Papillomavirus Research 5 (2018) 80–86

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

Hospitalization burden associated with malignant neoplasia and in situ carcinoma in vulva and vagina during a 5-year period (2009–2013) in Spain: An epidemiological study

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ARTICLE INFO

Keywords:
HPV
Vulva
Vagina
Malignant neoplasia
Hospitalizations
Carcinoma

ABSTRACT

Background: Vulvar and vaginal cancers are considered rare cancers in women. Human Papillomavirus is responsible for 30–76% of them. The aim of this study was to describe the burden of hospital admissions by malignant neoplasia (MN) and in situ carcinoma (ISC) of vulva and vagina from 2009 to 2013, in Spain

Methods: This observational, descriptive study used discharge information obtained from the national surveillance system for hospital data, Conjunto Mínimo Básico de Datos, CMBD, provided by the Ministry of Health.

Results: From 2009–2013, we found 9,896 hospitalizations coded as MN or ISC of vulva and vagina. Mean age of hospitalization was 69.94 ± 15.16 years; average length of hospital stay (ALOS) was 10.02 ± 12.40 days, and mean hospitalization costs were 5,140.31 ± 3,220.61 euros. Mean hospitalization rate was 9.874 per 100,000 women aged > 14 years old (95% CI: 9.689–10.058); mean mortality rate was 0.932 per 100,000 women aged > 14 years old (95% CI: 0.872–0.991) and mean case fatality rate was 9.438% (95% CI: 8.862–10.014).

Conclusion: MN and ISC of vulva and vagina are responsible for a considerable hospitalization burden. Information about these hospitalizations could be useful for cost effectiveness analysis and monitoring of HPV vaccination effectiveness.

1. Introduction

According to IARC (International Agency Research of Cancer) estimations, around 14.1 million new cancer cases and 8.2 million cancer deaths occurred during 2012 worldwide [1]. Previous data indicated that gynecological cancers accounted for 19% of total female cancers [2]. Vulvar and vaginal cancers are considered as rare cancers in women [3]. It is estimated that 34,000 new cases of vulvar cancer and 15,000 new cases of vaginal cancer occurred in 2012 worldwide [4]. Around 68% of the vaginal cancer cases occur in less developed countries. In contrast, 60% of vulvar cancer cases occur in more developed countries [3]. While cervical cancer is estimated to be higher in women between 30 and 39 years old, vulvar and vaginal cancers occur more frequently in older women, aged 70+ [5].

In Europe, the estimated annual number of cases of vulvar and vaginal cancer is 9,544 and 2,171, respectively [6].

Data about incidence of vulvar and vaginal intraepithelial neoplasia (VIN and VaIN, respectively) is estimated based on registries from Scandinavian countries. The age-standardized incidence rate of high grade VIN ranged between 2.5 and 8.8 per 100,000 women and, for high grade VaIN, between $0.5/10^5$ and $1.3/10^5$, worldwide [5]. The age of appearance of these lesions is also higher than for cervical neoplasia; as vulvar and vaginal pre-invasive neoplasia peaked in women aged 40–49 and 60–69, respectively [5]. In Europe, between 13,886-27,592 high-grade VIN (VIN2/3) cases and 2,549-4,719 high-grade VaIN (VaIN 2/3) cases are estimated to occur each year [6].

According to the most recent studies, human papillomavirus DNA was detected in 86.7% and 28.6% of VIN and invasive vulvar carcinoma (IVC), respectively and in 74% of invasive vaginal cancers and 96% of VaIN2/3. Most of the HPV positive invasive vulvar and vaginal carcinomas were squamous cell carcinoma basaloid or warty basaloid, and the prevalence of HPV was higher among women up to 55 years old [7,8].

Apart from the age of appearance and the type of carcinoma, there

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https://doi.org/10.1016/j.pvr.2018.02.001
Received 26 October 2017; Received in revised form 20 January 2018; Accepted 11 February 2018
Available online 16 February 2018

are other factors that can differentiate HPV positive from HPV negative vulvar and vaginal cancer. HPV positive vulvar cancers are usually preceded by precancerous high grade lesions and risk factors are similar to cervical cancer ones; such as number of sexual partners, age of sexual debut and other cofactors involved in human papillomavirus carcinogenesis such as such as tobacco smoking. In contrast, HPV negative vulvar cancers are usually associated with p53 mutations and it usually appears after long-term chronic lesions such as lichen sclerosus and no cervical cancer risk factors are usually found [9].

Regarding HPV type specific contribution, based on HPV DNA, type 16 is the most commonly detected one. It is estimated that HPV16/18 and HPV31/33/45/52/58 are present in 72.6% and 13% of HPV vulvar cancers; and 79.8% and 13% HPV VIN2/3, respectively. For HPV vaginal disease, HPV16/18 and HPV31/33/45/52/58 are present in 63.7% and 20.3% in cancer, and in 63.8% and 13.5% in high-grade lesions, respectively. The percentage of multiple infections in vulvar invasive cancer was 6.1%, in vaginal cancer 4.0%, in VaIN 2/3 11.0% and in high grade vulvar precancerous lesions 9.0% [10].

In Spain, information about vulvar and vaginal cancer incidence comes from the Spanish Regional System of Cancer Registry, REDECAN, which includes 14 regional registries from different areas of Spain. No national cancer registry exists currently. According to this registry, the age-standardized incidence of vulvar and vaginal cancer ranges between 0.8–1.5 and 1.5 and 0.0–0.5 cases per 100,000 women per year, respectively [3]. In line with global figures, Spanish incidence rates are highest in women aged 70+ [3].

