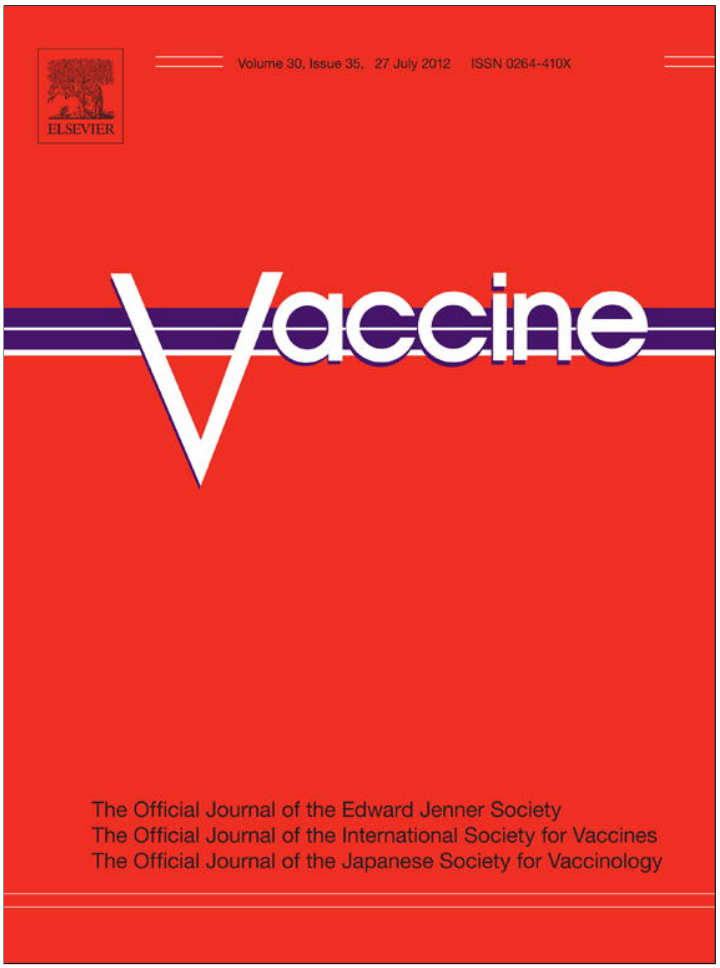

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Prevalence of type-specific human papillomavirus infection among women in France: Implications for screening, vaccination, and a future generation of multivalent HPV vaccines☆

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ABSTRACT

To assess human papillomavirus (HPV) prevalence and genotype distribution by age and cervical cytology/histology status among women undergoing routine gynecological examinations, and to discuss the possible impact on preventive strategies. Liquid-based cytology (LBC) samples were tested for HPV DNA, mRNA, and HPV genotypes. Women with atypical squamous cells of undetermined significance or greater (ASC-US+) and/or at least one positive HPV test were referred to colposcopy. Those with normal colposcopy results had biopsies taken at the 6 and 12 O'clock positions of the normal transformation zone. Of the 5002 women, 515 (10.3%) were <25 and 4487 (89.7%) were ≥25 years old. Overall HPV prevalence varied between 10.1% and 16.1% depending on the assay. Risk factors for HPV infection included greater number of recent sexual partners, history of abnormal cervical pathology, age <25 years, and smoking. HPV prevalence increased with the cytological and histological severity of cervical lesions. Prevalence of HPV 16/18 was 5.2% and 2.7% in women <25 and ≥25 years old, respectively. HPV 16 was the type most strongly associated with a diagnosis of cervical intraepithelial neoplasia grade 3 or higher (CIN3+) (odds ratio = 11.64 vs. HPV 16 absent, $P < 0.001$). A high proportion of high-grade cervical lesions (60.6% of genotyping assay-positive CIN2+) were associated with HPV types 31, 33, 45, 52, or 58. These data indicate that almost all young women could benefit from HPV prophylactic vaccination, but confirm the need for continued cervical screening and highlight the potential benefit of future vaccines targeting a wider range of HPV types.

