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Prevalence and genotype distribution of cervical human papillomavirus infection in the pre-vaccination era: a population-based study in the Canary Islands

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ABSTRACT

Objective National Spanish studies show that prevalence of cervical human papillomavirus (HPV) infection in the female population is increasingly frequent, with an overall estimate of 14% in women aged 18–65 years. The objective of this study is to know the prevalence and distribution of HPV types in the female population of the Canary Islands prior to the introduction of HPV vaccines and to investigate the associated clinical and sociodemographic factors.

Methods Based on the Primary Health Care database, a sample of adult women (aged 18–65 years) of Gran Canaria (GC) and Tenerife (TF) stratified into nine age groups was carried out between 2002 and 2007. Women were contacted by postal letter and telephone call and were visited in their primary care centre. A clinical-epidemiological survey was completed and cervical samples were taken for cytological study and HPV detection. HPV prevalence and its 95% CI were estimated, and multivariate analyses were performed using logistic regression to identify factors associated with the infection.

Results 6010 women participated in the study, 3847 from GC and 2163 from TF. The overall prevalence of HPV infection was 13.6% (CI 12.8%–14.5%) and 11.1% (CI 10.3%–11.9%) for high-risk types. The most frequent HPV type was 16 followed by types 51, 53, 31, 42 and 59. HPV types included in the nonavalent vaccine were detected in 54.1% of infected women. Factors associated with an increased risk of infection were: young ages (18–29 years), the number of sexual partners throughout life, not being married, being a smoker, and having had previous cervical lesions or genital warts.

Conclusions It is confirmed that prevalence of HPV infection in the female population of the Canary Islands is high, but similar to that of Spain, HPV 16 being the most frequent genotype. The determinants of infection are consistent with those of other populations.

INTRODUCTION

Cervical cancer is the fourth most common female cancer worldwide and the second most frequent among young women aged 15–44 years, with an estimated 569 847 new cases in 2018. In Spain, cervical cancer is the 15th most frequent cancer in women (4th in women aged 15–44 years), with an estimated 1942 new cases in 2018. In the Canary Islands autonomous community, 356 new cases were diagnosed in 2008–2011, with a crude rate of 10.1 cases per 100 000 women, one of the highest incidence rates in Spain.

Human papillomavirus (HPV) is a necessary but not sufficient cause of cervical cancer. More than 200 HPV genotypes are currently known, epidemiologically classified into low-oncogenic risk (LR-HPV) and high-oncogenic risk (HR-HPV) types. HR-HPV types include 16 and 18 genotypes, present in >70% of cervical cancer cases and included
in the three prophylactic HPV vaccines currently commercialised.7 8

No robust estimations of HPV infection prevalence are available for the Canary Islands, which hinders comparisons with the rest of Spain. Changes in Spanish women’s sexual behaviour in the last decades have led to increased HPV infection rates (up to 14% in women aged 18–65 years, 29% of them in women younger than 25 years).9 Baseline prevalence estimations of HPV infection and the genotype distributions are essential to monitor the impact of HPV-vaccination campaigns. Therefore, the goal of this study was to estimate the prevalence and distribution of HPV types in the female population of the Canary Islands before introducing HPV vaccination, as well as to study the clinical and sociodemographic factors associated with HPV infection.

METHODS
Participants
The study was conducted between 2002 and 2007 on a sample of women aged 18–65 years living in any of the two most populated Canarian Islands: Gran Canaria and Tenerife. Participants were randomly selected from the regional Health Administration databases, stratified and selected with a probability proportional to the different healthcare areas on both islands. Selected women were stratified into nine age groups (18–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59 and 60–65 years). The initial sample included 2276 women. For each age group, four reserve groups were obtained to supply the absences or refusals to participate. Participants were contacted by letter and a subsequent telephone call. A visit to the nearest healthcare centre was scheduled. A total of 24 345 letters were sent, 15 577 in Gran Canaria and 8768 in Tenerife, of which 23.3% agreed to participate. Women who did not attend the visit were recalled by phone to schedule another visit. Subsequently, a group of 934 women from Gran Canaria asked to participate in the study (volunteers) of which 665 finally attended the arranged appointment.

Patient and public involvement
No patients or the public were involved in the design, conduct, reporting or dissemination of this study.

Procedures
Participants were asked to fulfil an informed consent form and to complete a clinical and epidemiological questionnaire (adapted from International Agency for Research on Cancer (IARC) surveys). For cytological collection, the wooden Ayre spatula and endocervical brush (cytobrush) were used, stained with the Papanicolaou technique and the cytological diagnosis was made by a single pathologist according to the criteria of the Bethesda system. For the molecular study, a sterile cotton-tipped polystyrene swab without culture medium (Deltalab, Spain) was used. The obtained cell pellet was subjected to enzymatic digestion with stirring for 2 hours at 55°C with proteinase K following the inactivation of the process with incubation for 10 min at 90°C and subsequent centrifugation, obtaining DNA from the sample supernatant.