Last published data about burden of hospitalizations of malignant neoplasia and in situ carcinoma of vulva and vagina in Spain in 2011 showed that the time trend in hospitalization incidence rate had remained quite stable from 1997 to 2008 [11]. This paper showed, for the first time in Spain, the national burden of hospital admissions due to these diseases. During this period, almost 18,000 hospitalizations related to malignant neoplasia of vulva and vagina, and over 2,000 hospitalizations related to in situ carcinomas in these sites occurred in our country. The fact that no significant changes in the hospitalization rate were observed during 1997–2008 in that study can be explained by the absence of standardized screening programs for these types of cancers [12]. However, a decrease in the incidence of HPV related vulvar and vaginal cancers and precancerous lesions could be expected during the next decades as result of the HPV vaccination program. In Spain, this program started in 2007 and targeted 11–14 year-old girls with a 3-vaccine dose schedule [13,14]. Nowadays, the immunization program against papillomavirus has decreased the vaccination age to 12 years with a 2-dose schedule reaching a vaccine coverage rate of around 77% [15]. No formal catch up for women older than 15 years-old was implemented at the beginning of the HPV vaccination program, thus, vaccine coverage rate in females out of the national vaccination program is very low, under 1% [16].

This study, like the previous study, used a hospital discharge database, Conjunto Mínimo Básico de Datos (CMBD), that has proven to be useful for the evaluation of HPV related hospitalizations and other hospitalization associated diseases [11,17,18].

Our aim is to describe the burden of hospital admissions by malignant neoplasia (MN) and in situ carcinoma (ISC) of vulva and vagina in Spain from 2009 to 2013.

2. Methods

This was an epidemiological, descriptive study that used discharge information obtained from the national surveillance system for hospital data, CMBD, provided by the Ministry of Health. This database contains data about admission and discharge date, age, sex, geographical region, diagnosis and discharge status for all hospitalizations in our country. It uses clinical codes from the Spanish version of the 9th Internal Classification of Diseases (CIE-9-MC) [19]. It is estimated to cover around 98% of public hospital admissions, and 99.5% of the population in Spain [20]. We assumed that for population and hospitalizations not covered by CMBD, epidemiological characteristics are very similar.

We selected all hospital discharges related to MN and ISC of vulva and vagina in any diagnostic position during a 5 year period (2009–2013) (ICD-9-CM: 184, malignant neoplasia of other female genital organs and unspecified; 184.0 vagina; 184.1 labia majora, 184.2 labia minora, 184.3 clitoris, 184.4 vulva, unspecified, 184,8 other specified female genital organs; malignant neoplasia affecting sites next to female genital organs whose origin cannot be specified; 184.9, female genital organ, unspecified; 233.3 in situ carcinoma of other female genital organs and unspecified female genital organs; 233.30 unspecified female genital organ, 233.31 vagina, 233.32 vulva, 233.39 other female genital organ) [19]. For each case, we collected data about age, geographic region, funding scheme, type of discharge, average length of hospital stay (ALOS), diagnosis and therapeutic procedures associated to 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.

For statistical analysis, we calculated the average number of hospitalizations, ALOS and the average hospitalization cost (euros), per year and by age. Incidence rates of hospitalization (per 100,000 women aged more than 14 years old), mortality rates (per 100,000 women aged more than 14 years old), and case fatality rates (%) were calculated per year, age and region. As denominator we used the data of the female population aged more than 14 years old from the municipal registers adjusted by the population targeted by hospitals covered by the CMBD.

We used Chi square test to assess significant differences in proportions, and ANOVA for multiple comparisons. Poisson models were used to assess differences in the hospitalization and mortality rates (per 100,000 women aged > 14 years old) between the years of the studied period (2009–2013) and the age group. Hospitalization rate and mortality rate were used as dependent variables, and the year and the age were used as independent variables.

All of the results were reported with their corresponding 95% confidence intervals (95% CI). For all tests, we considered a p value less than 0,05 to be significant.

3. Results

From 2009–2013, we found 9,896 hospitalizations coded MN or ISC of vulva and vagina in 6,600 females, which corresponded to a number of 1.5 hospitalizations per patient. During the studied period, mean age of hospitalization was 69.94 ± 15.16 years, and no significant changes in age of hospitalization was observed ($p = 0.2811$). 1,741 hospitalizations were registered in women up to 55 years old, and 8,155 in women above 55 years old. Average length of hospital stay (ALOS) was 10.02 ± 12.40 days, and mean hospitalization costs were 5,140.31 ± 3,219.61 euros. During the study period, we found a significant decrease in ALOS, from 11.00 ± 13.51 days in 2009, to 9.59 ± 11.88 days in 2013, $p < 0.001$. By contrast, hospitalization costs significantly increased during the same period; from 4,565.99 ± 2,892.41 euros in 2009; to 5,131.69 ± 3,186.18 euros in 2013, $p < 0.001$. Both variables showed significant increase with the age ($p < 0.001$ for ALOS and $p < 0.001$ for hospitalization costs). In women up to 55 years old, ALOS was 7.47 ± 8.08 days and mean hospitalization cost was 5,189 ± 4,513 euros; while in women above 55 years old, ALOS was 10.56 ± 10.25 days and mean hospitalization cost was 5,122 ± 4,002 euros. Women between 25 and 29 years old registered the maximum hospitalization cost.

Mean hospitalization rate was 9.874 per 100,000 women aged more than 14 years old (95% CI: 9.689–10.058); mean mortality rate was 0.932 per 100,000 women aged more than 14 years old (95% CI: 0.872–0.991) and mean case fatality rate was 9.438% (95% CI: