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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037402
Article Type:	Original research
Date Submitted by the Author:	31-Jan-2020
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Keywords:	CYTOPATHOLOGY, Gynaecological oncology < GYNAECOLOGY, EPIDEMIOLOGY, INFECTIOUS DISEASES

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PREVALENCE AND GENOTYPE DISTRIBUTION OF CERVICAL HUMAN PAPILOMAVIRUS INFECTION IN THE PRE-VACCINATION ERA: A POPULATION-BASED STUDY IN THE CANARY ISLANDS

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ABSTRACT

Keywords: cytopathology, gynaecological oncology, epidemiology, infectious diseases.

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 socio-demographic factors.

Methods

Based on the Primary Health Care database, a sample of adult women (18-65 years) of Gran Canaria (GC) and Tenerife (TF) stratified into 9 age groups was carried out. Women were contacted by postal letter and telephone call and were visited in their primary care center. A clinical-epidemiological survey was completed and cervical samples were taken for cytological study and HPV detection. HPV prevalence and its 95% confidence interval were estimated, and multivariate analyzes were performed using logistic regression to identify factors associated with the infection.

Results

6,010 women participated in the study, 3,847 from GC and 2,163 from TF. The overall prevalence of HPV infection was 13.6% (12.8-14.5%) and 11.1% (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. The determinants of infection are consistent with those of other populations.

Strengths and limitations of this study:

- This is the first prevalence study of HPV infection in Canary Islands.
- The study design is population-based, including the main healthcare centers of the participant regions.
- Cytological and molecular samples were analyzed in the same laboratory by the same staff, using highly-sensitive and partially automated techniques that ensured consistency, homogeneity and reproducibility of diagnostic methods.
- Study recruitment time was extensive, from three to six years depending on the region.
- Characteristics of the study participants could be different over time .

1. 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.[1] In Spain, cervical cancer is the fifteenth most frequent cancer in women (fourth in women aged 15-44 years), with an estimated 1,942 new cases in 2018.[1] 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,[2] one of the highest incidence rates in Spain.[3]

Human papillomavirus (HPV) is a necessary but not sufficient cause of cervical cancer.[4] More than 200 HPV genotypes are currently known, epidemiologically classified into low-oncogenic risk (LR-HPV) and high-oncogenic risk (HR-HPV) types.[5] HR-HPV types include 16 and 18 genotypes, present in more than 70% of cervical cancer cases[6] and included in the three prophylactic HPV vaccines currently commercialized. [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 behavior in the last decades have leads to increased HPV infection rates (up to 14% in 18-65 years old women, 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 socio-demographic factors associated to HPV infection.

2. METHODS

2.1. Participants

The study was conducted between 2002 and 2007 on a sample of 18-65 years-old-women 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 2,276 women. Subsequently, a group of women from Gran Canaria who requested to participate in the study were included (volunteers). Participants were contacted by letter and a subsequent telephone call. A visit to the nearest healthcare center was scheduled. This study was favorably evaluated by the Ethics and Clinical Trial Committee of our hospital.

2.2. Patient and Public Involvement

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

2.3. Procedures

Participants were asked to fulfill an informed consent form and to complete a clinical and epidemiological questionnaire (adapted from IARC surveys). A cervical sample was collected for cytological study and HPV detection. The cytological sample was obtained using the Papanicolau method. Cytological diagnosis was carried out by one pathologist using the Bethesda system. To detect HPV infection, two separated polymerase chain reactions (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 (Immnogenetics®, Belgium - FUJIREBIO Europe, Belgium).

2.4. Statistical analyses

Descriptive analysis of socio-demographic variables was conducted, globally and stratified according to the study subpopulation (i.e. selected participants from Gran Canaria, volunteers from Gran Canaria, selected participants from Tenerife). Estimated HPV infection prevalence and genotype distribution and corresponding 95% confidence intervals (CI95%) were calculated as the number of HPV positive women among the total number of women 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 to 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 6,091 women were included: 3,212 selected from the general Gran Canaria population (52.7%), 665 volunteers from Gran Canaria (10.9%) and 2,214 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 5 cytological studies in their lives, while 3.5% of them had never undergone 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 sexual first intercourse. Demographic characteristics were slightly different between both islands (data not shown): education level, proportion of smokers and number of sexual partners were statistically higher in Tenerife than in Gran Canaria.

Table 1 – Characteristics of the study participants (n=6,091 women).

Study sample characteristics	N (%)
Distribution by population	
Gran Canaria (general population)	3,212 (52.7)
Gran Canaria (volunteers)	665 (10.9)
Tenerife	2,214 (36.3)
Country of birth	
Spain	5,397 (91.6)
Europe (excluding Spain)	111 (1.9)
Northern Africa	20 (0.3)
Sub-Saharian 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	1,396 (22.9)
Married/de facto partnership	3,919 (64.4)
Divorced/separated	573 (9.4)
Widowed	195 (3.2)
Missing data	8 (-)
Pregnancies	
No	1,343 (22.5)
Yes	4,613 (77.5)
Missing data	135 (-)
Number of live births [1]	
0	28 (0.7)
1	1,237 (28.7)
2	1,786 (41.5)
3	789 (18.3)
4	277 (6.4)
≥5	186 (4.3)
Missing data	310 (-)
Sexually transmitted disease	
Never	5,882 (96.6)
Ever [2]	209 (3.4)
Syphilis [3]	30 (0.5)
Genital herpes [3]	51 (0.8)
Gonorrhea [3]	23 (0.4)
HIV [3]	7 (0.1)
Genital warts [3]	120 (2.0)
Chlamydia [3]	30 (0.5)
Genital ulcer [3]	16 (0.3)
Others [3]	72 (1.2)
Smoking status	
Never smoked	3,443 (56.5)
Ex smoker	913 (15.0)
Current smoker	1,735 (28.5)
Previous cervical pap smears	
None	216 (3.5)
1	493 (8.1)
2-3	1,056 (17.3)
4-5	772 (12.7)
>5	3,273 (53.7)
Do not know	281 (4.6)
Previous cervical lesions [4]	
No	4,837 (92.5)
Yes	385 (7.4)
Do not know	5 (0.1)

Missing data	648 (-)
Age at first sexual intercourse (years)	
<15	187 (3.1)
15-16	828 (13.6)
17-18	1,863 (30.6)
19-20	1,281 (21.0)
21-25	1,421 (23.3)
>25	442 (7.3)
Missing data	69 (-)
Lifetime number of sexual partners	
1	3,232 (53.9)
2-3	1,571 (26.2)
4-5	614 (10.2)
6-10	405 (6.8)
11-20	126 (2.1)
>20	49 (0.8)
Missing data	94 (-)
Contraceptive methods used [5]	
Oral contraceptives	4,664 (76.6)
IUD	1,133 (18.6)
Condom	4,522 (74.2)
Rhythm method/coitus interruptus	3,049 (50.1)
Diaphragm/spermicide	234 (3.8)
Injection/implant	253 (4.2)
Tube ligation	802 (13.2)
Vasectomy	549 (9.0)

[1] Among ever pregnant women (N=4,613). [2] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [3] Do not add the total of women because a woman could have more than one sexually transmitted disease in lifetime. [4] Among women with a previous pap smear (N=5,875). [5] Do not add the total of women because a woman can use more than one contraceptive in lifetime.

Prevalence of cervical HPV infection

For the prevalence study, 6,010 women were included in the analysis after excluding 81 women due to poor DNA quality in their samples. The prevalence of any-type HPV infection was 13.6% (CI95% 12.8-14.5) while the prevalence of HR-HPV infection was 11.1% (CI95% 10.3-11.9). The youngest age group (18-24 years) showed the highest prevalence with 26.7% of any-type HPV infection (CI95% 23.1-30.4). 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 (Table 2).

Table 2 – Prevalence of Human Papillomavirus (HPV) by age group for any type and for any high-risk type (n=6,010 women).

Age group (years)	Number of tested women	Number of HPV positive women	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)
18-24	565	151	26.7 (23.1-30.4)	23.9 (20.4-27.4)
25-29	655	145	22.1 (19.0-25.3)	19.7 (16.6-22.7)
30-34	894	161	18.0 (15.5-20.5)	15.2 (12.9-17.6)
35-39	890	96	10.8 (8.7-12.8)	8.0 (6.2-9.8)
40-44	783	79	10.1 (8.0-12.2)	8.6 (6.6-10.5)
45-49	622	59	9.5 (7.2-11.8)	7.1 (5.1-9.1)
50-54	607	43	7.1 (5.0-9.1)	4.9 (3.2-6.7)
55-59	495	42	8.5 (6.0-10.9)	5.5 (3.5-7.5)
60-65	499	44	8.8 (6.3-11.3)	5.8 (3.8-7.9)
Total	**6,010**	**820**	**13.6 (12.8-14.5)**	**11.1 (10.3-11.9)**

HPV: Human Papillomavirus; HR: High-Risk; CI: Confidence Interval.

[1] HR HPV types includes 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.

Although volunteers from Gran Canaria showed higher prevalence of any-type HPV infection than participants from the general population from both Gran Canaria and Tenerife (14.5%, CI95% 11.8-17.2, versus 12.7%, CI95% 11.6-13.9; data not shown), 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%, CI95% 9.6-11.6, versus 12.1%, CI95% 10.7-13.4, p=0.002; data not shown).

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%).

Table 3 – Human Papillomavirus (HPV) type-specific distribution of the most common types (n=6,010 women).

HPV type	Number of HPV positive women (n=820)	HPV prevalence among all women (n=6,010) (%; 95% CI)	HPV prevalence among positive women (n=820) (%; 95% CI)
Single types	**359**	**6.0 (5.4-6.6)**	**43.8 (40.4-47.2)**
HR HPV types [1]			
16	75	1.2 (1.0-1.5)	9.1 (7.2-11.1)
51	34	0.6 (0.4-0.8)	4.1 (2.8-5.5)
53	28	0.5 (0.3-0.6)	3.4 (2.2-4.7)
31	16	0.3 (0.1-0.4)	2.0 (1.0-2.9)
59	14	0.2 (0.1-0.4)	1.7 (0.8-2.6)
33, 68, 70	11 each	0.2 (0.1-0.3) [4]	1.3 (0.6-2.1) [4]
66	10	0.2 (0.1-0.3)	1.2 (0.5-2.0)
52, 58	9 each	0.1 (0.1-0.2) [4]	1.1 (0.4-1.8) [4]
18	8	0.1 (0.0-0.2)	1.0 (0.3-1.6)
56	7	0.1 (0.0-0.2)	0.9 (0.2-1.5)
35, 39	5 each	0.1 (0.0-0.2) [4]	0.6 (0.1-1.1) [4]
73	4	0.1 (0.0-0.1)	0.5 (0.0-1.0)
45	3	0.0 (0.0-0.1)	0.4 (0.0-0.8)
67	2	0.0 (0.0-0.1)	0.2 (0.1-0.6)
69, 69/71	1 each	0.0 (0.0-0.0) [4]	0.1 (0.1-0.4) [4]
LR HPV types [2]			
42	17	0.3 (0.1-0.4)	2.1 (1.1-3.0)
84	12	0.2 (0.1-0.3)	1.5 (0.6-2.3)
62	11	0.2 (0.1-0.3)	1.3 (0.6-2.1)
61	10	0.2 (0.1-0.3)	1.2 (0.5-2.0)
6, 55, 81	9	0.1 (0.1-0.2)	1.1 (0.4-1.8)
89	5	0.1 (0.0-0.2)	0.6 (0.1-1.1)
54	4	0.1 (0.0-0.1)	0.5 (0.0-1.0)
11, 43, 72, 83	2 each	0.0 (0.0-0.1) [4]	0.2 (0.1-0.6) [4]
40	1	0.0 (0.0-0.0)	0.1 (0.1-0.4)
Untyped HPV	**28**	**0.5 (0.3-0.6)**	**3.4 (2.2-4.7)**
Multiple types	**433**	**7.2 (6.6-7.9)**	**52.8 (49.4-56.2)**
Number of multiple types			
2 types	203	3.4 (2.9-3.8)	24.8 (21.8-27.7)
3 types	115	1.9 (1.6-2.3)	14.0 (11.6-16.4)
4 types	73	1.2 (0.9-1.5)	8.9 (7.0-10.9)
5 or more types	42	0.7 (0.5-0.9)	5.1 (3.6-6.6)

Most frequent combinations			
16 with others	153	2.5 (2.1-2.9)	18.7 (16-21.3)
53 with others	81	1.3 (1.1-1.6)	9.9 (7.8-11.9)
51 with others	78	1.3 (1.0-1.6)	9.5 (7.5-11.5)
59 with others	67	1.1 (0.8-1.4)	8.2 (6.3-10.0)
42 with others	59	1.0 (0.7-1.2)	7.2 (5.4-9.0)
31 with others	54	0.9 (0.7-1.1)	6.6 (4.9-8.3)
52 with others	54	0.9 (0.7-1.1)	6.6 (4.9-8.3)
66 with others	50	0.8 (0.6-1.1)	6.1 (4.5-7.7)
54 with others	48	0.8 (0.6-1.0)	5.9 (4.2-7.5)
62 with others	46	0.8 (0.5-1.0)	5.6 (4.0-7.2)
89 with others	46	0.8 (0.5-1.0)	5.6 (4.0-7.2)
61 with others	44	0.7 (0.5-0.9)	5.4 (3.8-6.9)
56 with others	43	0.7 (0.5-0.9)	5.2 (3.7-6.8)
18 with others	42	0.7 (0.5-0.9)	5.1 (3.6-6.6)
58 with others	42	0.7 (0.5-0.9)	5.1 (3.6-6.6)
84 with others	38	0.6 (0.4-0.8)	4.6 (3.2-6.1)
39 with others	37	0.6 (0.4-0.8)	4.5 (3.1-5.9)
45 with others	34	0.6 (0.4-0.8)	4.1 (2.8-5.5)
68 with others	32	0.5 (0.3-0.7)	3.9 (2.6-5.2)
81 with others	28	0.5 (0.3-0.6)	3.4 (2.2-4.7)
6 with others	25	0.4 (0.3-0.6)	3.0 (1.9-4.2)
73 with others	23	0.4 (0.2-0.5)	2.8 (1.7-3.9)
33 with others	20	0.3 (0.2-0.5)	2.4 (1.4-3.5)
35 with others	19	0.3 (0.2-0.5)	2.3 (1.3-3.3)
55 with others	18	0.3 (0.2-0.4)	2.2 (1.2-3.2)
70 with others	15	0.2 (0.1-0.4)	1.8 (0.9-2.7)
83 with others	15	0.2 (0.1-0.4)	1.8 (0.9-2.7)
67 with others	13	0.2 (0.1-0.3)	1.6 (0.7-2.4)
82 with others	13	0.2 (0.1-0.3)	1.6 (0.7-2.4)
40 with others	10	0.2 (0.1-0.3)	1.2 (0.5-2.0)
71 with others	9	0.1 (0.1-0.2)	1.1 (0.4-1.8)
11 with others	8	0.1 (0.0-0.2)	1.0 (0.3-1.6)
72 with others	8	0.1 (0.0-0.2)	1.0 (0.3-1.6)
74 with others	6	0.1 (0.0-0.2)	0.7 (0.1-1.3)
69 with others	5	0.1 (0.0-0.2)	0.6 (0.1-1.1)
64 with others	2	0.0 (0.0-0.1)	0.2 (0.0-0.6)
69/71 with others	2	0.0 (0.0-0.1)	0.2 (0.0-0.6)
43 with others	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Combinations of vaccine types			
6/11 [3]	43	0.7 (0.5-0.9)	5.2 (3.7-6.8)
16/18 [3]	261	4.3 (3.8-4.9)	31.8 (28.6-35.0)
6/11/16/18 [3]	297	4.9 (4.4-5.5)	36.2 (32.9-39.5)
6/11/16/18/31/33/45/52/58 [3]	444	7.4 (6.7-8.0)	54.1 (50.7-57.6)

HPV: Human Papillomavirus; HR: High-Risk; LR: Low-Risk; CI: Confidence Interval.

[1] HR types includes 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. [2] LR types includes: 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89. [3] One or more of the vaccine types are concerned. [4] HPV prevalence for each of the types in the row.

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 9-valent vaccine were considered. Figure 1 and Supplementary table 1 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% (CI95% 64.0-74.2) of HPV positivity versus 5,693 non-pathological cytologies (94.7%) with 10.6% (CI95% 9.8-11.4) of HPV positivity (supplementary table 2), 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 (supplementary table 3).

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

lineal trend), not married, smokers, more than one sexual partner (statistically significant trend), history of cervical alterations or genital warts, and practicing coitus interruptus (table 4). When only cases of HR-HPV cervical infection were considered, the same variables showed statistical significance except for practicing coitus interruptus (supplementary table 4).

Table 4 – Crude and multivariate analyses of the association between cervical Human Papillomavirus (HPV) infection and selected subjects' characteristics (n=6,010 women).

Study sample characteristics	Number of HPV positive women / number of HPV tested women	HPV prevalence (%)	Basic model [1] POR (95% CI)	Adjusted model [2] POR (95% CI)
Population				
Gran Canaria	501 / 3,847	13.0	1.0 (ref)	1.0 (ref)
Tenerife	319 / 2,163	14.7	1.1 (0.98-1.3)	1.0 (0.8-1.1)
Country of birth				
Spain	711 / 5,331	13.3	1.0 (ref)	1.0 (ref)
Europe (excluding Spain)	17 / 109	15.6	1.3 (0.8-2.2)	0.8 (0.5-1.5)
Africa	8 / 33	24.2	**2.7 (1.2-6.0)**	2.3 (0.99-5.4)
Latin America and Caribbean	51 / 309	16.5	1.3 (0.9-1.8)	1.2 (0.8-1.7)
Asia and Oceania	2 / 29	6.9	0.6 (0.1-2.5)	0.8 (0.2-3.5)
Missing data	31 / 199	-	-	-
Outside Spain (include all countries)	78 / 480	16.3	**1.3 (1.0-1.7)**	1.1 (0.9-1.5)
Age distribution (years)				
18-24	151 / 565	26.7	**3.8 (2.6-5.4)**	**2.1 (1.3-3.2)**
25-29	145 / 655	22.1	**3.0 (2.1-4.2)**	**1.6 (1.0-2.4)**
30-34	161 / 894	18.0	**2.3 (1.6-3.4)**	1.3 (0.9-2.0)
35-39	96 / 890	10.8	1.3 (0.9-1.8)	0.8 (0.5-1.2)
40-44	79 / 783	10.1	1.2 (0.8-1.7)	0.8 (0.5-1.2)
45-49	59 / 622	9.5	1.1 (0.7-1.7)	0.7 (0.5-1.1)
50-54	43 / 607	7.1	0.8 (0.5-1.2)	**0.6 (0.4-0.9)**
55-59	42 / 495	8.5	1.0 (0.6-1.5)	0.8 (0.5-1.3)
60-65	44 / 499	8.8	1.0 (ref)	1.0 (ref)
p-value for trend			***p<0.001***	***p<0.001***
Level of education				
None / Preschool	40 / 449	8.9	1.0 (ref)	1.0 (ref)
Primary	307 / 2,649	11.6	1.0 (0.7-1.5)	1.0 (0.7-1.4)
Secondary	241 / 1,477	16.3	1.1 (0.8-1.6)	0.9 (0.6-1.3)
University or higher	213 / 1,331	16.0	1.2 (0.8-1.7)	0.9 (0.6-1.4)
Others	18 / 95	18.9	1.2 (0.6-2.2)	1.1 (0.5-2.0)

Missing data	1 / 9	-	-	-
p-value for trend (excluding others)			*p=0.2*	*p=0.5*
Marital status				
Single	329 / 1,379	23.9	**2.0 (1.6-2.4)**	**1.5 (1.2-1.9)**
Married/de facto partnership	347 / 3,872	9.0	1.0 (ref)	1.0 (ref)
Divorced/separated	118 / 560	21.1	**3.0 (2.4-3.8)**	**1.8 (1.4-2.4)**
Widowed	25 / 191	13.1	**2.1 (1.3-3.2)**	**1.7 (1.0-2.6)**
Missing data	1 / 8	-	-	-
Number of live births				
No [3]	279 / 1,346	20.7	1.0 (ref)	1.0 (ref)
1	157 / 1,222	12.8	**0.8 (0.6-0.9)**	0.8 (0.6-1.1)
2	171 / 1,760	9.7	**0.7 (0.6-0.9)**	1.0 (0.7-1.3)
3	80 / 781	10.2	0.9 (0.6-1.2)	1.2 (0.8-1.7)
≥4	37 / 458	8.1	0.7 (0.5-1.1)	0.9 (0.6-1.4)
Missing data	96 / 443	-	-	-
Smoking status				
Never smoked	376 / 3,402	11.1	1.0 (ref)	1.0 (ref)
Ex smoker	126 / 900	14.0	**1.4 (1.1-1.7)**	1.2 (0.9-1.5)
Current smoker	318 / 1,708	18.6	**1.7 (1.5-2.1)**	**1.2 (1.0-1.5)**
Age at first sexual intercourse (years)				
<15	40 / 184	21.7	1.5 (0.95-2.5)	0.7 (0.4-1.2)
15-16	166 / 817	20.3	1.4 (0.99-2.1)	0.8 (0.5-1.2)
17-18	273 / 1,835	14.9	1.1 (0.8-1.6)	0.7 (0.5-1.1)
19-20	143 / 1,266	11.3	0.9 (0.7-1.3)	0.7 (0.5-1.1)
21-25	146 / 1,402	10.4	1.0 (0.7-1.4)	0.9 (0.6-1.3)
>25	45 / 437	10.3	1.0 (ref)	1.0 (ref)
Missing data	7 / 69	-	-	-
p-value for trend			***p=0.001***	*p=0.3*
Lifetime number of sexual partners				
1	214 / 3,189	6.7	1.0 (ref)	1.0 (ref)
2-3	274 / 1,545	17.7	**2.7 (2.2-3.3)**	**2.3 (1.9-2.8)**
4-5	141 / 613	23.0	**3.6 (2.8-4.6)**	**2.8 (2.2-3.6)**
6-10	119 / 395	30.1	**5.3 (4.0-6.9)**	**3.9 (2.9-5.2)**
11-20	41 / 126	32.5	**5.9 (3.9-8.8)**	**4.2 (2.8-6.5)**
>20	18 / 49	36.7	**8.1 (4.4-14.8)**	**6.2 (3.3-11.5)**
Missing data	13 / 93	-	-	-
p-value for trend			***p<0.001***	***p<0.001***
Use of oral contraceptives				
Never	164 / 1,404	11.7	1.0 (ref)	1.0 (ref)
Ever	656 / 4,606	14.2	**1.2 (1.0-1.5)**	1.1 (0.9-1.4)
Rhythm method/coitus interruptus				
Never	381 / 2,998	12.7	1.0 (ref)	1.0 (ref)
Ever	439 / 3,012	14.6	**1.3 (1.1-1.5)**	**1.2 (1.0-1.4)**
Previous cervical lesions				
No	645 / 4,986	12.9	1.0 (ref)	1.0 (ref)
Yes	84 / 378	22.2	**2.1 (1.6-2.7)**	**1.6 (1.2-2.1)**
Missing data [4]	91 / 646	-	-	-
Genital warts				
Never	783 / 5,894	13.3	1.0 (ref)	1.0 (ref)
Ever	37 / 116	31.9	**2.8 (1.8-4.2)**	**1.7 (1.1-2.6)**

[1] Basic model: adjusted for age group (18-24, 25-34, 35-44, 45-54, 55-65) and population (Gran Canaria, Tenerife). [2] Adjusted model: adjusted for age group, population, level of education, marital status, smoking habits, lifetime number of sexual partners, previous cervical lesions, ever use of rhythm method, and ever had genital warts. [3] Includes women who were pregnant but had 0 live births. [4] Includes "Do not know" in the "Missing data" category. [5] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [6] Excludes ever had genital warts in the adjustment.

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%.[9-15] Two published studies were population-based: one by de Sanjosé et al.[10] (2003) with a random sample of 973 women from the metropolitan area of Barcelona reporting an HPV prevalence of 3.4% (CI95% 2.3-4.5), which is rather lower than ours, and one by García et al.[15] (2017) 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 behavior 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[9], a study conducted in 17 Autonomous Communities in Spain, using the HC2 test and reporting 14.3% (CI95% 13.1-15.5) of HPV prevalence and 12.2% (CI95% 11.1-13.4) 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, standardized by age, ranged from 1.7% in Spain to 12.5% in Belgium.[17] Bruni et al. (2010) in a meta-analysis including one 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 programs 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 Portugal[23] 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. In our study, after this first peak in women less than 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.[17,18,20,21,22] Such a bimodal pattern could be due to changes in the sexual behavior or the reactivation of latent viral infections[25], HPV types and their variants in such infections, individual susceptibility or regional differences in the screening programs.[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] though 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 Spain[9,10,11,14] and other European countries.[19,21,22,23,24]

Many studies have reported the percentage of multiple infections[9,12,13,15,18,19,20,21,23,24] ranging from 8.1% in Spain[13] to 54.3% in Denmark.[24] 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 (hybridization technology) with a high sensitivity for detecting multiple infections.

A total of 31.8% of HPV positive women (4.3% of the total population) were infected by types 16 and/or 18, 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; 1 out of 3 HPV infected women would have been protected by the bivalent or the quadrivalent vaccine and 1 out of 2 women would have been protected by the nonavalent one.

Cytopathological study and cervical HPV infection

Cytological alterations found in our study (5.3%) were similar to those observed in other studies, both in Spain[9,10,14] and Europe[19,20,22,23,24], 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.[9,10,12,19,21,22,23,24] The HPV prevalence in normal

cytologies was 10.6%, similar to that reported by Bruni et al.[18] in our geographical area (8.8%), though lower than that reported in most studies.[9,21,22,23,24]

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 behavior as compared to older ones.

Number of sexual partners in life extensively appears[10,11,14,26,27,28] 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] This finding could be explained by the sexual behavior of not married women, who may probably have more sexual partners.

Coitus interruptus was the only contraception related practice found to be associated to 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[26,27,29] though not by others.[10] Quitting smoking has been considered to potentially revert infection risk.[29] 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 cells[29] 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, though 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 behavior of men and women.

Regarding ***parity*** and HPV infection risk, similarly to other authors[20], we found some protective effect in women with one or two births in our basic model for any-type HPV, though 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.[10,20,26,27,30]

Infection by other ***sexually transmitted diseases*** analyzed 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 infenction;[14,20,27,28] 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).

Strengths and weaknesses

One of the main strengths of our study was our population-based design, which covered the main healthcare centers 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 six years for Gran Canaria, although two years had been originally planned. Potential variations over time could have influenced the socio-demographic 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.

ACKNOWLEDGEMENTS

We would like to acknowledge all patients for their participation in the study. We would also like to thank our colleagues and the study staff for their commitment to data collection. We are very grateful to Tenesoya Alamo, Tanausú de la Cruz and Maria Dolores Navarro for technical assistance. We have received donations of analytical kits from Sanofi Pasteur MSD (Merck Sharp & Dome Corp.), Roche Diagnostics® SL and Fujirebio® Ibérica SL.

COMPETING INTERESTS: None declared.

FUNDING

This research has been funded by: Fondo de Investigación Sanitaria (Instituto de Salud Carlos III), grant FIS 00/714; Fundación Canaria de Investigación y Salud, grant FUNCIS 00/14 and FUNCIS 02/19. Funders had no involvement in the study design, collection, analysis, interpretation of the data, writing of the report nor in the decision to submit the paper for publication.

CONTRIBUTORSHIP STATEMENT

MA designed the study, performed HPV diagnostic molecular methods, data analysis, interpretation of data, and drafted the manuscript. ER performed statistical analysis of data, designed the figures and drafted the manuscript. MP performed cytopathological

diagnosis. MS performed HPV diagnostic molecular methods. MAS designed and supervised a base data and processed the experimental data. AT, BV, LA, RH, HPV Canary Study Group received the patients and took cervical samples. MCC and ARdP were involved in planning and supervised the management of cervical a molecular samples. AL, JLT, OA, VB, NM, SC, AQ treated patients with cytological and molecular disorders. LB, SS and ES aided in interpreting the results and worked on the manuscript. All authors read and approved the final manuscript.

DATA SHARING

The database obtained from this study is kept under the supervision of the authors (Andujar M & Fornell R) in an anonymized form. This data will be shared in a raw form by emailing to mandsan@gobiernodecanarias.org.

REFERENCES

1. Ferlay J, Ervik M, Lam F, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today [accessed September, 2, 2019].
2. Health Service, Government of Canary Islands. Available from: http://www3.gobiernodecanarias.org/sanidad/scs [accessed September 2, 2019].
3. Bray F, Colombet M, Mery L, Piñeros M, et al, editors (2017) Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr [accessed September 2, 2019].

4. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244-65.
5. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518-27.
6. de Sanjose S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010;11:1048-56.
7. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine* 2012;30 Suppl 5:F123-38.
8. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 2015;372:711-23.
9. Castellsagué X, Iftner T, Roura E, et al. Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: The CLEOPATRE Study. *J Med Virol* 2012;84:947-56.
10. de Sanjose S, Almirall R, Lloveras B, et al. Cervical human papillomavirus infection in the female population in Barcelona, Spain. *Sex Transm Dis* 2003;30:788-93.
11. González C, Ortiz M, Canals J, et al. Higher prevalence of Human Papillomavirus infection in migrant women from Latin America in Spain. *Sex Transm Infect* 2006;82:260-62.
12. Bernal M, Burillo I, Mayordomo JI, Moros M, Benito R, Gil J. Human Papillomavirus (HPV) infection and intraepithelial neoplasia and invasive cancer of the uterine cervix: a case-control study in Zaragoza, Spain. *Infect Agent Cancer* 2008;3:8.
13. Martorell M, García-García JA, Ortiz C, et al. Prevalence and distribution of human papillomavirus findings in swab specimens from gynaecology clinics of the east coast of Spain. *Scand J Infect Dis* 2010;42:549-53.

14. Trigo-Daporta M, García-Campello M, Pérez-Ríos M,. High-risk human papillomavirus in Galicia, Spain: prevalence and evaluation of the sample representativeness. *Scand J Infect Dis* 2014;46:737-44.

15. García S, Dominguez-Gil M, Gayete J, et al. [Prevalence of human papillomavirus in Spanish women from a population screening program]. *Rev Esp Quimioter* 2017;30:177-82.

16. de Sanjosé S, Cortés X, Méndez C, et al. Age at sexual initiation and number of sexual partners in the female Spanish population: Results from the AFRODITA survey. *Eur J Obstet Gynecol Reprod Biol* 2008;140:234–40.

17. de Vuyst H, Clifford G, Li N, Franceschi S. HPV infection in Europe. *Eur J Cancer* 2009;45:2632-9.

18. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S. Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010;202:1789–99.

19. Klug SJ, Hukelmann M, Hollwitz B, et al. Prevalence of human papillomavirus types in women screened by cytology in Germany. *J Med Virol* 2007;79:616-25.

20. Ronco G, Ghisetti V, Segnan N, et al. Prevalence of human papillomavirus infection in women in Turin, Italy. *Eur J Cancer* 2005;41:297-305.

21. Heard I, Tondeur L, Arowas L, Falguieres m, Demazoin MC, Favre M. Human papillomavirus types distribution in organized cervical cancer screening in France. *PloS One* 2013;8:e79372.

22. Arbyn M, Benoy I, Simoens C, Bogers J, Beutels P, Depuydt C. Prevaccination distribution of human papillomavirus types in women attending at cervical cancer screening in Belgium. *Cancer Epidemiol Biomarkers Prev* 2009;18:321-30.

23. Pista A, Freire de Oliveira C, Cunha MJ, Paixao MT, Real O. Prevalence of Human Papillomavirus Infection in Women in Portugal. The CLEOPATRE Portugal Study. *Int J Gynecol Cancer* 2011;21:1150-8.

24. Kjaer S, Breugelmans G, Munk C, Junge J, Watson M, Iftner T. Population-based prevalence, type- and age-specific distribution of HPV in women before introduction of an HPV-vaccination program in Denmark. *Int J Cancer* 2008;123:1864-70.

25. Gravitt PE, Rositch AF, Silver MI, et al. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. *J Infect Dis* 2013;207:272-80.

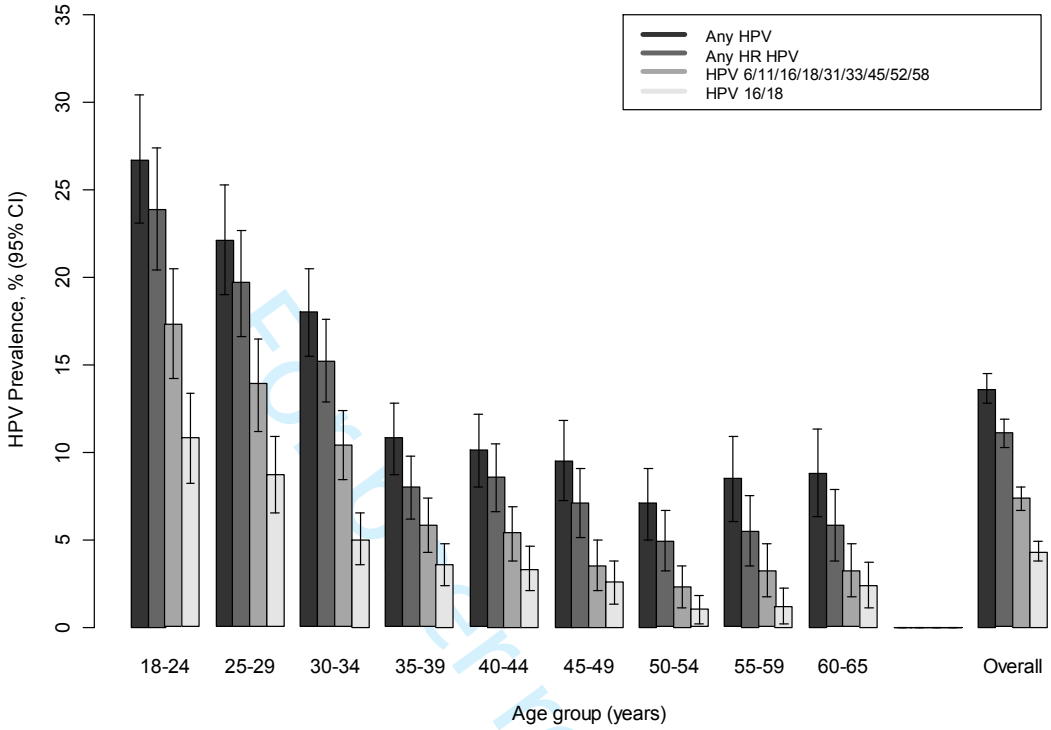
26. Roura E, Iftner T, Vidart JA, et al. Predictors of human papillomavirus infection in women undergoing routine cervical cancer screening in Spain: the CLEOPATRE study. *BMC Infect Dis* 2012;12:145.

27. Pista A, de Oliveira CF, Cunha MJ, Paixao MT, Real O; CLEOPATRE Portugal Study Group. Risk factors for human papillomavirus infection among women in Portugal: the CLEOPATRE Portugal Study. *Int J Gynaecol Obstet* 2012;118:112-6.

28. Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15:326–33.

29. Vaccarella S, Herrero R, Snijders PJ, et al. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. *Int J Epidemiol* 2008;37:536–46.

30. Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15:2148–53.



HPV: Human Papillomavirus; HR: High-Risk; CI: Confidence Interval.

OTHER TABLES:

Supplementary table 1 – Overall prevalence and age-specific prevalence of cervical HPV infections by any HPV type, any hr HPV type, HPV types 6/11/16/18/31/33/45/52/58 and HPV types 16/18 (n=6,010 women).

Age group (years)	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)	Prevalence of HPV 6/11/16/18/ 31/33/45/52/58 (%; 95% CI)	Prevalence of HPV 16/18/ (%; 95% CI)
18-24	26.7 (23.1-30.4)	23.9 (20.4-27.4)	17.3 (14.2-20.5)	10.8 (8.2-13.4)
25-29	22.1 (19.0-25.3)	19.7 (16.6-22.7)	13.9 (11.2-16.5)	8.7 (6.5-10.9)
30-34	18.0 (15.5-20.5)	15.2 (12.9-17.6)	10.4 (8.4-12.4)	5.0 (3.6-6.5)
35-39	10.8 (8.7-12.8)	8.0 (6.2-9.8)	5.8 (4.3-7.4)	3.6 (2.4-4.8)
40-44	10.1 (8.0-12.2)	8.6 (6.6-10.5)	5.4 (3.8-6.9)	3.3 (2.1-4.6)
45-49	9.5 (7.2-11.8)	7.1 (5.1-9.1)	3.5 (2.1-5.0)	2.6 (1.3-3.8)
50-54	7.1 (5.0-9.1)	4.9 (3.2-6.7)	2.3 (1.1-3.5)	1.0 (0.2-1.8)
55-59	8.5 (6.0-10.9)	5.5 (3.5-7.5)	3.2 (1.7-4.8)	1.2 (0.2-2.2)
60-65	8.8 (6.3-11.3)	5.8 (3.8-7.9)	3.2 (1.7-4.8)	2.4 (1.1-3.7)
Total	**13.6 (12.8-14.5)**	**11.1 (10.3-11.9)**	**7.4 (6.7-8.0)**	**4.3 (3.8-4.9)**

HPV: Human Papillomavirus; HR: High-Risk; CI: Confidence Interval.

[1] HR HPV types includes 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.

Supplementary table 2 – Human Papillomavirus (HPV) type-specific distribution of the most common types (n=6,010 women) by cytology result.

HPV type		NORMAL CYTOLOGY (n=5,693)			ABNORMAL CYTOLOGY (n=317)		
		Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)
Any HPV types		**601**	**10.6 (9.8-11.4)**	**-**	**219**	**69.1 (64.0-74.2)**	**-**
Single types		**260**	**4.6 (4.0-5.1)**	**43.3 (39.3-47.2)**	**99**	**31.2 (26.1-36.3)**	**45.2 (38.6-51.8)**
HR HPV types [1]							
	16	56	1.0 (0.7-1.2)	9.3 (7.0-11.6)	19	6.0 (3.4-8.6)	8.7 (4.9-12.4)
	51	22	0.4 (0.2-0.5)	3.7 (2.2-5.2)	12	3.8 (1.7-5.9)	5.5 (2.5-8.5)
	53	21	0.4 (0.2-0.5)	3.5 (2.0-5.0)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
	31	14	0.2 (0.1-0.4)	2.3 (1.1-3.5)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
	59	8	0.1 (0.0-0.2)	1.3 (0.4-2.2)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
	33	10	0.2 (0.1-0.3)	1.3 (0.4-2.2)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
	68	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
	70	7	0.1 (0.0-0.2)	1.2 (0.3-2.0)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)
	66	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	-	-	-
	52	6	0.1 (0.0-0.2)	1.0 (0.2-1.8)	3	0.9 (0.1-2.0)	1.4 (0.2-2.9)
	58	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	5	1.6 (0.2-2.9)	2.3 (0.3-4.3)
	18	7	0.1 (0.0-0.2)	1.2 (0.3-2.0)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
	56	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)
	35	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
	39	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
	73	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
	45	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)

67	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
69	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	-	-	-
69/71	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	-	-	-
LR HPV types [2]						
42	11	0.2 (0.1-0.3)	1.8 (0.8-2.9)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
84	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
62	9	0.2 (0.1-0.3)	1.5 (0.5-2.5)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
61	8	0.1 (0.0-0.2)	1.3 (0.4-2.2)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
6	8	0.1 (0.0-0.2)	1.3 (0.4-2.2)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
55	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
81	7	0.1 (0.0-0.2)	1.2 (0.3-2.0)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
89	5	0.1 (0.0-0.2)	0.8 (0.1-1.6)	-	-	-
54	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	-	-	-
11	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
43	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
72	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
83	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
40	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
X	**24**	**0.4 (0.3-0.6)**	**4.0 (2.4-5.6)**	**4**	**1.3 (0.0-2.5)**	**1.8 (0.1-3.6)**
Multiple types	**317**	**5.6 (5.0-6.2)**	**52.7 (48.8-56.7)**	**116**	**36.6 (31.3-41.9)**	**53.0 (46.4-59.6)**
Number of multiple types						
2 types	153	2.7 (2.3-3.1)	25.5 (22.0-28.9)	50	15.8 (11.8-19.8)	22.8 (17.3-28.4)
3 types	81	1.4 (1.1-1.7)	13.5 (10.7-16.2)	34	10.7 (7.3-14.1)	15.5 (10.7-20.3)
4 types	57	1.0 (0.7-1.3)	9.5 (7.1-11.8)	16	5.0 (2.6-7.5)	7.3 (3.9-10.8)
5 or more types	26	0.5 (0.3-0.6)	4.3 (2.7-6.0)	16	5.0 (2.6-7.5)	7.3 (3.9-10.8)
Most frequent combinations						
16 with others	113	2.0 (1.6-2.3)	18.8 (15.7-21.9)	40	12.6 (9.0-16.3)	18.3 (13.1-23.4)

51 with others	56	1.0 (0.7-1.2)	9.3 (7.0-11.6)	22	6.9 (4.1-9.7)	10.0 (6.1-14.0)
53 with others	50	0.9 (0.6-1.1)	8.3 (6.1-10.5)	31	9.8 (6.5-13.0)	14.2 (9.5-18.8)
31 with others	38	0.7 (0.5-0.9)	6.3 (4.4-8.3)	16	5.0 (2.6-7.5)	7.3 (3.9-10.8)
42 with others	42	0.7 (0.5-1.0)	7.0 (5.0-9.0)	17	5.4 (2.9-7.8)	7.8 (4.2-11.3)
6 with others	16	0.3 (0.1-0.4)	2.7 (1.4-3.9)	9	2.8 (1.0-4.7)	4.1 (1.5-6.7)
18 with others	36	0.6 (0.4-0.8)	6.0 (4.1-7.9)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
33 with others	17	0.3 (0.2-0.4)	2.8 (1.5-4.2)	3	0.9 (0.0-2.0)	1.4 (0.0-2.9)
59 with others	50	0.9 (0.6-1.1)	8.3 (6.1-10.5)	17	5.4 (2.9-7.8)	7.8 (4.2-11.3)
39 with others	27	0.5 (0.3-0.7)	4.5 (2.8-6.1)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
35 with others	13	0.2 (0.1-0.4)	2.2 (1.0-3.3)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
52 with others	40	0.7 (0.5-0.9)	6.7 (4.7-8.6)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
56 with others	29	0.5 (0.3-0.7)	4.8 (3.1-6.5)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
58 with others	32	0.6 (0.4-0.8)	5.3 (3.5-7.1)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
62 with others	37	0.6 (0.4-0.9)	6.2 (4.2-8.1)	9	2.8 (1.0-4.7)	4.1 (1.5-6.7)
61 with others	29	0.5 (0.3-0.7)	4.8 (3.1-6.5)	15	4.7 (2.4-7.1)	6.8 (3.5-10.2)
66 with others	38	0.7 (0.5-0.9)	6.3 (4.4-8.3)	12	3.8 (1.7-5.9)	5.5 (2.5-8.5)
45 with others	24	0.4 (0.3-0.6)	4.0 (2.4-5.6)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
68 with others	22	0.4 (0.2-0.5)	3.7 (2.2-5.2)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
54 with others	34	0.6 (0.4-0.8)	5.7 (3.8-7.5)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
70 with others	11	0.2 (0.1-0.3)	1.8 (0.8-2.9)	4	1.3 (0.0-2.5)	1.8 (0.1-6.3)
84 with others	30	0.5 (0.3-0.7)	5.0 (3.3-6.7)	8	2.5 (0.8-4.3)	3.7 (1.2-6.1)
55 with others	11	0.2 (0.1-0.3)	1.8 (0.8-2.9)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
11 with others	6	0.1 (0.0-0.2)	1.0 (0.2-1.8)	2	0.6 (0.0-1.5)	0.9 (0.3-2.2)
81 with others	19	0.3 (0.2-0.5)	3.2 (1.8-4.6)	9	2.8 (1.0-4.7)	4.1 (1.5-6.7)
40 with others	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	-	-	-
89 with others	32	0.6 (0.4-0.8)	5.3 (3.5-7.1)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
67 with others	9	0.2 (0.1-0.3)	1.5 (0.5-2.5)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)

69 with others	5	0.1 (0.0-0.2)	0.8 (0.1-1.6)	-	-	-
73 with others	16	0.3 (0.1-0.4)	2.7 (1.4-3.9)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
83 with others	9	0.2 (0.1-0.3)	1.5 (0.5-2.5)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
43 with others	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)	-	-	-
72 with others	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)
69/71 with others	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
71 with others	6	0.1 (0.0-0.2)	1.0 (0.2-1.8)	3	0.9 (0.0-2.0)	1.4 (0.0-2.9)
74 with others	5	0.1 (0.0-0.2)	0.8 (0.1-1.6)	1	0.3 (0.0-0.9)	0.5 (0.0-1.3)
64 with others	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	1	0.3 (0.0-0.9)	0.5 (0.0-1.3)
82 with others	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	3	0.9 (0.0-2.0)	1.4 (0.0-2.9)
Combinations of vaccine types						
6/11 [3]	31	0.5 (0.4-0.7)	5.2 (3.4-6.9)	12	3.8 (1.7-5.9)	5.5 (2.5-8.5)
16/18 [3]	199	3.5 (3.0-4.0)	33.1 (29.3-36.9)	62	19.6 (15.2-23.9)	28.3 (22.3-34.3)
6/11/16/18 [3]	225	4.0 (3.4-4.5)	37.4 (33.6-41.3)	72	22.7 (18.1-27.3)	32.9 (26.7-39.1)
6/11/16/18/31/33/45/52/58 [3]	334	5.9 (5.3-6.5)	55.6 (51.6-59.5)	110	34.7 (29.5-39.9)	50.2 (43.6-56.9)

HPV: Human Papillomavirus; HR: High-Risk; LR: Low-Risk; CI: Confidence Interval.

[1] HR types includes 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. [2] LR types includes: 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89. [3] One or more of the vaccine types are concerned.

Supplementary table 3 – Human Papillomavirus (HPV) type-specific distribution of the most common types (n=6,010 women) by result of abnormal cytology.

HPV type	ASCUS (n=214)			LSIL (n=91)			HSIL+ (n=12)		
	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)
Any HPV type	**130**	**60.7 (54.2-67.3)**	**-**	**79**	**86.8 (79.9-93.8)**	**-**	**10**	**83.3 (62.2-100.0)**	**-**
Single types	**66**	**30.8 (24.7-37.0)**	**50.8 (42.2-59.4)**	**29**	**31.9 (22.3-41.4)**	**36.7 (26.1-47.3)**	**4**	**33.3 (6.7-60.0)**	**40.0 (9.6-70.4)**
HR HPV types [1]									
16	13	6.1 (2.9-9.3)	10.0 (4.8-15.2)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
51	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	5	5.5 (0.8-10.2)	6.3 (1.0-11.7)	1	8.3 (0.0.-24.0)	10.0 (0.0-28.6)
53	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
31	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
59	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
33	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
68	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
70	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
66	-	-	-	-	-	-	-	-	-
52	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
58	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
18	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
56	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
35	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
39	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
73	-	-	-	-	-	-	1	8.3 (0.0.-24.0)	10.0 (0.0-28.6)

45	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
67	-	-	-	-	-	-	-	-	-
69	-	-	-	-	-	-	-	-	-
69/71	-	-	-	-	-	-	-	-	-
LR HPV types [2]									
42	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
84	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
62	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
61	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
6	-	-	-	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
55	7	3.3 (0.9-5.7)	5.4 (1.5-9.3)	-	-	-	-	-	-
81	-	-	-	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
89	-	-	-	-	-	-	-	-	-
54	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-	-
72	-	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-	-
X	**3**	**1.4 (0.0-3.0)**	**2.3 (0.0-4.9)**	**1**	**1.1 (0.0-3.2)**	**1.3 (0.0-3.7)**	**-**	**-**	**-**
Multiple types	**61**	**28.5 (22.5-34.6)**	**46.9 (38.3-55.5)**	**49**	**53.8 (43.6-64.1)**	**62.0 (51.3-72.7)**	**6**	**50.0 (21.7-78.3)**	**60.0 (29.6-90.4)**
Number of multiple types									
2 types	28	13.1 (8.6-17.6)	21.5 (14.5-28.6)	20	22.0 (13.5-30.5)	25.3 (15.7-34.9)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
3 types	19	8.9 (5.1-12.7)	14.6 (8.5-20.7)	12	13.2 (6.2-20.1)	15.2 (7.3-23.1)	3	25.0 (0.5-49.5)	30.0 (1.6-58.4)
4 types	9	4.2 (1.5-6.9)	6.9 (2.6-11.3)	7	7.7 (2.2-13.2)	8.9 (2.6-15.1)	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
5 or more types	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	10	11.0 (4.6-17.4)	12.7 (5.3-20.0)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)

Most frequent combinations									
16 with others	16	7.5 (4.0-11.0)	12.3 (6.7-18.0)	22	24.2 (15.4-33)	27.8 (18-37.7)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
51 with others	12	5.6 (2.5-8.7)	9.2 (4.3-14.2)	9	9.9 (3.8-16.0)	11.4 (4.4-18.4)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
53 with others	16	7.5 (4.0-11.0)	12.3 (6.7-18.0)	14	15.4 (8.0-22.8)	17.7 (9.3-26.1)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
31 with others	7	3.3 (0.9-5.7)	5.4 (1.5-9.3)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	3	25.0 (0.5-49.5)	30.0 (1.6-58.4)
42 with others	9	4.2 (1.5-6.9)	6.9 (2.6-11.3)	7	7.7 (2.2-13.2)	8.9 (2.6-15.1)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
6 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
18 with others	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
33 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
59 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
39 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
35 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
52 with others	4	1.9 (0.1-3.7)	3.1 (0.1-6.0)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
56 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	-	-	-
58 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	5	5.5 (0.8-10.2)	6.3 (1.0-11.7)	-	-	-
62 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
61 with others	7	3.3 (0.9-5.7)	5.4 (1.5-9.3)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	-	-	-
66 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	-	-	-
45 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	3	25 (0.5-49.5)	30.0 (1.6-58.4)
68 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
54 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
70 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
84 with others	4	1.9 (0.1-3.7)	3.1 (0.1-6.0)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
55 with others	4	1.9 (0.1-3.7)	3.1 (0.1-6.0)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
11 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
81 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-

40 with others	-	-	-	-	-	-	-	-	-
89 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	-	-	-
67 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
69 with others	-	-	-	-	-	-	-	-	-
73 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
83 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
43 with others	-	-	-	-	-	-	-	-	-
72 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
69/71 with others	-	-	-	-	-	-	-	-	-
71 with others	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
74 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
64 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
82 with others	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
Combinations of vaccine types									
6/11 [3]	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	-	-	-
16/18 [3]	31	14.5 (9.8-19.2)	23.8 (16.5-31.2)	27	29.7 (20.3-39.1)	34.2 (23.7-44.6)	4	33.3 (6.7-60.0)	40.0 (9.6-70.4)
6/11/16/18 [3]	37	17.3 (12.2-22.4)	28.5 (20.7-36.2)	31	34.1 (24.3-43.8)	39.2 (28.5-50.0)	4	33.3 (6.7-60.0)	40.0 (9.6-70.4)
6/11/16/18/31/33/45/52/58 [3]	57	26.6 (20.7-32.6)	43.8 (35.3-52.4)	45	49.5 (39.2-59.7)	57.0 (46.0-67.9)	8	66.7 (40.0-93.3)	80.0 (55.2-100.0)

HPV: Human Papillomavirus; HR: High-Risk; LR: Low-Risk; ASCUS: Atypical Squamous cells of Undetermined Significance; LSIL: Low-grade Squamous Intraepithelial Lesion; HSIL: High-grade Squamous Intraepithelial Lesion; CI: Confidence Interval.

[1] HR types includes 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. [2] LR types includes: 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89. [3] One or more of the vaccine types are concerned.

Supplementary table 4 – Crude and multivariate analyses of the association between cervical High-Risk Human Papillomavirus (HR HPV) infection and selected subjects' characteristics (n=5,858 women).

Study sample characteristics	Number of HR HPV positive women / number of HPV tested women (negative + HR HPV positive)	HPV prevalence (%)	Adjusted model [1] POR (95% CI)
Population			
Gran Canaria	407 / 3,753	10.8	1.0 (ref)
Tenerife	261 / 2,105	12.4	1.0 (0.8-1.2)
Age distribution (years)			
18-24	135 / 549	24.6	**2.9 (1.7-4.8)**
25-29	129 / 639	20.2	**2.2 (1.3-3.5)**
30-34	136 / 869	15.7	**1.7 (1.0-2.7)**
35-39	71 / 865	8.2	0.9 (0.5-1.4)
40-44	67 / 771	8.7	1.0 (0.6-1.6)
45-49	44 / 607	7.2	0.8 (0.5-1.3)
50-54	30 / 594	5.1	0.6 (0.4-1.1)
55-59	27 / 480	5.6	0.8 (0.5-1.4)
60-65	29 / 484	6.0	1.0 (ref)
p-value for trend			***p<0.001***
Level of education			
None / Preschool	29 / 438	6.6	1.0 (ref)
Primary	246 / 2,588	9.5	0.9 (0.6-1.5)
Secondary	201 / 1,437	14.0	0.9 (0.5-1.3)
University or higher	178 / 1,296	13.7	0.9 (0.5-1.4)
Others	13 / 90	14.4	0.8 (0.4-1.8)
Missing data	1 / 9	-	-
p-value for trend (excluding others)			*p=0.3*
Marital status			
Single	283 / 1,333	21.2	**1.5 (1.2-1.9)**
Married/de facto partnership	267 / 3,792	7.0	1.0 (ref)
Divorced/separated	99 / 541	18.3	**2.0 (1.5-2.7)**
Widowed	18 / 184	9.8	**1.8 (1.0-3.1)**
Missing data	1 / 8	-	-
Number of live births			
No [2]	240 / 1,307	18.4	1.0 (ref)
1	137 / 1,202	11.4	0.9 (0.7-1.2)
2	136 / 1,725	7.9	1.0 (0.8-1.4)
3	53 / 754	7.0	1.1 (0.7-1.6)
≥4	27 / 448	6.0	1.0 (0.6-1.7)
Missing data	75 / 422	-	-
Smoking status			
Never smoked	298 / 3,324	9.0	1.0 (ref)
Ex smoker	102 / 876	11.6	1.2 (0.9-1.5)

Current smoker	268 / 1,658	16.2	**1.3 (1.1-1.6)**
Age at first sexual intercourse (years)			
<15	35 / 179	19.6	1.0 (0.5-1.8)
15-16	136 / 787	17.3	1.0 (0.6-1.6)
17-18	235 / 1,797	13.1	1.0 (0.6-1.6)
19-20	118 / 1,241	9.5	1.0 (0.6-1.5)
21-25	112 / 1,368	8.2	1.2 (0.7-1.8)
>25	26 / 418	6.2	1.0 (ref)
Missing data	6 / 68	-	-
p-value for trend			*p=0.6*
Lifetime number of sexual partners			
1	160 / 3,135	5.1	1.0 (ref)
2-3	224 / 1,495	15.0	**2.3 (1.9-2.9)**
4-5	124 / 596	20.8	**3.1 (2.3-4.0)**
6-10	100 / 376	26.6	**4.1 (3.0-5.6)**
11-20	36 / 121	29.8	**4.6 (2.9-7.3)**
>20	16 / 47	34.0	**7.1 (3.7-13.6)**
Missing data	8 / 88	-	-
p-value for trend			***p<0.001***
Use of oral contraceptives			
Never	126 / 1,366	9.2	1.0 (ref)
Ever	542 / 4,492	12.1	1.2 (0.97-1.5)
Rhythm method/coitus interruptus			
Never	316 / 2,933	10.8	1.0 (ref)
Ever	352 / 2,925	12.0	1.1 (0.96-1.4)
Previous cervical lesions			
No	527 / 4,868	10.8	1.0 (ref)
Yes	70 / 364	19.2	**1.5 (1.1-2.0)**
Missing data [3]	71 / 626	-	-
Genital warts			
Never	633 / 5,744	11.0	1.0 (ref)
Ever	35 / 114	30.7	**2.0 (1.3-3.2)**

[1] Adjusted model: adjusted for age group, population, level of education, marital status, smoking habits, lifetime number of sexual partners, previous cervical lesions, and ever had genital warts. [2] Includes women who were pregnant but had 0 live births. [3] Includes "Do not know" in the "Missing data" category. [4] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [5] Excludes ever had genital warts in the adjustment.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	10-16

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

PREVALENCE AND GENOTYPE DISTRIBUTION OF CERVICAL HUMAN PAPILOMAVIRUS INFECTION IN THE PRE-VACCINATION ERA: A POPULATION-BASED STUDY IN THE CANARY ISLANDS

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037402.R1
Article Type:	Original research
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Pathology, Obstetrics and gynaecology
Keywords:	CYTOPATHOLOGY, Gynaecological oncology < GYNAECOLOGY, EPIDEMIOLOGY, INFECTIOUS DISEASES

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PREVALENCE AND GENOTYPE DISTRIBUTION OF CERVICAL HUMAN PAPILOMAVIRUS INFECTION IN THE PRE-VACCINATION ERA: A POPULATION-BASED STUDY IN THE CANARY ISLANDS

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ABSTRACT

Keywords: epidemiology, infectious diseases, human papillomavirus, cervical cancer, prevalence.

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 socio-demographic factors.

Methods

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

Results

6,010 women participated in the study, 3,847 from GC and 2,163 from TF. The overall prevalence of HPV infection was 13.6% (12.8-14.5%) and 11.1% (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, being HPV 16 the most frequent genotype. The determinants of infection are consistent with those of other populations.

Strengths and limitations of this study:

- This is the first prevalence study of HPV infection in Canary Islands.
- The study design is population-based, including the main healthcare centers of the participant regions.
- Cytological and molecular samples were analyzed in the same laboratory by the same staff, using highly-sensitive and partially automated techniques that ensured consistency, homogeneity and reproducibility of diagnostic methods.
- Study recruitment time was extensive, from three to six years depending on the region.
- Characteristics of the study participants could be different over time.

1. 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.[1] In Spain, cervical cancer is the fifteenth most frequent cancer in women (fourth in women aged 15-44 years), with an estimated 1,942 new cases in 2018.[1] 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, [2] one of the highest incidence rates in Spain.[3]

Human papillomavirus (HPV) is a necessary but not sufficient cause of cervical cancer.[4] More than 200 HPV genotypes are currently known, epidemiologically classified into low-oncogenic risk (LR-HPV) and high-oncogenic risk (HR-HPV) types.[5] HR-HPV types include 16 and 18 genotypes, present in more than 70% of cervical cancer cases[6] and included in the three prophylactic HPV vaccines currently commercialized.[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 behavior in the last decades have leads to increased HPV infection rates (up to 14% in 18-65 years old women, 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 socio-demographic factors associated to HPV infection.

2. METHODS

2.1. Participants

The study was conducted between 2002 and 2007 on a sample of 18-65 years-old-women 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 2,276 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 center was scheduled. A total of 24,345 letters were sent, 15,577 in Gran Canaria and 8,768 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. This study was favorably evaluated by the Ethics and Clinical Trial Committee of our hospital Complejo Hospitalario Universitario Insular Materno Infantil.

2.2. Patient and Public Involvement

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

2.3. Procedures

Participants were asked to fulfill an informed consent form and to complete a clinical and epidemiological questionnaire (adapted from IARC surveys). For cytological collection, the wooden Ayre spatula and endocervical brush (cytobrush) were used, stained with the Papanicolau 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 minutes at 90° C and subsequent centrifugation, obtaining DNA from the sample supernatant.

To detect HPV infection, two separated polymerase chain reactions (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 (Immnogenetics®, Belgium - FUJIREBIO Europe, Belgium).

2.4. Statistical analyses

Descriptive analysis of socio-demographic variables was conducted, globally and stratified according to the study subpopulation (i.e. selected participants from Gran Canaria, volunteers from Gran Canaria, selected participants from Tenerife). Estimated

HPV infection prevalence and genotype distribution and corresponding 95% confidence intervals (CI95%) 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 to 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 6,091 women were included: 3,212 selected from the general Gran Canaria population (52.7%), 665 volunteers from Gran Canaria (10.9%) and 2,214 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 5 cytological studies in their lives, while 3.5% of them had never undergone 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 sexual first 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 (Supplementary Table 1).

Table 1 – Characteristics of the study participants (n=6,091 women).

Study sample characteristics	N (%)
Distribution by population	
Gran Canaria (general population)	3,212 (52.7)
Gran Canaria (volunteers)	665 (10.9)
Tenerife	2,214 (36.3)
Country of birth	
Spain	5,397 (91.6)
Europe (excluding Spain)	111 (1.9)
Northern Africa	20 (0.3)
Sub-Saharian 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	1,396 (22.9)
Married/de facto partnership	3,919 (64.4)
Divorced/separated	573 (9.4)
Widowed	195 (3.2)
Missing data	8 (-)
Pregnancies	
No	1,343 (22.5)
Yes	4,613 (77.5)

Missing data	135 (-)
Number of live births [1]	
0	28 (0.7)
1	1,237 (28.7)
2	1,786 (41.5)
3	789 (18.3)
4	277 (6.4)
≥5	186 (4.3)
Missing data	310 (-)
Sexually transmitted disease	
Never	5,882 (96.6)
Ever [2]	209 (3.4)
Syphilis [3]	30 (0.5)
Genital herpes [3]	51 (0.8)
Gonorrhea [3]	23 (0.4)
HIV [3]	7 (0.1)
Genital warts [3]	120 (2.0)
Chlamydia [3]	30 (0.5)
Genital ulcer [3]	16 (0.3)
Others [3]	72 (1.2)
Smoking status	
Never smoked	3,443 (56.5)
Ex smoker	913 (15.0)
Current smoker	1,735 (28.5)
Previous cervical pap smears	
None	216 (3.5)
1	493 (8.1)
2-3	1,056 (17.3)
4-5	772 (12.7)
>5	3,273 (53.7)
Do not know	281 (4.6)
Previous cervical lesions [4]	
No	4,837 (92.5)
Yes	385 (7.4)
Do not know	5 (0.1)
Missing data	648 (-)
Age at first sexual intercourse (years)	
<15	187 (3.1)
15-16	828 (13.6)
17-18	1,863 (30.6)
19-20	1,281 (21.0)
21-25	1,421 (23.3)
>25	442 (7.3)
Missing data	69 (-)
Lifetime number of sexual partners	
1	3,232 (53.9)
2-3	1,571 (26.2)
4-5	614 (10.2)
6-10	405 (6.8)
11-20	126 (2.1)
>20	49 (0.8)
Missing data	94 (-)
Contraceptive methods used [5]	

Oral contraceptives	4,664 (76.6)
IUD	1,133 (18.6)
Condom	4,522 (74.2)
Rhythm method/coitus interruptus	3,049 (50.1)
Diaphragm/spermicide	234 (3.8)
Injection/implant	253 (4.2)
Tube ligation	802 (13.2)
Vasectomy	549 (9.0)

[1] Among ever pregnant women (N=4,613). [2] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [3] Do not add the total of women because a woman could have more than one sexually transmitted disease in lifetime. [4] Among women with a previous pap smear (N=5,875). [5] Do not add the total of women because a woman can use more than one contraceptive in lifetime.

Prevalence of cervical HPV infection

For the prevalence study, 6,010 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% (CI95% 12.8-14.5) while the prevalence of HR-HPV infection was 11.1% (CI95% 10.3-11.9) (Table 2). The youngest age group (18-24 years) showed the highest prevalence with 26.7% of any-type HPV infection (CI95% 23.1-30.4). 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).

Table 2 – Prevalence of Human Papillomavirus (HPV) by age group for any type and for any high-risk type (n=6,010 women).

Age group (years)	Number of tested women	Number of HPV positive women	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)
18-24	565	151	26.7 (23.1-30.4)	23.9 (20.4-27.4)
25-29	655	145	22.1 (19.0-25.3)	19.7 (16.6-22.7)
30-34	894	161	18.0 (15.5-20.5)	15.2 (12.9-17.6)
35-39	890	96	10.8 (8.7-12.8)	8.0 (6.2-9.8)
40-44	783	79	10.1 (8.0-12.2)	8.6 (6.6-10.5)
45-49	622	59	9.5 (7.2-11.8)	7.1 (5.1-9.1)
50-54	607	43	7.1 (5.0-9.1)	4.9 (3.2-6.7)
55-59	495	42	8.5 (6.0-10.9)	5.5 (3.5-7.5)
60-65	499	44	8.8 (6.3-11.3)	5.8 (3.8-7.9)
Total	**6,010**	**820**	**13.6 (12.8-14.5)**	**11.1 (10.3-11.9)**

HPV: Human Papillomavirus; HR: High-Risk; CI: Confidence Interval.

[1] HR HPV types includes 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.

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%, CI95% 11.8-17.2, versus 12.7%, CI95% 11.6-13.9; 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%, CI95% 9.6-11.6, versus 12.1%, CI95% 10.7-13.4, p=0.002; Supplementary Table 2).

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%).

Table 3 – Human Papillomavirus (HPV) type-specific distribution of the most common types (n=6,010 women).

HPV type		Number of HPV positive women (n=820)	HPV prevalence among all women (n=6,010) (%; 95% CI)	HPV prevalence among positive women (n=820) (%; 95% CI)
Single types		**359**	**6.0 (5.4-6.6)**	**43.8 (40.4-47.2)**
HR HPV types [1]				
	16	75	1.2 (1.0-1.5)	9.1 (7.2-11.1)
	51	34	0.6 (0.4-0.8)	4.1 (2.8-5.5)
	53	28	0.5 (0.3-0.6)	3.4 (2.2-4.7)

31	16	0.3 (0.1-0.4)	2.0 (1.0-2.9)
59	14	0.2 (0.1-0.4)	1.7 (0.8-2.6)
33, 68, 70	11 each	0.2 (0.1-0.3) [4]	1.3 (0.6-2.1) [4]
66	10	0.2 (0.1-0.3)	1.2 (0.5-2.0)
52, 58	9 each	0.1 (0.1-0.2) [4]	1.1 (0.4-1.8) [4]
18	8	0.1 (0.0-0.2)	1.0 (0.3-1.6)
56	7	0.1 (0.0-0.2)	0.9 (0.2-1.5)
35, 39	5 each	0.1 (0.0-0.2) [4]	0.6 (0.1-1.1) [4]
73	4	0.1 (0.0-0.1)	0.5 (0.0-1.0)
45	3	0.0 (0.0-0.1)	0.4 (0.0-0.8)
67	2	0.0 (0.0-0.1)	0.2 (0.1-0.6)
69, 69/71	1 each	0.0 (0.0-0.0) [4]	0.1 (0.1-0.4) [4]
LR HPV types [2]			
42	17	0.3 (0.1-0.4)	2.1 (1.1-3.0)
84	12	0.2 (0.1-0.3)	1.5 (0.6-2.3)
62	11	0.2 (0.1-0.3)	1.3 (0.6-2.1)
61	10	0.2 (0.1-0.3)	1.2 (0.5-2.0)
6, 55, 81	9	0.1 (0.1-0.2)	1.1 (0.4-1.8)
89	5	0.1 (0.0-0.2)	0.6 (0.1-1.1)
54	4	0.1 (0.0-0.1)	0.5 (0.0-1.0)
11, 43, 72, 83	2 each	0.0 (0.0-0.1) [4]	0.2 (0.1-0.6) [4]
40	1	0.0 (0.0-0.0)	0.1 (0.1-0.4)
Untyped HPV	**28**	**0.5 (0.3-0.6)**	**3.4 (2.2-4.7)**
Multiple types	**433**	**7.2 (6.6-7.9)**	**52.8 (49.4-56.2)**
Number of multiple types			
2 types	203	3.4 (2.9-3.8)	24.8 (21.8-27.7)
3 types	115	1.9 (1.6-2.3)	14.0 (11.6-16.4)
4 types	73	1.2 (0.9-1.5)	8.9 (7.0-10.9)
5 or more types	42	0.7 (0.5-0.9)	5.1 (3.6-6.6)
Most frequent combinations			
16 with others	153	2.5 (2.1-2.9)	18.7 (16-21.3)
53 with others	81	1.3 (1.1-1.6)	9.9 (7.8-11.9)
51 with others	78	1.3 (1.0-1.6)	9.5 (7.5-11.5)
59 with others	67	1.1 (0.8-1.4)	8.2 (6.3-10.0)
42 with others	59	1.0 (0.7-1.2)	7.2 (5.4-9.0)
31 with others	54	0.9 (0.7-1.1)	6.6 (4.9-8.3)
52 with others	54	0.9 (0.7-1.1)	6.6 (4.9-8.3)
66 with others	50	0.8 (0.6-1.1)	6.1 (4.5-7.7)
54 with others	48	0.8 (0.6-1.0)	5.9 (4.2-7.5)
62 with others	46	0.8 (0.5-1.0)	5.6 (4.0-7.2)
89 with others	46	0.8 (0.5-1.0)	5.6 (4.0-7.2)
61 with others	44	0.7 (0.5-0.9)	5.4 (3.8-6.9)
56 with others	43	0.7 (0.5-0.9)	5.2 (3.7-6.8)
18 with others	42	0.7 (0.5-0.9)	5.1 (3.6-6.6)
58 with others	42	0.7 (0.5-0.9)	5.1 (3.6-6.6)
84 with others	38	0.6 (0.4-0.8)	4.6 (3.2-6.1)

39 with others	37	0.6 (0.4-0.8)	4.5 (3.1-5.9)
45 with others	34	0.6 (0.4-0.8)	4.1 (2.8-5.5)
68 with others	32	0.5 (0.3-0.7)	3.9 (2.6-5.2)
81 with others	28	0.5 (0.3-0.6)	3.4 (2.2-4.7)
6 with others	25	0.4 (0.3-0.6)	3.0 (1.9-4.2)
73 with others	23	0.4 (0.2-0.5)	2.8 (1.7-3.9)
33 with others	20	0.3 (0.2-0.5)	2.4 (1.4-3.5)
35 with others	19	0.3 (0.2-0.5)	2.3 (1.3-3.3)
55 with others	18	0.3 (0.2-0.4)	2.2 (1.2-3.2)
70 with others	15	0.2 (0.1-0.4)	1.8 (0.9-2.7)
83 with others	15	0.2 (0.1-0.4)	1.8 (0.9-2.7)
67 with others	13	0.2 (0.1-0.3)	1.6 (0.7-2.4)
82 with others	13	0.2 (0.1-0.3)	1.6 (0.7-2.4)
40 with others	10	0.2 (0.1-0.3)	1.2 (0.5-2.0)
71 with others	9	0.1 (0.1-0.2)	1.1 (0.4-1.8)
11 with others	8	0.1 (0.0-0.2)	1.0 (0.3-1.6)
72 with others	8	0.1 (0.0-0.2)	1.0 (0.3-1.6)
74 with others	6	0.1 (0.0-0.2)	0.7 (0.1-1.3)
69 with others	5	0.1 (0.0-0.2)	0.6 (0.1-1.1)
64 with others	2	0.0 (0.0-0.1)	0.2 (0.0-0.6)
69/71 with others	2	0.0 (0.0-0.1)	0.2 (0.0-0.6)
43 with others	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Combinations of vaccine types			
6/11 [3]	43	0.7 (0.5-0.9)	5.2 (3.7-6.8)
16/18 [3]	261	4.3 (3.8-4.9)	31.8 (28.6-35.0)
6/11/16/18 [3]	297	4.9 (4.4-5.5)	36.2 (32.9-39.5)
6/11/16/18/31/33/45/52/58 [3]	444	7.4 (6.7-8.0)	54.1 (50.7-57.6)

HPV: Human Papillomavirus; HR: High-Risk; LR: Low-Risk; CI: Confidence Interval.

[1] HR types includes 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. [2] LR types includes: 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89. [3] One or more of the vaccine types are concerned. [4] HPV prevalence for each of the types in the row.

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 9-valent vaccine were considered. Figure 1 and 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% (CI95% 64.0-74.2) of HPV positivity versus 5,693 non-pathological cytologies (94.7%) with 10.6% (CI95% 9.8-11.4) of HPV positivity (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 (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 lineal trend), not married, smokers, more than one sexual partner (statistically significant trend), history of cervical alterations or genital warts, and practicing coitus interruptus (Table 4). When only cases of HR-HPV cervical infection were considered, the same variables showed statistical significance except for practicing coitus interruptus (Supplementary Table 6).

Table 4 – Crude and multivariate analyses of the association between cervical Human Papillomavirus (HPV) infection and selected subjects' characteristics (n=6,010 women).

Study sample characteristics	Number of HPV positive	HPV prevalence	Basic model [1] POR (95% CI)	Adjusted model [2] POR (95% CI)

	women / number of HPV tested women	(%)		
Population				
Gran Canaria	501 / 3,847	13.0	1.0 (ref)	1.0 (ref)
Tenerife	319 / 2,163	14.7	1.1 (0.98-1.3)	1.0 (0.8-1.1)
Country of birth				
Spain	711 / 5,331	13.3	1.0 (ref)	1.0 (ref)
Europe (excluding Spain)	17 / 109	15.6	1.3 (0.8-2.2)	0.8 (0.5-1.5)
Africa	8 / 33	24.2	**2.7 (1.2-6.0)**	2.3 (0.99-5.4)
Latin America and Caribbean	51 / 309	16.5	1.3 (0.9-1.8)	1.2 (0.8-1.7)
Asia and Oceania	2 / 29	6.9	0.6 (0.1-2.5)	0.8 (0.2-3.5)
Missing data	31 / 199	-	-	-
Outside Spain (include all countries)	78 / 480	16.3	**1.3 (1.0-1.7)**	1.1 (0.9-1.5)
Age distribution (years)				
18-24	151 / 565	26.7	**3.8 (2.6-5.4)**	**2.1 (1.3-3.2)**
25-29	145 / 655	22.1	**3.0 (2.1-4.2)**	**1.6 (1.0-2.4)**
30-34	161 / 894	18.0	**2.3 (1.6-3.4)**	1.3 (0.9-2.0)
35-39	96 / 890	10.8	1.3 (0.9-1.8)	0.8 (0.5-1.2)
40-44	79 / 783	10.1	1.2 (0.8-1.7)	0.8 (0.5-1.2)
45-49	59 / 622	9.5	1.1 (0.7-1.7)	0.7 (0.5-1.1)
50-54	43 / 607	7.1	0.8 (0.5-1.2)	**0.6 (0.4-0.9)**
55-59	42 / 495	8.5	1.0 (0.6-1.5)	0.8 (0.5-1.3)
60-65	44 / 499	8.8	1.0 (ref)	1.0 (ref)
p-value for trend			***p<0.001***	***p<0.001***
Level of education				
None / Preschool	40 / 449	8.9	1.0 (ref)	1.0 (ref)
Primary	307 / 2,649	11.6	1.0 (0.7-1.5)	1.0 (0.7-1.4)
Secondary	241 / 1,477	16.3	1.1 (0.8-1.6)	0.9 (0.6-1.3)
University or higher	213 / 1,331	16.0	1.2 (0.8-1.7)	0.9 (0.6-1.4)
Others	18 / 95	18.9	1.2 (0.6-2.2)	1.1 (0.5-2.0)
Missing data	1 / 9	-	-	-
p-value for trend (excluding others)			*p=0.2*	*p=0.5*
Marital status				
Single	329 / 1,379	23.9	**2.0 (1.6-2.4)**	**1.5 (1.2-1.9)**
Married/de facto partnership	347 / 3,872	9.0	1.0 (ref)	1.0 (ref)
Divorced/separated	118 / 560	21.1	**3.0 (2.4-3.8)**	**1.8 (1.4-2.4)**
Widowed	25 / 191	13.1	**2.1 (1.3-3.2)**	**1.7 (1.0-2.6)**
Missing data	1 / 8	-	-	-
Number of live births				
No [3]	279 / 1,346	20.7	1.0 (ref)	1.0 (ref)
1	157 / 1,222	12.8	**0.8 (0.6-0.9)**	0.8 (0.6-1.1)
2	171 / 1,760	9.7	**0.7 (0.6-0.9)**	1.0 (0.7-1.3)
3	80 / 781	10.2	0.9 (0.6-1.2)	1.2 (0.8-1.7)
≥4	37 / 458	8.1	0.7 (0.5-1.1)	0.9 (0.6-1.4)
Missing data	96 / 443	-	-	-
Smoking status				
Never smoked	376 / 3,402	11.1	1.0 (ref)	1.0 (ref)
Ex smoker	126 / 900	14.0	**1.4 (1.1-1.7)**	1.2 (0.9-1.5)
Current smoker	318 / 1,708	18.6	**1.7 (1.5-2.1)**	**1.2 (1.0-1.5)**
Age at first sexual intercourse				

(years)				
<15	40 / 184	21.7	1.5 (0.95-2.5)	0.7 (0.4-1.2)
15-16	166 / 817	20.3	1.4 (0.99-2.1)	0.8 (0.5-1.2)
17-18	273 / 1,835	14.9	1.1 (0.8-1.6)	0.7 (0.5-1.1)
19-20	143 / 1,266	11.3	0.9 (0.7-1.3)	0.7 (0.5-1.1)
21-25	146 / 1,402	10.4	1.0 (0.7-1.4)	0.9 (0.6-1.3)
>25	45 / 437	10.3	1.0 (ref)	1.0 (ref)
Missing data	7 / 69	-	-	-
p-value for trend			***p=0.001***	*p=0.3*
Lifetime number of sexual partners				
1	214 / 3,189	6.7	1.0 (ref)	1.0 (ref)
2-3	274 / 1,545	17.7	**2.7 (2.2-3.3)**	**2.3 (1.9-2.8)**
4-5	141 / 613	23.0	**3.6 (2.8-4.6)**	**2.8 (2.2-3.6)**
6-10	119 / 395	30.1	**5.3 (4.0-6.9)**	**3.9 (2.9-5.2)**
11-20	41 / 126	32.5	**5.9 (3.9-8.8)**	**4.2 (2.8-6.5)**
>20	18 / 49	36.7	**8.1 (4.4-14.8)**	**6.2 (3.3-11.5)**
Missing data	13 / 93	-	-	-
p-value for trend			***p<0.001***	***p<0.001***
Use of oral contraceptives				
Never	164 / 1,404	11.7	1.0 (ref)	1.0 (ref)
Ever	656 / 4,606	14.2	**1.2 (1.0-1.5)**	1.1 (0.9-1.4)
Rhythm method/coitus interruptus				
Never	381 / 2,998	12.7	1.0 (ref)	1.0 (ref)
Ever	439 / 3,012	14.6	**1.3 (1.1-1.5)**	**1.2 (1.0-1.4)**
Previous cervical lesions				
No	645 / 4,986	12.9	1.0 (ref)	1.0 (ref)
Yes	84 / 378	22.2	**2.1 (1.6-2.7)**	**1.6 (1.2-2.1)**
Missing data [4]	91 / 646	-	-	-
Genital warts				
Never	783 / 5,894	13.3	1.0 (ref)	1.0 (ref)
Ever	37 / 116	31.9	**2.8 (1.8-4.2)**	**1.7 (1.1-2.6)**

[1] Basic model: adjusted for age group (18-24, 25-34, 35-44, 45-54, 55-65) and population (Gran Canaria, Tenerife). [2] Adjusted model: adjusted for age group, population, level of education, marital status, smoking habits, lifetime number of sexual partners, previous cervical lesions, ever use of rhythm method, and ever had genital warts. [3] Includes women who were pregnant but had 0 live births. [4] Includes "Do not know" in the "Missing data" category. [5] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [6] Excludes ever had genital warts in the adjustment.

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%.[9-15] Two published studies were population-based: one by de Sanjosé et al.[10] (2003) with a random sample of 973

women from the metropolitan area of Barcelona reporting an HPV prevalence of 3.4% (CI95% 2.3-4.5), which is rather lower than ours, and one by García et al.[15] (2017) 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 behavior 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[9], a study conducted in 17 Autonomous Communities in Spain, using the HC2 test and reporting 14.3% (CI95% 13.1-15.5) of HPV prevalence and 12.2% (CI95% 11.1-13.4) 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, standardized by age, ranged from 1.7% in Spain to 12.5% in Belgium.[17] Bruni et al. (2010) in a meta-analysis including one 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 programs 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 Portugal[23] 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 less than 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.[17,18,20,21,22] Such a bimodal pattern could be due to changes in the sexual behavior or the reactivation of latent viral infections[25], HPV types and their variants in such infections, individual susceptibility or regional differences in the screening programs.[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] though 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 Spain[9,10,11,14] and other European countries.[19,21,22,23,24]

Many studies have reported the percentage of multiple infections[9,12,13,15,18,19,20,21,23,24] ranging from 8.1% in Spain[13] to 54.3% in Denmark.[24] 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 (hybridization technology) with a high sensitivity for detecting multiple infections.