To detect HPV infection, two separated PCR were conducted: one using My09/My11 consensus primer and the other using Gp5+/Gp6+ consensus primer. DNA quality was evaluated by PCR testing for the β-globin gene. Samples that were negative for both HPV DNA and β-globin were excluded from the final analysis. Samples showing positive results for any of the HPV PCR reactions or any cytological alteration (atypical squamous cells of undetermined significance (ASCUS) or higher) were genotyped using the Linear Array HPV Genotyping Test (CE-IVD; Roche Diagnostics) or the INNO-LIPA HPV Genotyping Extra Amp kit (Immugenetics (now Fuji-rebio Europe), Belgium).

Statistical analyses
Descriptive analysis of sociodemographic variables was conducted, globally and stratified according to the study subpopulation (ie, selected participants from Gran Canaria, volunteers from Gran Canaria, selected participants from Tenerife). Estimated HPV infection prevalence and genotype distribution and corresponding 95% CIs (Confidence Interval) were calculated as the number of HPV-positive women among the total number of women tested for each age group, study subpopulation and cytological outcome (normal, abnormal). For each genotype, estimated prevalences were calculated independently including the presence of a given type either as a single type or in combination with others (multiple infections). Multivariate analysis was conducted using basic and adjusted logistic regression models in order to assess potential risk factors associated with infections by any HPV type and by HR types. Variables were introduced one by one into a basic regression model adjusted for age group and subpopulation. Variables showing statistically significant association (p value <0.05) were kept as adjustment variables in the final model. Statistical analysis was carried out with the R software (R Development Core Team, 2005, http://www.r-project.org).

RESULTS
Study population
Table 1 shows the characteristics of the study population. A total of 6091 women were included: 3212 selected from the general Gran Canaria population (52.7%), 665 volunteers from Gran Canaria (10.9%) and 2214 selected from Tenerife (36.3%). Up to 8.4% of participants were not born in Spain and came mostly from Latin American countries (5.4%); participants’ mean age was 40.7 years; 64.4% were married at recruitment; 77.5% had been pregnant at least once and the mean number of children was 2.2. Regarding cytology screening, 53.7% of subjects had undergone more than five cytological studies in their lives, while 3.5% of them had never undergone
Table 1: Characteristics of the study participants (n=6091 women)

| Study sample characteristics | N (%) |
|-----------------------------|-------|
| **Distribution by population** |       |
| Gran Canaria (general population) | 3212 (52.7) |
| Gran Canaria (volunteers) | 665 (10.9) |
| Tenerife | 2214 (36.3) |
| **Country of birth** |       |
| Spain | 5397 (91.6) |
| Europe (excluding Spain) | 111 (1.9) |
| Northern Africa | 20 (0.3) |
| Sub-Saharan Africa | 15 (0.3) |
| Latin America and Caribbean | 318 (5.4) |
| Asia and Oceania | 30 (0.5) |
| **Missing data** | 200 (−) |
| **Age distribution (years)** |       |
| 18–24 | 572 (9.4) |
| 25–29 | 663 (10.9) |
| 30–34 | 905 (14.9) |
| 35–39 | 902 (14.8) |
| 40–44 | 793 (13.0) |
| 45–49 | 631 (10.4) |
| 50–54 | 613 (10.1) |
| 55–59 | 502 (8.2) |
| 60–65 | 510 (8.4) |
| **Marital status** |       |
| Single | 1396 (22.9) |
| Married/De facto partnership | 3919 (64.4) |
| Divorced/Separated | 573 (9.4) |
| Widowed | 195 (3.2) |
| **Missing data** | 8 (−) |
| **Pregnancies** |       |
| No | 1343 (22.5) |
| Yes | 4613 (77.5) |
| **Missing data** | 135 (−) |
| **Number of live births*** |       |
| 0 | 28 (0.7) |
| 1 | 1237 (20.7) |
| 2 | 1786 (31.5) |
| 3 | 789 (13.3) |
| 4 | 277 (6.4) |
| ≥5 | 186 (4.3) |
| **Missing data** | 310 (−) |
| **Sexually transmitted disease** |       |
| Never | 5882 (96.6) |
| Ever† | 209 (3.4) |
| Syphilis‡ | 30 (0.5) |

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one. Regarding HPV infection-related epidemiological factors, 56.5% of subjects were non-smokers and 28.5% were smokers at recruitment; 53.9% of subjects had only one sexual partner and 47.3% were younger than 19 years at first sexual intercourse. Demographic characteristics were slightly different between both islands: education level, proportion of smokers and number of sexual partners were statistically higher in Tenerife than in Gran Canaria. Regarding the subgroup of Gran Canaria volunteers, they were younger, with a high level of education, more divorced or separated, ex-smokers and with more previous cervical pap smears compared with the general population of the island (see online supplementary table 1).

