efficient management of this disease.

Based on our data, the estimated annual cost of hospitalizations due to MN and ISC of the cervix was more than 30.5 million euros, more than 22.0 million of which were due to MN. This annual cost is higher than the one obtained in the previous study of 19 million euros.³⁰ However, the total cost of cervical cancer extends beyond the hospital burden, and a study published in 2005 found that the total direct cost per cervical cancer case was 7,041.7 euros.³⁶

This study has some limitations due to the use of the CMDB database, which only records hospitalized cases; accordingly, we cannot estimate the incidence or prevalence rates. The reliability of the CMDB is influenced by the quality of the clinical histories collected and the coding of hospital discharges.³⁷ Moreover, it is possible that patients with multiple hospital admissions were overcounted.³⁸ The mortality rate and comorbidity data related to HPV infection within the CMDB must be interpreted with caution. For mortality rate, deaths outside of the hospital are not considered, and thus the rate is likely underestimated. For HPV infection comorbidity, HPV infection is known to be an essential cause of cervical cancer development; however, it is not always documented, as it has no implications on disease management. The information on vaccination status is not available in CMDB database. It is not possible to make further analysis according to HPV vaccination. Despite these limitations, hospital discharge databases have been shown to be adequate tools for cancer surveillance.³⁹

Conclusion

Our study describes an important decrease in the hospitalization burden of MN and ISC of the cervix in Spain during a

12-year period, including 7 years after introducing the HPV vaccination program. This decrease could be attributable to different factors, and further research is necessary to confirm the causes. This information could be used for further monitoring of the impact of HPV vaccination in our country and for cost-effectiveness analyses on HPV vaccination.

Methods

This epidemiological study used discharge information obtained from the national surveillance system for hospital data (CMBD) provided by the Ministry of Health. This database contains admission and discharge dates, age, sex, diagnosis, clinical procedures and discharge status for all hospitalizations in Spain. It uses clinical codes from the Spanish version of the 9th Internal Classification of Diseases (CIE-9-MC).⁴⁰ The CMBD is estimated to cover approximately 98% of public hospital admissions and 99.5% of the population in Spain.⁴¹ We assumed that the epidemiological characteristics of the population and hospitalizations not covered by the CMBD were very similar to the ones in our study. The patient information was anonymized and de-identified prior to the analysis. Local Ethics Committee (Comité de Ética de la Investigación de la Universidad Rey Juan Carlos) ruled that no formal ethics approval was required in this particular case.

We selected all hospital discharges related to MN and ISC of the cervix diagnosed in any location during a 12-year period (2003–2014) (ICD-9-CM: 180: MN of the cervix; 180.0: MN of the endocervix; 180.1: MN of the exocervix; 180.8: MN in other specific sites of the cervix: cervical nerve, squamocolumnar junction, MN affecting sites contiguous to the uterine cervix with undetermined place of origin; 180.9: cervix uteri not specified; 233.1: ISC of the cervix uteri).⁴⁰ For each case, we collected data on age, type of discharge, length of hospital stay, diagnosis and therapeutic procedures associated with each hospitalization and outcome (recovery or death). Costs related to hospitalization were estimated by the Ministry of Health using the diagnostic cost group (DCG) system, which classifies hospitalizations into groups that are expected to generate similar use of hospital resources. Classification is based on diagnoses, procedures, age, presence of complications and co-morbidities.

Statistical analysis: We calculated the average number of hospitalizations, average length of hospital stay (ALOS) and average hospitalization cost (euros) per year and by age. Incidence rates of hospitalization, mortality rates (per 100,000 women), and case fatality rates (CFRs) (%) were calculated per year and age group. We used data on the female population from municipal registries adjusted by the population targeted by hospitals covered by the CMBD as the denominator, and we divided the female population into 6 age groups: 0–19, 20–29, 30–44, 45–59, 60–74, and ≥ 75 years old.

We used Chi square tests to assess significant differences in proportions and ANOVA for multiple comparisons. Poisson models were used to assess the differences in the hospitalization and mortality rates (per 100,000 women) and CFRs (%) between the study period years (2003–2014) and age groups. Hospitalization and mortality rates and CFRs were used as the dependent variable, and adjusted for year and age.

All results were reported with their corresponding 95% CIs. For all tests, we considered a p value less than 0.05 to be significant.

Disclosure of potential conflicts of interest

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