A total of 31.8% of HPV positive women (4.3% of the total population) were infected by types 16 and/or 18, 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; 1 out of 3 HPV infected women would have been protected by the bivalent or the quadrivalent vaccine and 1 out of 2 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.

Cytopathological study and cervical HPV infection

Cytological alterations found in our study (5.3%) were similar to those observed in other studies, both in Spain[9,10,14] and Europe[19,20,22,23,24], 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.[9,10,12,19,21,22,23,24] The HPV prevalence in normal cytologies was 10.6%, similar to that reported by Bruni et al.[18] in our geographical area (8.8%), though lower than that reported in most studies.[9,21,22,23,24]

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 behavior as compared to older ones.

Number of sexual partners in life extensively appears[10,11,14,26,27,28] 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] This finding could be explained by the sexual behavior of not married women, who may probably have more sexual partners.

Coitus interruptus was the only contraception related practice found to be associated to 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[26,27,29] though not by others.[10] Quitting smoking has been considered to potentially revert infection risk.[29] 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 cells[29] 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, though 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 behavior of men and women.

Regarding ***parity*** and HPV infection risk, similarly to other authors[20], we found some protective effect in women with one or two births in our basic model for any-type HPV, though 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.[10,20,26,27,30]

Infection by other ***sexually transmitted diseases*** analyzed 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 infection;[14,20,27,28] 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 centers 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 six years for Gran Canaria, although two years had been originally planned. Potential variations over time could have influenced the socio-demographic 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.

ACKNOWLEDGEMENTS

We would like to acknowledge all patients for their participation in the study. We would also like to thank our colleagues and the study staff for their commitment to data collection and to Dr. Jorge Luis Doreste from University of Las Palmas de Gran

Canaria for statistical analysis for simple size of the study. We are very grateful to Tenesoya Alamo, Tanausú de la Cruz and Maria Dolores Navarro for technical assistance. We have received donations of analytical kits from Sanofi Pasteur MSD (Merck Sharp & Dome Corp.), Roche Diagnostics® SL and Fujirebio® Ibérica SL.

COMPETING INTERESTS: None declared.

FUNDING

This research has been funded by: Fondo de Investigación Sanitaria (Instituto de Salud Carlos III), grant FIS 00/714; Fundación Canaria de Investigación y Salud, grant FUNCIS 00/14 and FUNCIS 02/19 and Fundación Amurga. Funders had no involvement in the study design, collection, analysis, interpretation of the data, writing of the report nor in the decision to submit the paper for publication.

CONTRIBUTORSHIP STATEMENT

MA designed the study, performed HPV diagnostic molecular methods, data analysis, interpretation of data, and drafted the manuscript. ER performed statistical analysis of data, designed the figures and drafted the manuscript. MP performed cytopathological diagnosis. MS performed HPV diagnostic molecular methods. MAS designed and supervised a base data and processed the experimental data. AT, BV, LA, RH, HPV Canary Study Group received the patients and took cervical samples. MCC and ARdP were involved in planning and supervised the management of cervical a molecular samples. AL, JLT, OA, VB, NM, SC, AQ treated patients with cytological and molecular disorders. LB, SS and ES aided in interpreting the results and worked on the manuscript. All authors read and approved the final manuscript.

DATA SHARING

The database obtained from this study is kept under the supervision of the authors (Andujar M & Roura E) in an anonymized form. This data will be shared in a raw form by emailing to mandsan@gobiernodecanarias.org.

REFERENCES

1. Ferlay J, Ervik M, Lam F, et al. (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today [accessed September, 2, 2019].
2. Health Service, Government of Canary Islands. Available from: http://www3.gobiernodecanarias.org/sanidad/scs [accessed September 2, 2019].
3. Bray F, Colombet M, Mery L, et al, editors (2017) Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr [accessed September 2, 2019].
4. Bosch FX, Lorincz A, Muñoz N, et al. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244-65.
5. Muñoz N, Bosch FX, de Sanjosé S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003;348:518-27.
6. de Sanjosé S, Quint WG, Alemany L, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol* 2010;11:1048-56.

7. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine* 2012;30 Suppl 5:F123-38.
8. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 2015;372:711-23.
9. Castellsagué X, Iftner T, Roura E, et al. Prevalence and genotype distribution of human papillomavirus infection of the cervix in Spain: The CLEOPATRE Study. *J Med Virol* 2012;84:947-56.
10. de Sanjosé S, Almirall R, Lloveras B, et al. Cervical human papillomavirus infection in the female population in Barcelona, Spain. *Sex Transm Dis* 2003;30:788-93.
11. González C, Ortiz M, Canals J, et al. Higher prevalence of Human Papillomavirus infection in migrant women from Latin America in Spain. *Sex Transm Infect* 2006;82:260-62.
12. Bernal M, Burillo I, Mayordomo JI, et al. Human Papillomavirus (HPV) infection and intraepithelial neoplasia and invasive cancer of the uterine cervix: a case-control study in Zaragoza, Spain. *Infect Agent Cancer* 2008;3:8.
13. Martorell M, García-García JA, Ortiz C, et al. Prevalence and distribution of human papillomavirus findings in swab specimens from gynaecology clinics of the east coast of Spain. *Scand J Infect Dis* 2010;42:549-53.
14. Trigo-Daporta M, García-Campello M, Pérez-Ríos M, et al. High-risk human papillomavirus in Galicia, Spain: prevalence and evaluation of the sample representativeness. *Scand J Infect Dis* 2014;46:737-44.
15. García S, Dominguez-Gil M, Gayete J, et al. [Prevalence of human papillomavirus in Spanish women from a population screening program]. *Rev Esp Quimioter* 2017;30:177-82.

16. de Sanjosé S, Cortés X, Méndez C, et al. Age at sexual initiation and number of sexual partners in the female Spanish population: Results from the AFRODITA survey. *Eur J Obstet Gynecol Reprod Biol* 2008;140:234–40.

17. de Vuyst H, Clifford G, Li N, et al. HPV infection in Europe. *Eur J Cancer* 2009;45:2632-9.

18. Bruni L, Diaz M, Castellsagué X, et al. Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. *J Infect Dis* 2010;202:1789–99.

19. Klug SJ, Hukelmann M, Hollwitz B, et al. Prevalence of human papillomavirus types in women screened by cytology in Germany. *J Med Virol* 2007;79:616-25.

20. Ronco G, Ghisetti V, Segnan N, et al. Prevalence of human papillomavirus infection in women in Turin, Italy. *Eur J Cancer* 2005;41:297-305.

21. Heard I, Tondeur L, Arowas L, et al. Human papillomavirus types distribution in organized cervical cancer screening in France. *PloS One* 2013;8:e79372.

22. Arbyn M, Benoy I, Simoens C, et al. Prevaccination distribution of human papillomavirus types in women attending at cervical cancer screening in Belgium. *Cancer Epidemiol Biomarkers Prev* 2009;18:321-30.

23. Pista A, Freire de Oliveira C, Cunha MJ, et al. Prevalence of Human Papillomavirus Infection in Women in Portugal. The CLEOPATRE Portugal Study. *Int J Gynecol Cancer* 2011;21:1150-8.

24. Kjaer S, Breugelmans G, Munk C, et al. Population-based prevalence, type- and age-specific distribution of HPV in women before introduction of an HPV-vaccination program in Denmark. *Int J Cancer* 2008;123:1864-70.

25. Gravitt PE, Rositch AF, Silver MI, et al. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. *J Infect Dis* 2013;207:272-80.

26. Roura E, Iftner T, Vidart JA, et al. Predictors of human papillomavirus infection in women undergoing routine cervical cancer screening in Spain: the CLEOPATRE study. *BMC Infect Dis* 2012;12:145.

27. Pista A, de Oliveira CF, Cunha MJ, et al. Risk factors for human papillomavirus infection among women in Portugal: the CLEOPATRE Portugal Study. *Int J Gynaecol Obstet* 2012;118:112-6.

28. Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15:326–33.

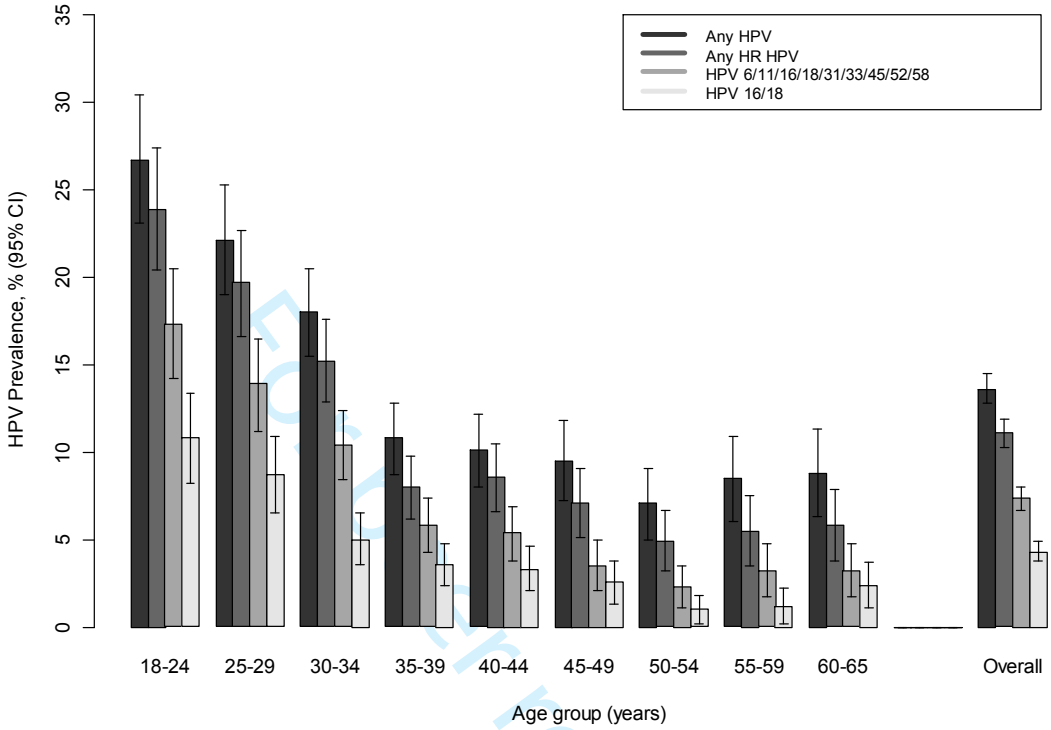
29. Vaccarella S, Herrero R, Snijders PJ, et al. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. *Int J Epidemiol* 2008;37:536–46.

30. Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15:2148–53.

31. Franceschi S, Plummer M, Clifford G, et al. Differences in the risk of cervical cancer and human papillomavirus infection by education level. Br J Cancer. 2009;101:865-70.

Legend of Fig. 1

Figure 1 – Overall prevalence and age-specific prevalence of cervical HPV infections by any HPV type, any hr HPV type, HPV types 16/18, and HPV types 6/11/16/18/31/33/45/52/58.



HPV: Human Papillomavirus; HR: High-Risk; CI: Confidence Interval.

Supplementary Table 1 – Characteristics of the study participants by population.

Study sample characteristics	GRAN CANARIA (GENERAL POP.) (n=3,212) N (%)	GRAN CANARIA (VOLUNTEERS) (n=665) N (%)	TENERIFE (n=2,214) N (%)
Age distribution (years)	*P(GCgp-TF)=0.08* [5]	*P(GCgp-GCv)=0.003* [6]	*P(GC-TF)=0.07* [7]
18-24	276 (8.6)	65 (9.8)	231 (10.4)
25-29	374 (11.6)	59 (8.9)	230 (10.4)
30-34	480 (14.9)	94 (14.1)	331 (15.0)
35-39	460 (14.3)	110 (16.5)	332 (15.0)
40-44	435 (13.5)	88 (13.2)	270 (12.2)
45-49	342 (10.6)	86 (12.9)	203 (9.2)
50-54	307 (9.6)	65 (9.8)	241 (10.9)
55-59	254 (7.9)	66 (9.9)	182 (8.2)
60-65	284 (8.8)	32 (4.8)	194 (8.8)
Level of education	*P(GCgp-TF)<0.001* [5]	*P(GCgp-GCv) <0.001* [6]	*P(GC-TF) <0.001* [7]
None	94 (2.9)	11 (1.7)	65 (2.9)
Preschool	167 (5.2)	22 (3.3)	99 (4.5)
Primary	1610 (50.2)	301 (45.3)	771 (34.8)
Secondary	778 (24.3)	188 (28.3)	533 (24.1)
Certificate of advanced study	339 (10.6)	97 (14.6)	319 (14.4)
Bachelor's degree	190 (5.9)	42 (6.3)	358 (16.2)
Others	26 (0.8)	3 (0.5)	69 (3.1)
Missing data	8 (-)	1 (-)	0 (-)
Marital status	*P(GCgp-TF)<0.001* [5]	*P(GCgp-GCv) <0.001* [6]	*P(GC-TF))=0.03* [7]
Single	757 (23.6)	148 (22.3)	491 (22.2)
Married/de facto partnership	2106 (65.7)	408 (61.4)	1405 (63.5)
Divorced/separated	247 (7.7)	90 (13.6)	236 (10.7)
Widowed	97 (3.0)	18 (2.7)	80 (3.6)
Missing data	5 (-)	1 (-)	2 (-)
Pregnancies	*P(GCgp-TF)=0.6* [5]	*P(GCgp-GCv)=0.9* [6]	*P(GC-TF) =0.6* [7]
No	701 (22.2)	147 (22.6)	495 (23.0)
Yes	2450 (77.8)	504 (77.4)	1659 (77.0)
Missing data	61 (-)	14 (-)	60 (-)
Number of live births [1]	*P(GCgp-TF)=0.6* [5]	*P(GCgp-GCv)=0.02* [6]	*P(GC-TF) =0.7* [7]
0	11 (0.5)	4 (0.8)	13 (0.9)
1	669 (29.2)	120 (25.1)	448 (29.3)
2	936 (40.8)	219 (45.7)	631 (41.3)
3	440 (19.2)	72 (15.0)	277 (18.1)
4	136 (5.9)	41 (8.6)	100 (6.5)
≥5	103 (4.5)	23 (4.8)	60 (3.9)
Missing data	155 (-)	25 (-)	130 (-)
Sexually transmitted disease [2]	*P(GCgp-TF)=0.1* [5]	*P(GCgp-GCv)=0.4* [6]	*P(GC-TF) =0.2* [7]
Never	3113 (96.9)	640 (96.2)	2129 (96.2)
Ever	99 (3.1)	25 (3.8)	85 (3.8)
Smoking status	*P(GCgp-TF)<0.001* [5]	*P(GCgp-GCv)=0.04* [6]	*P(GC-TF)<0.001* [7]
Never smoked	1897 (59.1)	375 (56.4)	1171 (52.9)
Ex smoker	454 (14.1)	120 (18)	339 (15.3)
Current smoker	861 (26.8)	170 (25.6)	704 (31.8)
Previous cervical pap smears	*P(GCgp-TF)<0.001* [5]	*P(GCgp-GCv)=0.02* [6]	*P(GC-TF)<0.001* [7]