Prevalence of cervical HPV infection

For the prevalence study, 6010 women were included in the analysis after excluding 81 women due to poor DNA quality in their samples. Prevalence of any-type HPV infection was 13.6% (95% CI 12.8 to 14.5) while the prevalence of HR-HPV infection was 11.1% (95% CI 10.3 to 11.9) (table 2). The youngest age group (18–24 years) showed the highest prevalence with 26.7% of any-type HPV infection (95% CI 23.1 to 30.4). Prevalence progressively decreased with increasing age, although the two oldest groups (55–65 years) showed a slightly non-significant increase compared with the immediately younger group (figure 1).

Although volunteers from Gran Canaria showed higher prevalence of any-type HPV infection than participants from the general population from both Gran Canaria (14.5%, 95% CI 11.8 to 17.2 vs 12.7%, 95% CI 11.6 to 13.9; see online supplementary table 2), the difference was not statistically significant. A comparison between the two populations from Gran Canaria (general population and volunteers) and the population from Tenerife showed statistically significant differences in HR-HPV infection prevalence (10.6%, 95% CI 9.6 to 11.6 vs 12.1%, 95% CI 10.7 to 13.4, p=0.002; see online supplementary table 2).

Table 2  Prevalence of human papillomavirus (HPV) by age group for any type and for any high-risk (HR) type (n=6010 women)

| Age group (years) | Number of tested women | Number of HPV-positive women | Any HPV prevalence (%) (95% CI) | Any HR-HPV prevalence (%) (95% CI) |
|-------------------|------------------------|------------------------------|---------------------------------|-----------------------------------|
| 18–24             | 565                    | 151                          | 26.7 (23.1 to 30.4)             | 23.9 (20.4 to 27.4)              |
| 25–29             | 655                    | 145                          | 22.1 (19.0 to 25.3)             | 19.7 (16.6 to 22.7)              |
| 30–34             | 894                    | 161                          | 18.0 (15.5 to 20.5)             | 15.2 (12.9 to 17.6)              |
| 35–39             | 890                    | 96                           | 10.8 (8.7 to 12.8)              | 8.0 (6.2 to 9.8)                 |
| 40–44             | 783                    | 79                           | 10.1 (8.0 to 12.2)              | 8.6 (6.6 to 10.5)                |
| 45–49             | 622                    | 59                           | 9.5 (7.2 to 11.8)               | 7.1 (5.1 to 9.1)                |
| 50–54             | 607                    | 43                           | 7.1 (5.0 to 9.1)                | 4.9 (3.2 to 6.7)                |
| 55–59             | 495                    | 42                           | 8.5 (6.0 to 10.9)               | 5.5 (3.5 to 7.5)                |
| 60–65             | 499                    | 44                           | 8.8 (6.3 to 11.3)               | 5.8 (3.8 to 7.9)                |
| Total             | 6010                   | 820                          | 13.6 (12.8 to 14.5)             | 11.1 (10.3 to 11.9)             |

*HR-HPV types include high-risk types and possibly/probably high-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 53, 66, 67, 68, 69, 69/71, 70, 73.
Table 3 shows the distribution of the most frequent HPV genotypes. Single-type HPV infection was detected in 6% of subjects and multiple infections in 7.2% (corresponding to 43.8% and 52.8% of all HPV-positive women, respectively). Among HR-HPV types, type 16 was the most frequent one found in 27.8% of positive women (including both single and multiple HPV types), followed by types 51 (13.7%), 53 (13.3%), 59 (9.9%), 31 (8.5%), 52 (7.7%) and 18 (6.1%).

Among LR-HPV types, type 42 was the most common one (9.3%). In an analysis combining the genotypes included in the HPV vaccines, 31.8% of HPV-positive women were infected by types 16 and/or 18 while the percentage increased to 36.2% when types 6 and/or 11 were added and to 54.1% when the nine types included in the nonavalent vaccine were considered. Figure 1 and online supplementary table 3 show the genotype distribution per age group.

Cytopathological study and cervical HPV infection

The cytological study yielded 317 pathological findings (5.3%) with 69.1% (95% CI 64.0 to 74.2) of HPV positivity vs 5693 non-pathological cytologies (94.7%) with 10.6% (95% CI 9.8 to 11.4) of HPV positivity (see online supplementary table 4), 214 cases of ASCUS were detected (3.6%) with 60.7% of HPV positivity, 91 cases of low-grade squamous intraepithelial lesions (LSIL) (1.5%) with 86.8% of HPV positivity and 12 cases of high-grade squamous intraepithelial lesions or worse (HSIL+) (0.2%) with 83.3% of HPV positivity. Genotype 16 was the most frequently type found in these cytological alterations. Multiple infections were more frequent in women with LSIL or HSIL+ as compared with ASCUS (see online supplementary table 5).

Cervical HPV infection and associated risk factors

Considering all cases of cervical HPV infection (LR-HPV and HR-HPV) and according to the final adjusted model, the following statistically significant variables were detected in the association with HPV infection: younger ages (18–29 years, with a significant linear trend), not married, smokers, more than one sexual partner (statistically significant trend), history of cervical alterations or genital warts and practising coitus interruptus (table 4). When only cases of HR-HPV cervical infection were considered, the same variables showed statistical significance except for practising coitus interruptus (see online supplementary table 6).

