

## ORIGINAL

# The management of human papilloma virus infection: results of the paloma clinical trial and derived research projects

*El manejo de la infección por el virus del papiloma humano: resultados del ensayo clínico paloma y proyectos de investigación derivados*

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## Abstract

We present the results of an investigative trial that very significantly validate the use of Papilocare®, a vaginal application gel, for the clearance of the presence in the lower female genital tract of the human papilloma virus and the regression of low-grade intraepithelial lesions that its infection initially causes in the cervix. Based on these results, two new lines of research are proposed and detailed.

*Key words:* Papilloma virus, clearance, low grade intraepithelial lesion, conization.

## Resumen

Se presentan los resultados de un ensayo de investigación que validan de forma muy significativa el uso de Papilocare®, un gel de aplicación vaginal, para la eliminación de la presencia en el tracto genital inferior femenino del virus del papiloma humano y la regresión de las lesiones intraepiteliales de bajo grado que su infección provoca inicialmente en el cuello uterino. A partir de estos resultados, se proponen y detallan dos nuevas líneas de investigación.

*Palabras clave:* virus del papiloma, aclaramiento, lesión intraepitelial de bajo grado, conización.

## Introduction

In 1974 Harald zur Hausen identified and described the structure of the human papillomavirus (HPV)<sup>1</sup>, a sexually transmitted virus<sup>2</sup> that has subsequently been identified as a necessary causative agent of cervical cancer (CC)<sup>3</sup> and of a proportion discharge from other cancers, as shown in **tables I** and **II**.

**Table I:** Annual number of causal HPV cancers in Europe.

Cancer of	Men	Women
Penis	1.090	
Anus	1.700	2.930
Head and neck	12.700	2.530
Vulva and vagina		3.850
Cervix		23.250

Source: Ref. 4.

The latest data available for Spain are expressed in **table II**:

**Table II:** Date of Spain.

Cancer of	Number of cases	% HPV +
Anus	360	324
Cervix	1.948	1.948
Penis	330	132
Vulva	570	228
Vagina	105	74
Oro-pharynx	800	216
Pre-neoplastic cervix	54.600	54.600

These data confirm the great relevance of the causal HPV oncological pathology and, consequently, of the enormous importance of its prevention.

The CLEOPATRE<sup>6</sup> study revealed the prevalence of HPV infection in women in Spain, data that have not been subsequently corrected. The study evaluated 1,918,805 women between 18-65 years of age, distributed proportionally by population rate in all the Spanish Autonomous Communities. **Figure 1** reflects what was

detected in the study: around 30% of women under 30 years of age are HPV + and around 10% from this age, for a global of 14%.

The natural history of CC, perhaps the best known cancer in its development of all of us who suffer, has been precisely identified, encompassing the entire oncogenic process, from the initial viral presence to invasive cancer, passing through intraepithelial lesions, low and high grade<sup>7</sup>.

We have solid evidence that vaccination against HPV has high rates of efficacy, effectiveness, efficiency and safety and that the current recommendation of secondary preventive methodology –early diagnosis, screening– of the CC is well established<sup>8</sup>, taking its joint action –vaccine, screening– to what we have called “Integral Cervical Cancer Prevention”, aimed at responding positively to the call made by the World Health Organization to eradicate CC<sup>9</sup> from our world, the first cancer in which this health action of so much draft is possible.

But we did not have any strategy that, applied to women who are carriers of HPV, a significant fraction of the female population, as previously noted, would facilitate the clearance of the virus and the regression of the initial lesion caused in the epithelium by its presence, the low-grade squamous intraepithelial lesión (LG.SIL). We did not have it, but the recent publication of the results of the PALOMA study has filled this gap<sup>10</sup>, a study preceded by the demonstration that the application of Papilocare®, a vaginal administration gel that basically contains *Coriolus versicolor*, a fungus containing polysaccharidopeptides, Polysaccharide-K / Krestin (PSK) and Polysaccharidopeptide (PSP), caused a very intense normalization of the vaginal ecosystem and, in addition, very clearly improved the epithelialization of the cervix<sup>11</sup>. The PALOMA trial was designed as a phase IIb - III, prospective, randomized to a Papilocare® treatment group versus routine clinical practice, that is, follow-up without further ado, clinical practice for which the expected results are known, HPV clearance at 6 months of 29%<sup>12</sup>, and a regression of the LG.SIL at 2 years of 59%<sup>13</sup>. Papilocare® significantly demonstrated to cause a 63% clearance of high-risk HPV 16 after 6 months of treatment and to re-epithelialize the neck of uterus of women carrying high-risk strains of HPV in 87.8% of cases, percentages markedly higher than those obtained, as indicated above, with current clinical practice. The PALOMA results, which were confirmed by two independent studies carried out in parallel<sup>14,15</sup>, open a door until now closed, that of being able to intervene in the day-to-day care in the treatment of the presence of HPV in the lower genital tract and in that of LG.SIL.