None	85 (2.6)	21 (3.2)	110 (5)
1	281 (8.7)	32 (4.8)	180 (8.1)
2-3	561 (17.5)	128 (19.2)	367 (16.6)
4-5	406 (12.6)	77 (11.6)	289 (13.1)
>5	1704 (53.1)	371 (55.8)	1198 (54.1)
Do not know	175 (5.4)	36 (5.4)	70 (3.2)
Previous cervical lesions [3]	*P(GCgp-TF)=0.09 [5]*	*P(GCgp-GCv)=0.3 [6]*	*P(GC-TF) =0.2 [7]*
No	2561 (92.9)	521 (91.7)	1755 (92.2)
Yes	190 (6.9)	47 (8.3)	148 (7.8)
Do not know	5 (0.2)	0 (0.0)	0 (0.0)
Missing data	371 (-)	76 (-)	201 (-)
Age at first sexual intercourse (years)	*P(GCgp-TF)=0.007 [5]*	*P(GCgp-GCv)=0.2 [6]*	*P(GC-TF) =0.006 [7]*
<15	92 (2.9)	19 (2.9)	76 (3.5)
15-16	415 (13.1)	80 (12.2)	333 (15.2)
17-18	947 (29.8)	207 (31.5)	709 (32.4)
19-20	689 (21.7)	157 (23.9)	435 (19.9)
21-25	772 (24.3)	158 (24.0)	491 (22.4)
>25	259 (8.2)	36 (5.5)	147 (6.7)
Missing data	38 (-)	8 (-)	23 (-)
Lifetime number of sexual partners	*P(GCgp-TF)<0.001 [5]*	*P(GCgp-GCv)=0.2 [6]*	*P(GC-TF)<0.001 [7]*
1	1922 (60.7)	377 (57.2)	933 (43.0)
2-3	755 (23.8)	154 (23.4)	662 (30.5)
4-5	250 (7.9)	68 (10.3)	296 (13.6)
6-10	172 (5.4)	42 (6.4)	191 (8.8)
11-20	49 (1.5)	13 (2.0)	64 (2.9)
>20	19 (0.6)	5 (0.8)	25 (1.2)
Missing data	45 (-)	6 (-)	43 (-)
Contraceptive methods used [4]			
	P(GCgp-TF)=0.2 [5]	*P(GCgp-GCv)=0.9 [6]*	*P(GC-TF)=0.1 [7]*
Oral contraceptives	2477 (77.1)	515 (77.4)	1672 (75.5)
	P(GCgp-TF)=0.2 [5]	*P(GCgp-GCv)=0.008 [6]*	*P(GC-TF)=0.04 [7]*
IUD	597 (18.6)	154 (23.2)	382 (17.3)
	P(GCgp-TF)<0.004 [5]	*P(GCgp-GCv)=0.2 [6]*	*P(GC-TF)<0.001 [7]*
Condom	2311 (71.9)	495 (74.4)	1716 (77.5)
	P(GCgp-TF)=0.04 [5]	*P(GCgp-GCv)=0.05 [6]*	*P(GC-TF)=0.1 [7]*
Rhythm method/coitus interruptus	1559 (48.5)	351 (52.8)	1139 (51.4)
	P(GCgp-TF)=0.1 [5]	*P(GCgp-GCv)=0.4 [6]*	*P(GC-TF)=0.2 [7]*
Diaphragm/spermicide	136 (4.2)	23 (3.5)	75 (3.4)
	P(GCgp-TF)<0.001 [5]	*P(GCgp-GCv)=0.2 [6]*	*P(GC-TF)<0.001 [7]*
Injection/implant	160 (5.0)	26 (3.9)	67 (3.0)
	P(GCgp-TF)=0.3 [5]	*P(GCgp-GCv)=0.4 [6]*	*P(GC-TF)=0.2 [7]*
Tube ligation	430 (13.4)	97 (14.6)	275 (12.4)
	P(GCgp-TF)<0.001 [5]	*P(GCgp-GCv)=0.06 [6]*	*P(GC-TF)<0.001 [7]*
Vasectomy	332 (10.3)	85 (12.8)	132 (6.0)

GCgp: Gran Canaria (general population); GCv: Gran Canaria (volunteers); GC: Gran Canaria (including general population and volunteers); TF: Tenerife.

[1] Among ever pregnant women. [2] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [3] Among women with a previous pap smear. [4] Do not add the total of women

because a woman can use more than one contraceptive in lifetime. [5] P-value of Pearson's Chi-squared test between Gran Canaria (general population) and Tenerife. [6] P-value of Pearson's Chi-squared test between Gran Canaria (general population) and Gran Canaria (volunteers). [7] P-value of Pearson's Chi-squared test between Gran Canaria (general population and volunteers) and Tenerife.

Supplementary Table 2 – Prevalence of Human Papillomavirus (HPV) by age group for any type and for any high-risk type and by population.

GRAN CANARIA – GENERAL POPULATION (n=3,185)

Age group (years)	Number of tested women	Number of HPV positive women	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)
18-24	274	64	23.4 (18.3-28.4)	21.9 (17.0-26.8)
25-29	372	81	21.8 (17.6-26.0)	19.1 (15.1-23.1)
30-34	478	74	15.5 (12.2-18.7)	12.3 (9.4-15.3)
35-39	455	42	9.2 (6.6-11.9)	6.6 (4.3-8.9)
40-44	432	45	10.4 (7.5-13.3)	9.3 (6.5-12.0)
45-49	339	37	10.9 (7.6-14.2)	8.3 (5.3-11.2)
50-54	304	20	6.6 (3.8-9.4)	4.9 (2.5-7.4)
55-59	252	14	5.6 (2.7-8.4)	4.0 (1.6-6.4)
60-65	279	28	10.0 (6.5-13.6)	5.7 (3.0-8.5)
Total	**3,185**	**405**	**12.7 (11.6-13.9)**	**10.3 (9.3-11.4)**

HPV: Human Papillomavirus; CI: Confidence Interval; HR: High-Risk.

[1] HR types includes 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.

GRAN CANARIA – VOLUNTEERS (n=662)

Age group (years)	Number of tested women	Number of HPV positive women	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)
18-24	65	17	26.2 (15.5-36.8)	23.1 (12.8-33.3)
25-29	59	12	20.3 (10.1-30.6)	16.9 (7.4-26.5)
30-34	94	19	20.2 (12.1-28.3)	19.1 (11.2-27.1)
35-39	109	17	15.6 (8.8-22.4)	12.8 (6.6-19.1)
40-44	88	11	12.5 (5.6-19.4)	9.1 (3.1-15.1)
45-49	85	8	9.4 (3.2-15.6)	4.7 (0.2-9.2)
50-54	65	3	4.6 (0.0-9.7)	4.6 (0.0-9.7)
55-59	65	7	10.8 (3.2-18.3)	6.2 (0.3-12.0)
60-65	32	2	6.2 (0.0-14.6)	6.2 (0.0-14.6)
Total	**662**	**96**	**14.5 (11.8-17.2)**	**11.8 (9.3-14.2)**

HPV: Human Papillomavirus; CI: Confidence Interval; HR: High-Risk.

[1] HR types includes 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.

GRAN CANARIA (n=3,847)

Age group (years)	Number of tested women	Number of HPV positive women	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)
18-24	339	81	23.9 (19.4-28.4)	22.1 (17.7-26.5)
25-29	431	93	21.6 (17.7-25.5)	18.8 (15.1-22.5)
30-34	572	93	16.3 (13.2-19.3)	13.5 (10.7-16.3)
35-39	564	59	10.5 (7.9-13.0)	7.8 (5.6-10.0)
40-44	520	56	10.8 (8.1-13.4)	9.2 (6.7-11.7)
45-49	424	45	10.6 (7.7-13.5)	7.5 (5.0-10.1)
50-54	369	23	6.2 (3.8-8.7)	4.9 (2.7-7.1)
55-59	317	21	6.6 (3.9-9.4)	4.4 (2.2-6.7)
60-65	311	30	9.6 (6.4-12.9)	5.8 (3.2-8.4)
Total	**3,847**	**501**	**13.0 (12.0-14.1)**	**10.6 (9.6-11.6)**

HPV: Human Papillomavirus; CI: Confidence Interval; HR: High-Risk.

[1] HR types includes 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.

TENERIFE (n=2,163)

Age group (years)	Number of tested women	Number of HPV positive women	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)
18-24	226	70	31.0 (24.9-37.0)	26.5 (20.8-32.3)
25-29	224	52	23.2 (17.7-28.7)	21.4 (16.1-26.8)
30-34	322	68	21.1 (16.7-25.6)	18.3 (14.1-22.5)
35-39	326	37	11.3 (7.9-14.8)	8.3 (5.3-11.3)
40-44	263	23	8.7 (5.3-12.2)	7.2 (4.1-10.4)
45-49	198	14	7.1 (3.5-10.6)	6.1 (2.7-9.4)
50-54	238	20	8.4 (4.9-11.9)	5.0 (2.3-7.8)
55-59	178	21	11.8 (7.1-16.5)	7.3 (3.5-11.1)
60-65	188	14	7.4 (3.7-11.2)	5.9 (2.5-9.2)
Total	**2,163**	**319**	**14.7 (13.3-16.2)**	**12.1 (10.7-13.4)**

HPV: Human Papillomavirus; CI: Confidence Interval; HR: High-Risk.

[1] HR types includes 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.

Supplementary Table 3 – Overall prevalence and age-specific prevalence of cervical HPV infections by any HPV type, any hr HPV type, HPV types 6/11/16/18/31/33/45/52/58 and HPV types 16/18 (n=6,010 women).

Age group (years)	Any HPV prevalence (%; 95% CI)	Any HR HPV prevalence [1] (%; 95% CI)	Prevalence of HPV 6/11/16/18/ 31/33/45/52/58 (%; 95% CI)	Prevalence of HPV 16/18/ (%; 95% CI)
18-24	26.7 (23.1-30.4)	23.9 (20.4-27.4)	17.3 (14.2-20.5)	10.8 (8.2-13.4)
25-29	22.1 (19.0-25.3)	19.7 (16.6-22.7)	13.9 (11.2-16.5)	8.7 (6.5-10.9)
30-34	18.0 (15.5-20.5)	15.2 (12.9-17.6)	10.4 (8.4-12.4)	5.0 (3.6-6.5)
35-39	10.8 (8.7-12.8)	8.0 (6.2-9.8)	5.8 (4.3-7.4)	3.6 (2.4-4.8)
40-44	10.1 (8.0-12.2)	8.6 (6.6-10.5)	5.4 (3.8-6.9)	3.3 (2.1-4.6)
45-49	9.5 (7.2-11.8)	7.1 (5.1-9.1)	3.5 (2.1-5.0)	2.6 (1.3-3.8)
50-54	7.1 (5.0-9.1)	4.9 (3.2-6.7)	2.3 (1.1-3.5)	1.0 (0.2-1.8)
55-59	8.5 (6.0-10.9)	5.5 (3.5-7.5)	3.2 (1.7-4.8)	1.2 (0.2-2.2)
60-65	8.8 (6.3-11.3)	5.8 (3.8-7.9)	3.2 (1.7-4.8)	2.4 (1.1-3.7)
Total	**13.6 (12.8-14.5)**	**11.1 (10.3-11.9)**	**7.4 (6.7-8.0)**	**4.3 (3.8-4.9)**

HPV: Human Papillomavirus; HR: High-Risk; CI: Confidence Interval.

[1] HR HPV types includes 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.

Supplementary Table 4 – Human Papillomavirus (HPV) type-specific distribution of the most common types (n=6,010 women) by cytology result.

HPV type		NORMAL CYTOLOGY (n=5,693)			ABNORMAL CYTOLOGY (n=317)		
		Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)
Any HPV types		**601**	**10.6 (9.8-11.4)**	**-**	**219**	**69.1 (64.0-74.2)**	**-**
Single types		**260**	**4.6 (4.0-5.1)**	**43.3 (39.3-47.2)**	**99**	**31.2 (26.1-36.3)**	**45.2 (38.6-51.8)**
HR HPV types [1]							
	16	56	1.0 (0.7-1.2)	9.3 (7.0-11.6)	19	6.0 (3.4-8.6)	8.7 (4.9-12.4)
	51	22	0.4 (0.2-0.5)	3.7 (2.2-5.2)	12	3.8 (1.7-5.9)	5.5 (2.5-8.5)
	53	21	0.4 (0.2-0.5)	3.5 (2.0-5.0)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
	31	14	0.2 (0.1-0.4)	2.3 (1.1-3.5)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
	59	8	0.1 (0.0-0.2)	1.3 (0.4-2.2)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
	33	10	0.2 (0.1-0.3)	1.3 (0.4-2.2)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
	68	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
	70	7	0.1 (0.0-0.2)	1.2 (0.3-2.0)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)
	66	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	-	-	-
	52	6	0.1 (0.0-0.2)	1.0 (0.2-1.8)	3	0.9 (0.1-2.0)	1.4 (0.2-2.9)
	58	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	5	1.6 (0.2-2.9)	2.3 (0.3-4.3)
	18	7	0.1 (0.0-0.2)	1.2 (0.3-2.0)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
	56	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)
	35	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
	39	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
	73	3	0.1 (0.0-0.1)	0.5 (0.0-1.1)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
	45	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)

67	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
69	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	-	-	-
69/71	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	-	-	-
LR HPV types [2]						
42	11	0.2 (0.1-0.3)	1.8 (0.8-2.9)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
84	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
62	9	0.2 (0.1-0.3)	1.5 (0.5-2.5)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
61	8	0.1 (0.0-0.2)	1.3 (0.4-2.2)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
6	8	0.1 (0.0-0.2)	1.3 (0.4-2.2)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
55	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
81	7	0.1 (0.0-0.2)	1.2 (0.3-2.0)	2	0.6 (0.2-1.5)	0.9 (0.3-2.2)
89	5	0.1 (0.0-0.2)	0.8 (0.1-1.6)	-	-	-
54	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	-	-	-
11	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
43	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
72	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
83	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
40	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	1	0.3 (0.3-0.9)	0.5 (0.4-1.3)
X	**24**	**0.4 (0.3-0.6)**	**4.0 (2.4-5.6)**	**4**	**1.3 (0.0-2.5)**	**1.8 (0.1-3.6)**
Multiple types	**317**	**5.6 (5.0-6.2)**	**52.7 (48.8-56.7)**	**116**	**36.6 (31.3-41.9)**	**53.0 (46.4-59.6)**
Number of multiple types						
2 types	153	2.7 (2.3-3.1)	25.5 (22.0-28.9)	50	15.8 (11.8-19.8)	22.8 (17.3-28.4)
3 types	81	1.4 (1.1-1.7)	13.5 (10.7-16.2)	34	10.7 (7.3-14.1)	15.5 (10.7-20.3)
4 types	57	1.0 (0.7-1.3)	9.5 (7.1-11.8)	16	5.0 (2.6-7.5)	7.3 (3.9-10.8)
5 or more types	26	0.5 (0.3-0.6)	4.3 (2.7-6.0)	16	5.0 (2.6-7.5)	7.3 (3.9-10.8)
Most frequent combinations						
16 with others	113	2.0 (1.6-2.3)	18.8 (15.7-21.9)	40	12.6 (9.0-16.3)	18.3 (13.1-23.4)

51 with others	56	1.0 (0.7-1.2)	9.3 (7.0-11.6)	22	6.9 (4.1-9.7)	10.0 (6.1-14.0)
53 with others	50	0.9 (0.6-1.1)	8.3 (6.1-10.5)	31	9.8 (6.5-13.0)	14.2 (9.5-18.8)
31 with others	38	0.7 (0.5-0.9)	6.3 (4.4-8.3)	16	5.0 (2.6-7.5)	7.3 (3.9-10.8)
42 with others	42	0.7 (0.5-1.0)	7.0 (5.0-9.0)	17	5.4 (2.9-7.8)	7.8 (4.2-11.3)
6 with others	16	0.3 (0.1-0.4)	2.7 (1.4-3.9)	9	2.8 (1.0-4.7)	4.1 (1.5-6.7)
18 with others	36	0.6 (0.4-0.8)	6.0 (4.1-7.9)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
33 with others	17	0.3 (0.2-0.4)	2.8 (1.5-4.2)	3	0.9 (0.0-2.0)	1.4 (0.0-2.9)
59 with others	50	0.9 (0.6-1.1)	8.3 (6.1-10.5)	17	5.4 (2.9-7.8)	7.8 (4.2-11.3)
39 with others	27	0.5 (0.3-0.7)	4.5 (2.8-6.1)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
35 with others	13	0.2 (0.1-0.4)	2.2 (1.0-3.3)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
52 with others	40	0.7 (0.5-0.9)	6.7 (4.7-8.6)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
56 with others	29	0.5 (0.3-0.7)	4.8 (3.1-6.5)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
58 with others	32	0.6 (0.4-0.8)	5.3 (3.5-7.1)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
62 with others	37	0.6 (0.4-0.9)	6.2 (4.2-8.1)	9	2.8 (1.0-4.7)	4.1 (1.5-6.7)
61 with others	29	0.5 (0.3-0.7)	4.8 (3.1-6.5)	15	4.7 (2.4-7.1)	6.8 (3.5-10.2)
66 with others	38	0.7 (0.5-0.9)	6.3 (4.4-8.3)	12	3.8 (1.7-5.9)	5.5 (2.5-8.5)
45 with others	24	0.4 (0.3-0.6)	4.0 (2.4-5.6)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
68 with others	22	0.4 (0.2-0.5)	3.7 (2.2-5.2)	10	3.2 (1.2-5.1)	4.6 (1.8-7.3)
54 with others	34	0.6 (0.4-0.8)	5.7 (3.8-7.5)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
70 with others	11	0.2 (0.1-0.3)	1.8 (0.8-2.9)	4	1.3 (0.0-2.5)	1.8 (0.1-6.3)
84 with others	30	0.5 (0.3-0.7)	5.0 (3.3-6.7)	8	2.5 (0.8-4.3)	3.7 (1.2-6.1)
55 with others	11	0.2 (0.1-0.3)	1.8 (0.8-2.9)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
11 with others	6	0.1 (0.0-0.2)	1.0 (0.2-1.8)	2	0.6 (0.0-1.5)	0.9 (0.3-2.2)
81 with others	19	0.3 (0.2-0.5)	3.2 (1.8-4.6)	9	2.8 (1.0-4.7)	4.1 (1.5-6.7)
40 with others	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	-	-	-
89 with others	32	0.6 (0.4-0.8)	5.3 (3.5-7.1)	14	4.4 (2.2-6.7)	6.4 (3.2-9.6)
67 with others	9	0.2 (0.1-0.3)	1.5 (0.5-2.5)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)