DISCUSSION
Prevalence of cervical HPV infection

The prevalence of cervical HPV infection (LR-HPV and HR-HPV) in the whole studied population was 13.6% and 11.1% for HR-HPV. HPV prevalence in Spain reported in other published studies ranges from 2.7% to 17.5%.3–15 Two published studies were population-based: one by de Sanjosé et al10 with a random sample of 973 women from the metropolitan area of Barcelona reporting an HPV prevalence of 3.4% (95% CI 2.3 to 4.5), which is rather lower than ours, and one by García et al13 conducted in Castilla y León and reporting 9.6% of HPV prevalence, closer to ours. Differences between both studies could be explained by changes in sexual behaviour in the Spanish population in recent years, with lower age at first sexual intercourse and more sexual partners.16

Non population-based studies include CLEOPATRE (Prevalence and Genotype Distribution of Human Papillomavirus Infection of the Cervix in Spain),9 a study conducted in 17 Autonomous Communities in Spain, using the HC2 test and reporting 14.3% (95% CI 13.1 to 15.5) of HPV prevalence and 12.2% (95% CI 11.1 to 13.4) of HR-HPV infection, both results were similar to ours.

Studies conducted in other European countries reported varied results, with diverse populations and different HPV testing methods. In a review of 18 European studies conducted in 14 countries using the HPV-test as first screening (HC2 or PCR) the HR-HPV prevalence, standardised by age, ranged from 1.7% in Spain to 12.5% in Belgium.17 Bruni et al in a meta-analysis including 1 million women worldwide with normal cytological findings observed 8.8% global adjusted HPV prevalence in Southern Europe, 9% in Western Europe and 10% in Northern Europe.18 Studies conducted among women from different European screening programmes showed HPV prevalences ranging from 6.4% in Germany,19 8.8% in Italy,20 13.7% in France,21 15.2% in Belgium,22 19.4% in Portugal23 to 26.4% in a population-based study in Denmark.24

Prevalence of cervical HPV infection per age group

As expected, the highest HPV prevalence found in our study was observed in women aged 18–24 years (26.7%), an age group potentially associated with a higher number of sexual partners. This finding was also observed in previous Spanish and European studies.9 16 17 In our study, after this first peak in women <25 years, the prevalence declines in older ages, although a slightly, not significant, increased was observed in women older than 55 years. This second peak in older women was also reported by other authors.17 18 20–22 Such a bimodal pattern could be due to changes in the sexual behaviour or the reactivation of latent viral infections.25 HPV types and their variants in such infections, individual susceptibility or regional differences in the screening programmes.18

HPV genotypes

HPV 16 was the most prevalent genotype in our population, present in 27.8% of positive samples. This prevalence was similar to that reported in other studies in Spain,10 14 although higher than the 16.9% found in the CLEOPATRE study.9 After HPV 16, the most frequent types in decreasing order were: HPV 51, 53, 59, 31 and 52. Our results are similar to most studies conducted in Spain9–11 14 and other European countries.10 21–24
### Table 3  Human papillomavirus (HPV) type-specific distribution of the most common types (n=6010 women)