Papilocare® also showed a very high tolerability, expressed in that there were no serious adverse effects

related to the treatment and only two dropouts due to mild intolerance were noted.

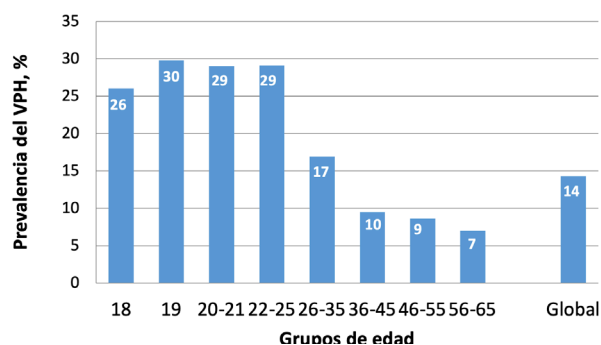
The research group was also interested in sub-analyzing whether these high efficacy data from Papilocare® were reproduced in women over 40 years of age, a group that, being a carrier of HPV, is at a clear high-risk of developing CC, given its immunosenescence<sup>17</sup>, a concept coined a few years ago, related to the gradual deterioration of the immune system caused by the natural advancement of age and that involves both the host's ability to respond to infections and the development of long-term immune memory. The analysis of this group of women over 40 years of age has concluded<sup>18</sup> that the data obtained in the PALOMA study are improved: 90.5% regression of the LG.SIL in the treated group versus 33% in the control group; 66.7% clearance of high-risk HPV in the treated group versus 44.4% in the control group.

We believe that all these results are of great importance, since they provide a solid basis for a therapeutic indication lacking evidence so far.

As a consequence of these excellent results, the research group has considered two new projects:

- Apply Papilocare® post-conization to explore if a normalization of the vaginal microbiota is obtained, usually altered by the presence of HPV: modifications of the microbiota play a decisive role in the development of CC<sup>19</sup>.
- To test whether the anal application of Papilocare® obtains the same results as its vaginal application in women with rectal HPV: there is evidence that a high fraction of women with HPV in the lower genital tract also present it in anus<sup>20</sup>, a relevant fact and that together with the lack of agreements and application of early diagnosis techniques and programs<sup>21,22</sup> could explain the tendency to increase the incidence of anal cancer, 90% causal HPV<sup>23</sup>, which the registries note<sup>24</sup>

Figure 1: Prevalence of VPH according age (%).



## Conflict of interests

JaC has received travel and / or research grants and / or conference and / or consulting fees from Genomics, GSK, Merck, Procure Health, Qiagen, Roche, and SPMSD.

DD has received conference and / or consulting fees from Sanofi Pasteur, MSD, and Procure Health.

ACL has received consulting fees from Procure Health. LS ha recibido honorarios por conferencias y/o asesorías de Shionogi, Iprad y Procure Health.

FL has received travel and / or research grants and / or conference and / or consulting fees from Bayer, Boiron, Novonordisk, Iprad, and Procure Health.

JoC has a professional relationship with Procure Health for medical advice.

CE has an employment relationship with Procure Health.

YG has an employment relationship with Procure Health.

SP has received research grants and / or fees for conferences and / or consultancies and / or for being a member of the advisory committee from Pfizer, Amgen, MSD, Sandoz, Procure Health, Bayer, MSD, Serelys, Shionogi, Servier, Abbott, Novo Nordisk, Theramex and Gedeon Richter.

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