69 with others	5	0.1 (0.0-0.2)	0.8 (0.1-1.6)	-	-	-
73 with others	16	0.3 (0.1-0.4)	2.7 (1.4-3.9)	7	2.2 (0.6-3.8)	3.2 (0.9-5.5)
83 with others	9	0.2 (0.1-0.3)	1.5 (0.5-2.5)	6	1.9 (0.4-3.4)	2.7 (0.6-4.9)
43 with others	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)	-	-	-
72 with others	4	0.1 (0.0-0.1)	0.7 (0.0-1.3)	4	1.3 (0.0-2.5)	1.8 (0.1-3.6)
69/71 with others	2	0.0 (0.0-0.1)	0.3 (0.0-0.8)	-	-	-
71 with others	6	0.1 (0.0-0.2)	1.0 (0.2-1.8)	3	0.9 (0.0-2.0)	1.4 (0.0-2.9)
74 with others	5	0.1 (0.0-0.2)	0.8 (0.1-1.6)	1	0.3 (0.0-0.9)	0.5 (0.0-1.3)
64 with others	1	0.0 (0.0-0.1)	0.2 (0.0-0.5)	1	0.3 (0.0-0.9)	0.5 (0.0-1.3)
82 with others	10	0.2 (0.1-0.3)	1.7 (0.6-2.7)	3	0.9 (0.0-2.0)	1.4 (0.0-2.9)
Combinations of vaccine types						
6/11 [3]	31	0.5 (0.4-0.7)	5.2 (3.4-6.9)	12	3.8 (1.7-5.9)	5.5 (2.5-8.5)
16/18 [3]	199	3.5 (3.0-4.0)	33.1 (29.3-36.9)	62	19.6 (15.2-23.9)	28.3 (22.3-34.3)
6/11/16/18 [3]	225	4.0 (3.4-4.5)	37.4 (33.6-41.3)	72	22.7 (18.1-27.3)	32.9 (26.7-39.1)
6/11/16/18/31/33/45/52/58 [3]	334	5.9 (5.3-6.5)	55.6 (51.6-59.5)	110	34.7 (29.5-39.9)	50.2 (43.6-56.9)

HPV: Human Papillomavirus; HR: High-Risk; LR: Low-Risk; CI: Confidence Interval.

[1] HR types includes 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. [2] LR types includes: 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89. [3] One or more of the vaccine types are concerned.

Supplementary Table 5 – Human Papillomavirus (HPV) type-specific distribution of the most common types (n=6,010 women) by result of abnormal cytology.

HPV type	ASCUS (n=214)			LSIL (n=91)			HSIL+ (n=12)		
	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)	Number of HPV positive women	HPV prevalence among all women (%; 95% CI)	HPV prevalence among positive women (%; 95% CI)
Any HPV type	**130**	**60.7 (54.2-67.3)**	**-**	**79**	**86.8 (79.9-93.8)**	**-**	**10**	**83.3 (62.2-100.0)**	**-**
Single types	**66**	**30.8 (24.7-37.0)**	**50.8 (42.2-59.4)**	**29**	**31.9 (22.3-41.4)**	**36.7 (26.1-47.3)**	**4**	**33.3 (6.7-60.0)**	**40.0 (9.6-70.4)**
HR HPV types [1]									
16	13	6.1 (2.9-9.3)	10.0 (4.8-15.2)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
51	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	5	5.5 (0.8-10.2)	6.3 (1.0-11.7)	1	8.3 (0.0.-24.0)	10.0 (0.0-28.6)
53	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
31	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
59	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
33	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
68	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
70	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
66	-	-	-	-	-	-	-	-	-
52	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
58	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
18	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
56	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
35	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
39	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
73	-	-	-	-	-	-	1	8.3 (0.0.-24.0)	10.0 (0.0-28.6)

45	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
67	-	-	-	-	-	-	-	-	-
69	-	-	-	-	-	-	-	-	-
69/71	-	-	-	-	-	-	-	-	-
LR HPV types [2]									
42	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
84	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
62	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
61	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	-	-	-
6	-	-	-	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
55	7	3.3 (0.9-5.7)	5.4 (1.5-9.3)	-	-	-	-	-	-
81	-	-	-	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
89	-	-	-	-	-	-	-	-	-
54	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-
43	-	-	-	-	-	-	-	-	-
72	-	-	-	-	-	-	-	-	-
83	-	-	-	-	-	-	-	-	-
40	-	-	-	-	-	-	-	-	-
X	**3**	**1.4 (0.0-3.0)**	**2.3 (0.0-4.9)**	**1**	**1.1 (0.0-3.2)**	**1.3 (0.0-3.7)**	**-**	**-**	**-**
Multiple types	**61**	**28.5 (22.5-34.6)**	**46.9 (38.3-55.5)**	**49**	**53.8 (43.6-64.1)**	**62.0 (51.3-72.7)**	**6**	**50.0 (21.7-78.3)**	**60.0 (29.6-90.4)**
Number of multiple types									
2 types	28	13.1 (8.6-17.6)	21.5 (14.5-28.6)	20	22.0 (13.5-30.5)	25.3 (15.7-34.9)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
3 types	19	8.9 (5.1-12.7)	14.6 (8.5-20.7)	12	13.2 (6.2-20.1)	15.2 (7.3-23.1)	3	25.0 (0.5-49.5)	30.0 (1.6-58.4)
4 types	9	4.2 (1.5-6.9)	6.9 (2.6-11.3)	7	7.7 (2.2-13.2)	8.9 (2.6-15.1)	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
5 or more types	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	10	11.0 (4.6-17.4)	12.7 (5.3-20.0)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)

Most frequent combinations									
16 with others	16	7.5 (4.0-11.0)	12.3 (6.7-18.0)	22	24.2 (15.4-33)	27.8 (18-37.7)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
51 with others	12	5.6 (2.5-8.7)	9.2 (4.3-14.2)	9	9.9 (3.8-16.0)	11.4 (4.4-18.4)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
53 with others	16	7.5 (4.0-11.0)	12.3 (6.7-18.0)	14	15.4 (8.0-22.8)	17.7 (9.3-26.1)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
31 with others	7	3.3 (0.9-5.7)	5.4 (1.5-9.3)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	3	25.0 (0.5-49.5)	30.0 (1.6-58.4)
42 with others	9	4.2 (1.5-6.9)	6.9 (2.6-11.3)	7	7.7 (2.2-13.2)	8.9 (2.6-15.1)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
6 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
18 with others	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
33 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	-	-	-
59 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
39 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
35 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	2	2.2 (0.0-5.2)	2.5 (0.0-6.0)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
52 with others	4	1.9 (0.1-3.7)	3.1 (0.1-6.0)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	2	16.7 (0.0-37.8)	20.0 (0.0-44.8)
56 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	-	-	-
58 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	5	5.5 (0.8-10.2)	6.3 (1.0-11.7)	-	-	-
62 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
61 with others	7	3.3 (0.9-5.7)	5.4 (1.5-9.3)	8	8.8 (3.0-14.6)	10.1 (3.5-16.8)	-	-	-
66 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	-	-	-
45 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	3	25 (0.5-49.5)	30.0 (1.6-58.4)
68 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
54 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
70 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
84 with others	4	1.9 (0.1-3.7)	3.1 (0.1-6.0)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	-	-	-
55 with others	4	1.9 (0.1-3.7)	3.1 (0.1-6.0)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
11 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
81 with others	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-

40 with others	-	-	-	-	-	-	-	-	-
89 with others	8	3.7 (1.2-6.3)	6.2 (2.0-10.3)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	-	-	-
67 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
69 with others	-	-	-	-	-	-	-	-	-
73 with others	3	1.4 (0.0-3.0)	2.3 (0.0-4.9)	4	4.4 (0.2-8.6)	5.1 (0.2-9.9)	0	0.0 (0.0-0.0)	0.0 (0.0-0.0)
83 with others	5	2.3 (0.3-4.4)	3.8 (0.5-7.2)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
43 with others	-	-	-	-	-	-	-	-	-
72 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	3	3.3 (0.0-7.0)	3.8 (0.0-8.0)	-	-	-
69/71 with others	-	-	-	-	-	-	-	-	-
71 with others	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	1	1.1 (0.0-3.2)	1.3 (0.0-3.7)	-	-	-
74 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
64 with others	1	0.5 (0.0-1.4)	0.8 (0.0-2.3)	-	-	-	-	-	-
82 with others	2	0.9 (0.0-2.2)	1.5 (0.0-3.7)	-	-	-	1	8.3 (0.0-24.0)	10.0 (0.0-28.6)
Combinations of vaccine types									
6/11 [3]	6	2.8 (0.6-5.0)	4.6 (1.0-8.2)	6	6.6 (1.5-11.7)	7.6 (1.8-13.4)	-	-	-
16/18 [3]	31	14.5 (9.8-19.2)	23.8 (16.5-31.2)	27	29.7 (20.3-39.1)	34.2 (23.7-44.6)	4	33.3 (6.7-60.0)	40.0 (9.6-70.4)
6/11/16/18 [3]	37	17.3 (12.2-22.4)	28.5 (20.7-36.2)	31	34.1 (24.3-43.8)	39.2 (28.5-50.0)	4	33.3 (6.7-60.0)	40.0 (9.6-70.4)
6/11/16/18/31/33/45/52/58 [3]	57	26.6 (20.7-32.6)	43.8 (35.3-52.4)	45	49.5 (39.2-59.7)	57.0 (46.0-67.9)	8	66.7 (40.0-93.3)	80.0 (55.2-100.0)

HPV: Human Papillomavirus; HR: High-Risk; LR: Low-Risk; CI: Confidence Interval.

[1] HR types includes 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. [2] LR types includes: 6, 11, 40, 42, 43, 54, 55, 61, 62, 72, 81, 83, 84, 89. [3] One or more of the vaccine types are concerned.

Supplementary Table 6 – Crude and multivariate analyses of the association between cervical High-Risk Human Papillomavirus (HR HPV) infection and selected subjects' characteristics (n=5,858 women).

Study sample characteristics	Number of HR HPV positive women / number of HPV tested women (negative + HR HPV positive)	HPV prevalence (%)	Adjusted model [1] POR (95% CI)
Population			
Gran Canaria	407 / 3,753	10.8	1.0 (ref)
Tenerife	261 / 2,105	12.4	1.0 (0.8-1.2)
Age distribution (years)			
18-24	135 / 549	24.6	**2.9 (1.7-4.8)**
25-29	129 / 639	20.2	**2.2 (1.3-3.5)**
30-34	136 / 869	15.7	**1.7 (1.0-2.7)**
35-39	71 / 865	8.2	0.9 (0.5-1.4)
40-44	67 / 771	8.7	1.0 (0.6-1.6)
45-49	44 / 607	7.2	0.8 (0.5-1.3)
50-54	30 / 594	5.1	0.6 (0.4-1.1)
55-59	27 / 480	5.6	0.8 (0.5-1.4)
60-65	29 / 484	6.0	1.0 (ref)
p-value for trend			***p<0.001***
Level of education			
None / Preschool	29 / 438	6.6	1.0 (ref)
Primary	246 / 2,588	9.5	0.9 (0.6-1.5)
Secondary	201 / 1,437	14.0	0.9 (0.5-1.3)
University or higher	178 / 1,296	13.7	0.9 (0.5-1.4)
Others	13 / 90	14.4	0.8 (0.4-1.8)
Missing data	1 / 9	-	-
p-value for trend (excluding others)			*p=0.3*
Marital status			
Single	283 / 1,333	21.2	**1.5 (1.2-1.9)**
Married/de facto partnership	267 / 3,792	7.0	1.0 (ref)
Divorced/separated	99 / 541	18.3	**2.0 (1.5-2.7)**
Widowed	18 / 184	9.8	**1.8 (1.0-3.1)**
Missing data	1 / 8	-	-
Number of live births			
No [2]	240 / 1,307	18.4	1.0 (ref)
1	137 / 1,202	11.4	0.9 (0.7-1.2)
2	136 / 1,725	7.9	1.0 (0.8-1.4)
3	53 / 754	7.0	1.1 (0.7-1.6)
≥4	27 / 448	6.0	1.0 (0.6-1.7)
Missing data	75 / 422	-	-
Smoking status			
Never smoked	298 / 3,324	9.0	1.0 (ref)
Ex smoker	102 / 876	11.6	1.2 (0.9-1.5)

Current smoker	268 / 1,658	16.2	**1.3 (1.1-1.6)**
Age at first sexual intercourse (years)			
<15	35 / 179	19.6	1.0 (0.5-1.8)
15-16	136 / 787	17.3	1.0 (0.6-1.6)
17-18	235 / 1,797	13.1	1.0 (0.6-1.6)
19-20	118 / 1,241	9.5	1.0 (0.6-1.5)
21-25	112 / 1,368	8.2	1.2 (0.7-1.8)
>25	26 / 418	6.2	1.0 (ref)
Missing data	6 / 68	-	-
p-value for trend			*p=0.6*
Lifetime number of sexual partners			
1	160 / 3,135	5.1	1.0 (ref)
2-3	224 / 1,495	15.0	**2.3 (1.9-2.9)**
4-5	124 / 596	20.8	**3.1 (2.3-4.0)**
6-10	100 / 376	26.6	**4.1 (3.0-5.6)**
11-20	36 / 121	29.8	**4.6 (2.9-7.3)**
>20	16 / 47	34.0	**7.1 (3.7-13.6)**
Missing data	8 / 88	-	-
p-value for trend			***p<0.001***
Use of oral contraceptives			
Never	126 / 1,366	9.2	1.0 (ref)
Ever	542 / 4,492	12.1	1.2 (0.97-1.5)
Rhythm method/coitus interruptus			
Never	316 / 2,933	10.8	1.0 (ref)
Ever	352 / 2,925	12.0	1.1 (0.96-1.4)
Previous cervical lesions			
No	527 / 4,868	10.8	1.0 (ref)
Yes	70 / 364	19.2	**1.5 (1.1-2.0)**
Missing data [3]	71 / 626	-	-
Genital warts			
Never	633 / 5,744	11.0	1.0 (ref)
Ever	35 / 114	30.7	**2.0 (1.3-3.2)**

[1] Adjusted model: adjusted for age group, population, level of education, marital status, smoking habits, lifetime number of sexual partners, previous cervical lesions, and ever had genital warts. [2] Includes women who were pregnant but had 0 live births. [3] Includes "Do not know" in the "Missing data" category. [4] Includes syphilis, genital herpes, gonorrhea, HIV (positive test), genital warts, Chlamydia, genital ulcer, others. [5] Excludes ever had genital warts in the adjustment.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7-8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-10
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	11-16

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.