| HPV type | Number of HPV-positive women (n=820) | HPV prevalence among all women (n=6010) (%; 95% CI) | HPV prevalence among positive women (n=820) (%; 95% CI) |
|----------|--------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Single types** | | | |
| **HPV prevalence among positive women (n=820) (%; 95% CI)** | | | |
| **HR HPV types** | | | |
| 16 | 75 | 1.2 (1.0 to 1.5) | 9.1 (7.2 to 11.1) |
| 51 | 34 | 0.6 (0.4 to 0.8) | 4.1 (2.8 to 5.5) |
| 53 | 28 | 0.5 (0.3 to 0.6) | 3.4 (2.2 to 4.7) |
| 31 | 16 | 0.3 (0.1 to 0.4) | 2.0 (1.0 to 2.9) |
| 59 | 14 | 0.2 (0.1 to 0.4) | 1.7 (0.8 to 2.6) |
| 33, 68, 70 | 11 each | 0.2 (0.1 to 0.3)† | 1.3 (0.6 to 2.1)† |
| 66 | 10 | 0.2 (0.1 to 0.3) | 1.2 (0.5 to 2.0) |
| **52 to 58** | **Nine each** | **0.1 (0.1 to 0.2)†** | **1.1 (0.4 to 1.8)†** |
| 18 | 8 | 0.1 (0.0 to 0.2) | 1.0 (0.3 to 1.6) |
| 56 | 7 | 0.1 (0.0 to 0.2) | 0.9 (0.2 to 1.5) |
| **35 to 39** | **Five each** | **0.1 (0.0 to 0.2)†** | **0.6 (0.1 to 1.1)†** |
| 73 | 4 | 0.1 (0.0 to 0.1) | 0.5 (0.0 to 1.0) |
| 45 | 3 | 0.0 (0.0 to 0.1) | 0.4 (0.0 to 0.8) |
| 67 | 2 | 0.0 (0.0 to 0.1) | 0.2 (0.1 to 0.6) |
| 69, 69/71 | One each | 0.0 (0.0 to 0.0)† | 0.1 (0.1 to 0.4)† |
| **LR HPV types** | | | |
| 42 | 17 | 0.3 (0.1 to 0.4) | 2.1 (1.1 to 3.0) |
| 84 | 12 | 0.2 (0.1 to 0.3) | 1.5 (0.6 to 2.3) |
| 62 | 11 | 0.2 (0.1 to 0.3) | 1.3 (0.6 to 2.1) |
| 61 | 10 | 0.2 (0.1 to 0.3) | 1.2 (0.5 to 2.0) |
| 6, 55, 81 | 9 | 0.1 (0.1 to 0.2) | 1.1 (0.4 to 1.8) |
| 89 | 5 | 0.1 (0.0 to 0.2) | 0.6 (0.1 to 1.1) |
| 54 | 4 | 0.1 (0.0 to 0.1) | 0.5 (0.0 to 1.0) |
| 11, 43, 72, 83 | Two each | 0.0 (0.0 to 0.1)† | 0.2 (0.1 to 0.6)† |
| 40 | 1 | 0.0 (0.0 to 0.0) | 0.1 (0.1 to 0.4) |
| **Untyped HPV** | **28** | **0.5 (0.3 to 0.6)** | **3.4 (2.2 to 4.7)** |
| **Multiple types** | **433** | **7.2 (6.6 to 7.9)** | **52.8 (49.4 to 56.2)** |
| **Number of multiple types** | | | |
| Two types | 203 | 3.4 (2.9 to 3.8) | 24.8 (21.8 to 27.7) |
| Three types | 115 | 1.9 (1.6 to 2.3) | 14.0 (11.6 to 16.4) |
| Four types | 73 | 1.2 (0.9 to 1.5) | 8.9 (7.0 to 10.9) |
| Five or more types | 42 | 0.7 (0.5 to 0.9) | 5.1 (3.6 to 6.6) |

**Most frequent combinations**

| 16 with others | 153 | 2.5 (2.1 to 2.9) | 18.7 (16 to 21.3) |
| 53 with others | 81 | 1.3 (1.1 to 1.6) | 9.9 (7.8 to 11.9) |
| 51 with others | 78 | 1.3 (1.0 to 1.6) | 9.5 (7.5 to 11.5) |
| 59 with others | 67 | 1.1 (0.8 to 1.4) | 8.2 (6.3 to 10.0) |
| 42 with others | 59 | 1.0 (0.7 to 1.2) | 7.2 (5.4 to 9.0) |
| 31 with others | 54 | 0.9 (0.7 to 1.1) | 6.6 (4.9 to 8.3) |
| 52 with others | 54 | 0.9 (0.7 to 1.1) | 6.6 (4.9 to 8.3) |
| 66 with others | 50 | 0.8 (0.6 to 1.1) | 6.1 (4.5 to 7.7) |
| 54 with others | 48 | 0.8 (0.6 to 1.0) | 5.9 (4.2 to 7.5) |

Continued
Many studies have reported the percentage of multiple infections ranging from 8.1% in Spain to 54.3% in Denmark. The one from Denmark was similar to ours (52.8%), although it included a higher percentage of infections by more HPV types. This finding could be explained by the use of a HPV detection technique (hybridisation technology) with a high sensitivity for detecting multiple infections.

### Table 3

| HPV type              | Number of HPV positive women (n=820) | HPV prevalence among all women (n=6010) (%) | HPV prevalence among positive women (n=820) (%) |
|-----------------------|--------------------------------------|--------------------------------------------|-----------------------------------------------|
| 62 with others        | 46                                   | 0.8 (0.5 to 1.0)                           | 5.6 (4.0 to 7.2)                              |
| 89 with others        | 46                                   | 0.8 (0.5 to 1.0)                           | 5.6 (4.0 to 7.2)                              |
| 61 with others        | 44                                   | 0.7 (0.5 to 0.9)                           | 5.4 (3.8 to 6.9)                              |
| 56 with others        | 43                                   | 0.7 (0.5 to 0.9)                           | 5.2 (3.7 to 6.8)                              |
| 18 with others        | 42                                   | 0.7 (0.5 to 0.9)                           | 5.1 (3.6 to 6.6)                              |
| 58 with others        | 42                                   | 0.7 (0.5 to 0.9)                           | 5.1 (3.6 to 6.6)                              |
| 84 with others        | 38                                   | 0.6 (0.4 to 0.8)                           | 4.6 (3.2 to 6.1)                              |
| 39 with others        | 37                                   | 0.6 (0.4 to 0.8)                           | 4.5 (3.1 to 5.9)                              |
| 45 with others        | 34                                   | 0.6 (0.4 to 0.8)                           | 4.1 (2.8 to 5.5)                              |
| 68 with others        | 32                                   | 0.5 (0.3 to 0.7)                           | 3.9 (2.6 to 5.2)                              |
| 81 with others        | 28                                   | 0.5 (0.3 to 0.6)                           | 3.4 (2.2 to 4.7)                              |
| six with others       | 25                                   | 0.4 (0.3 to 0.6)                           | 3.0 (1.9 to 4.2)                              |
| 73 with others        | 23                                   | 0.4 (0.2 to 0.5)                           | 2.8 (1.7 to 3.9)                              |
| 33 with others        | 20                                   | 0.3 (0.2 to 0.5)                           | 2.4 (1.4 to 3.5)                              |
| 35 with others        | 19                                   | 0.3 (0.2 to 0.5)                           | 2.3 (1.3 to 3.3)                              |
| 55 with others        | 18                                   | 0.3 (0.2 to 0.4)                           | 2.2 (1.2 to 3.2)                              |
| 70 with others        | 15                                   | 0.2 (0.1 to 0.4)                           | 1.8 (0.9 to 2.7)                              |
| 83 with others        | 15                                   | 0.2 (0.1 to 0.4)                           | 1.8 (0.9 to 2.7)                              |
| 67 with others        | 13                                   | 0.2 (0.1 to 0.3)                           | 1.6 (0.7 to 2.4)                              |
| 82 with others        | 13                                   | 0.2 (0.1 to 0.3)                           | 1.6 (0.7 to 2.4)                              |
| 40 with others        | 10                                   | 0.2 (0.1 to 0.3)                           | 1.2 (0.5 to 2.0)                              |
| 71 with others        | 9                                    | 0.1 (0.1 to 0.2)                           | 1.1 (0.4 to 1.8)                              |
| 11 with others        | 8                                    | 0.1 (0.0 to 0.2)                           | 1.0 (0.3 to 1.6)                              |
| 72 with others        | 8                                    | 0.1 (0.0 to 0.2)                           | 1.0 (0.3 to 1.6)                              |
| 74 with others        | 6                                    | 0.1 (0.0 to 0.2)                           | 0.7 (0.1 to 1.3)                              |
| 69 with others        | 5                                    | 0.1 (0.0 to 0.2)                           | 0.6 (0.1 to 1.1)                              |
| 64 with others        | 2                                    | 0.0 (0.0 to 0.1)                           | 0.2 (0.0 to 0.6)                              |
| 69/71 with others     | 2                                    | 0.0 (0.0 to 0.1)                           | 0.2 (0.0 to 0.6)                              |
| 43 with others        | 0                                    | 0.0 (0.0 to 0.0)                           | 0.0 (0.0 to 0.0)                              |

#### Combinations of vaccine types

| HPV type | Number | HPV prevalence among all women (%) | HPV prevalence among positive women (%) |
|----------|--------|-----------------------------------|-----------------------------------------|
| 6/11§    | 43     | 0.7 (0.5 to 0.9)                  | 5.2 (3.7 to 6.8)                        |
| 16/18§   | 261    | 4.3 (3.8 to 4.9)                  | 31.8 (28.6 to 35.0)                     |
| 6/11/16/18§ | 297 | 4.9 (4.4 to 5.5)                  | 36.2 (32.9 to 39.5)                     |
| 6/11/16/18/31/33/45/52/58§ | 444 | 7.4 (6.7 to 8.0)                  | 54.1 (50.7 to 57.6)                     |

Bold is used to highlight the three main groups of determinations: single, multiple and untyped.

*HR types include high-risk types and possibly/probably high-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 53, 66, 67, 68, 69, 69/71, 70, 73.

†HPV prevalence for each of the types in the row.

‡LR types include 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89.

§One or more of the vaccine types are concerned.

HPV, human papillomavirus; HR, high-risk; LR, low risk.
| Study sample characteristics | Number of HPV positive women / number of HPV tested women | HPV prevalence (%) | Basic model* POR (95% CI) | Adjusted model† POR (95% CI) |
|-----------------------------|--------------------------------------------------------|--------------------|---------------------------|-----------------------------|
| **Population**              |                                                        |                    |                           |                             |
| Gran Canaria                | 501/3847                                               | 13.0               | 1.0 (ref)                 | 1.0 (ref)                   |
| Tenerife                    | 319/2163                                               | 14.7               | 1.1 (0.98 to 1.3)         | 1.0 (0.8 to 1.1)            |
| **Country of birth**        |                                                        |                    |                           |                             |
| Spain                       | 711/5331                                               | 13.3               | 1.0 (ref)                 | 1.0 (ref)                   |
| Europe (excluding Spain)    | 17/109                                                 | 15.6               | 1.3 (0.8 to 2.2)          | 0.8 (0.5 to 1.5)            |
| Africa                      | 8/33                                                    | 24.2               | **2.7 (1.2 to 6.0)**      | 2.3 (0.99 to 5.4)           |
| Latin America and Caribbean | 51/309                                                 | 16.5               | 1.3 (0.9 to 1.8)          | 1.2 (0.8 to 1.7)            |
| Asia and Oceania            | 2/29                                                   | 6.9                | 0.6 (0.1 to 2.5)          | 0.8 (0.2 to 3.5)            |
| Missing data                | 31/199                                                 | –                  | –                         | –                           |
| Outside Spain (include all countries) | 78/480                                           | 16.3               | **1.3 (1.0 to 1.7)**      | 1.1 (0.9 to 1.5)            |
| **Age distribution (years)**|                                                        |                    |                           |                             |
| 18–24                       | 151/565                                                | 26.7               | **3.8 (2.6 to 5.4)**      | **2.1 (1.3 to 3.2)**        |
| 25–29                       | 145/655                                                | 22.1               | **3.0 (2.1 to 4.2)**      | **1.6 (1.0 to 2.4)**        |
| 30–34                       | 161/894                                                | 18.0               | **2.3 (1.6 to 3.4)**      | **1.3 (0.9 to 2.0)**        |
| 35–39                       | 96/890                                                 | 10.8               | 1.3 (0.9 to 1.8)          | 0.8 (0.5 to 1.2)            |
| 40–44                       | 79/783                                                 | 10.1               | 1.2 (0.8 to 1.7)          | 0.8 (0.5 to 1.2)            |
| 45–49                       | 59/622                                                 | 9.5                | 1.1 (0.7 to 1.7)          | 0.7 (0.5 to 1.1)            |
| 50–54                       | 43/607                                                 | 7.1                | 0.8 (0.5 to 1.2)          | **0.6 (0.4 to 0.9)**        |
| 55–59                       | 42/495                                                 | 8.5                | 1.0 (0.6 to 1.5)          | 0.8 (0.5 to 1.3)            |
| 60–65                       | 44/499                                                 | 8.8                | 1.0 (ref)                 | 1.0 (ref)                   |
| **P value for trend**       |                                                        |                    |                           |                             |
| Level of education          |                                                        |                    |                           |                             |
| None / Preschool            | 40/449                                                 | 8.9                | 1.0 (ref)                 | 1.0 (ref)                   |
| Primary                     | 307/2649                                               | 11.6               | 1.0 (0.7 to 1.5)          | 1.0 (0.7 to 1.4)            |
| Secondary                   | 241/1477                                               | 16.3               | 1.1 (0.8 to 1.6)          | 0.9 (0.6 to 1.3)            |
| University or higher        | 213/1331                                               | 16.0               | 1.2 (0.8 to 1.7)          | 0.9 (0.6 to 1.4)            |
| Others                      | 18/95                                                  | 18.9               | 1.2 (0.6 to 2.2)          | 1.1 (0.5 to 2.0)            |
| Missing data                | 1/9                                                    | –                  | –                         | –                           |
| **P value for trend (excluding others)** |                                                        |                    |                           |                             |
| Marital status              |                                                        |                    |                           |                             |
| Single                      | 329/1379                                               | 23.9               | **2.0 (1.6 to 2.4)**      | **1.5 (1.2 to 1.9)**        |
| Married/de facto partnership| 347/3872                                               | 9.0                | 1.0 (ref)                 | 1.0 (ref)                   |
| Divorced/separated          | 118/560                                                | 21.1               | **3.0 (2.4 to 3.8)**      | **1.8 (1.4 to 2.4)**        |
| Widowed                     | 25/191                                                 | 13.1               | **2.1 (1.3 to 3.2)**      | **1.7 (1.0 to 2.6)**        |
| Missing data                | 1/8                                                    | –                  | –                         | –                           |
| **Number of live births**   |                                                        |                    |                           |                             |
| No‡                         | 279/1346                                               | 20.7               | 1.0 (ref)                 | 1.0 (ref)                   |
| 1                           | 157/1222                                               | 12.8               | **0.8 (0.6 to 0.9)**      | **0.8 (0.6 to 1.1)**        |
| 2                           | 171/1760                                               | 9.7                | **0.7 (0.6 to 0.9)**      | **1.0 (0.7 to 1.3)**        |
| 3                           | 80/781                                                 | 10.2               | 0.9 (0.6 to 1.2)          | 1.2 (0.8 to 1.7)            |
| ≥4                          | 37/458                                                 | 8.1                | 0.7 (0.5 to 1.1)          | 0.9 (0.6 to 1.4)            |
| Missing data                | 96/443                                                 | –                  | –                         | –                           |
| Smoking status              |                                                        |                    |                           |                             |

Continued
which were included in the bivalent vaccine. Regarding HPV types included in the quadrivalent vaccine (HPV 6, 11, 16 and 18), at least one of them was found in 36.2% of women (4.9% of the total population). This prevalence increased up to 54.1% with the addition of HPV types 31/33/45/52/58, included in the nonavalent vaccine. Such proportions were higher than those reported in Denmark 24 (27.7%) and in the CLEOPATRE study (22.1% in Spain 9 and 32.6% in Portugal 23). These data illustrate the degree of protection offered by HPV vaccines; one out of three HPV-infected women would have been protected by the bivalent or the quadrivalent vaccine and one out of two women would have been protected by the nonavalent one. However, the frequency of HPV types 51, 53, 59,…
frequently found in our population, indicate the need to continue the cytological screening population.

Cytological study and cervical HPV infection
Cytological alterations found in our study (5.3%) were similar to those observed in other studies, both in Spain9 10 14 and Europe,19 20 22–24 ranging between 1.6% and 7%. The HPV prevalence increased with lesion severity (60.7% in women with ASCUS; 86.8% in women with LSIL and 83.3% in women with HSIL+). This finding was in agreement with other published studies.9 10 12 19 21–23

The HPV prevalence in normal cytologies was 10.6%, similar to that reported by Bruni et al in our geographical area (8.8%), although lower than that reported in most studies.9 21–24

Risk factors and cervical HPV infection
Age consistently appears as a risk factor for HPV infection, both in our study and other published ones,14 20 26 27 directly associated with younger women’s sexual behaviour as compared with older ones.

Number of sexual partners in life extensively appears9 10 14 26–28 as a risk factor for HPV infection and was the factor with the largest impact in our study. As in our study, most authors failed to find a relationship with age at first intercourse.10 26 27 This later parameter seems to influence number of sexual partners but does not seem to be an independent risk factor for HPV infection.

In our analysis, not being married (divorced, widow or single) was a statistically significant risk factor for HPV infection, as was also reported in other studies.10 20 26 27 This finding could be explained by the sexual behaviour of not married women, who may probably have more sexual partners.

Coitus interruptus was the only contraception-related practice found to be associated with higher risk of any-type HPV infection, both in the basic and the adjusted models, although such an association was not found for HR-HPV types. This factor might possibly be linked to younger groups, where other risk increasing factors coexist.

Smoking was a risk factor for HPV infection in our population, in accordance with data reported by other authors,26 27 28 although not by others.10 Quitting smoking has been considered to potentially revert infection risk.25 In order to explain for the relationship between smoking and increased risk of HPV infection, it has been postulated that tobacco and its metabolites may alter the immune system of the cervical epithelium, thus reducing the number of CD4 lymphocytes and Langerhans cells25 and impairing the activity of natural killer cells.

The presence of genital warts and previous cervical alterations was associated with higher risk in our population, as well as in other studies,26 which is not surprising since both events are directly related.

Country of origin especially African ones, appeared as a risk factor for HPV infection in our basic model, although not in our adjusted model. Earlier published Spanish studies showed higher HPV infection risk in women born out of Spain,10 11 26 probably due to differences in the sexual behaviour of men and women.

Regarding parity and HPV infection risk, similar to other authors,29 we found some protective effect in women with one or two births in our basic model for any-type HPV, although not for the adjusted model or for HR-HPV types, a finding also reported by some authors.10 26 27 In a meta-analysis published by the IARC,30 a slight risk increase in nulliparous women (younger and more sexually active) as compared with women who have been pregnant was described.

The relationship between taking oral contraceptives (OC) and the risk of HPV infection is controversial. In our population, a slightly increased risk was found for women taking OC in the basic model though not in the adjusted model, a finding also described in other studies.26 27 30

Infection by other sexually transmitted diseases analysed in our population increased the risk in the basic model but not in the adjusted model (data not shown), consistent with other published studies.26 27

Some authors have reported no association between using condoms and increased risk of HPV infection14 26 27 28; some even reported some protective effect.26 In our study, like with other contraceptive methods we failed to find an association with HPV infection (data not shown). The evidence is controversial regarding the association between HPV infection and level of education,26 27 31

Strengths and weaknesses
One of the main strengths of our study was our population-based design, which covered the main healthcare centres on the islands and recruited potential participants from an official source, ensuring a random sample. Additionally, the fact that all cytological and molecular studies were conducted in the same laboratory, by the same technical and medical staff, using highly sensitive and partially automated analytic systems ensured consistency, homogeneity and reproducibility of diagnostic methods.

The prolonged recruitment time was a weakness of this study. Three years were needed for Tenerife and 6 years for Gran Canaria, although 2 years had been originally planned. Potential variations over time could have influenced the sociodemographic characteristics of the population. Thus, the characteristics of participants recruited at the beginning of the recruitment period could have been different from those of women recruited by the end.

CONCLUSIONS
This study provides population-based references for the prevalence of HPV infection in the Canary Islands, which enables future assessment of the impact of HPV vaccination campaigns. The prevalence of HPV infection in the female population of Gran Canaria and Tenerife was high, although similar to that of previous studies conducted in Spain, with genotype HPV 16 being the
most frequent one. These results support the potential benefits of HPV vaccines in terms of reducing infection as well as the consequent development of HPV-related lesions, including cancer.

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**Competing interests**

None declared.

**Patient consent for publication**

Not required.

**Ethics approval**

This study was favourably evaluated by the Ethics and Clinical Trial Committee of the hospital Complejo Hospitalario Universitario Insular Materno Infantil.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data are available on reasonable request. The database obtained from this study is kept under the supervision of the authors (MA and ER) in an anonymised form. These data will be shared in a raw form by emailing to mandsan@gobiernodecanarias.org.

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