1. Introduction

Cervical cancer is the third most common cancer in women worldwide [1]. Two prophylactic human papillomavirus (HPV) vaccines are currently available for cervical cancer prevention. Gardasil® (Sanofi Pasteur MSD, Lyon, France) is a quadrivalent vaccine for the HPV high-risk (HR) types 16 and 18, and low-risk types 6 and 11. Cervarix® (GlaxoSmithKline, Rixensart, Belgium) is a bivalent vaccine for HR types 16 and 18. The eight most common HR types (16, 18, 31, 33, 35, 45, 52, and 58) are responsible for approximately 90% of cervical cancer cases worldwide [2], with HPV-16 and 18 accounting for 70–80% of cases [3,4].

A new generation of multivalent HPV vaccines, aiming to protect against a broader range of HPV types (16, 18, 31, 33, 45, 52, 58, 6, and 11), is under clinical evaluation. Since 2007 in France, HPV vaccination has been recommended for 14-year-old girls, with catch-up vaccination for women 15–23 years (before sexual debut or sexually active for <1 year) [5].

Prevalence of cervical HPV infections with vaccine types provides a measure of the potential benefits of HPV vaccination

Abbreviations: AHPV, APTIMA® HPV assay; ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HC2, Hybrid Capture® 2 assay; HPV, human papillomavirus; HR, high-risk; HSIL, high-grade squamous intraepithelial lesions; LBC, liquid-based cytology; OR, odds ratio; LSIL, low-grade squamous intraepithelial lesions; PPV, positive predictive value.

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programs targeting female adolescents before sexual debut. Herein we assessed the prevalence of HPV infection using three HPV detection assays, and determined HPV genotype distribution among women undergoing routine gynecological examination in Paris, France, stratified by age group and cervical cytological/histological status. This should help make public health decisions regarding screening and HPV vaccination for the control of cervical cancer.

2. Methods

2.1. Participants

This cross-sectional study enrolled women 20–65 years attending 17 private gynecology practices in Paris metropolitan area for a routine gynecological examination (April 2008–February 2009) [6]. None had received HPV vaccination. Exclusions were: total hysterectomy, abnormal cervical cytology in the past 6 months, or pregnancy. The study was approved by an independent ethics committee at the Pitié Salpétrière University Hospital (Paris, France). Women signed a written consent form.

2.2. Procedures

Demographic, reproductive, and sexual health data were recorded. A cervical sample was collected from each participant. Liquid-based cytology (LBC) sample collection using the Thin-Prep medium (Hologic, Inc., Bedford, MA) and cytological analysis are described elsewhere [6].

LBC samples were tested for (i) HPV DNA (Laboratoire Lavergne, Paris, France) using the Hybrid Capture® 2 assay (HC2; QIAGEN, Gaithersburg, MD), which detects 13 HR types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), (ii) HPV mRNA (CDL Pharma, Marseille, France) using the APTIMA® HPV assay (AHPV; Gen-Probe, Inc., San Diego, CA), which detects 14 HR types (same plus HPV-66) [7], and (iii) HPV genotyping (CDL Pharma) using the PCR-based PapilloCheck® assay (Greiner Bio-One GmbH, Frickenhausen, Germany), which identifies 13 HR types (same as for HC2) and 12 low-risk types (6, 11, 40, 42, 43, 44/55, 53, 66, 70, 73, 82).

Women with atypical squamous cells of undetermined significance or greater (ASC-US+) cytology and/or ≥1 positive HPV test were referred for colposcopy. To control for verification bias, 14% of women with negative cytology and HPV tests results randomly underwent colposcopy (random control group). All women with abnormal colposcopy underwent ≥1 biopsy from the most severe area, and ≥1 biopsy from each quadrant of the atypical transformation zone. Women with normal colposcopy (not in the random control group) underwent two biopsies as previously described [6].

2.3. Statistics

Women were stratified by age (<25 and ≥25 years). The <25 years is approximately the recommended age for HPV vaccination (with catch-up vaccination); ≥25 years corresponds to the recommended age for cervical cancer screening in France.

Associations between potential risk factors and HPV infection were analyzed by logistic regression using a logit link, fitting terms for age (<25 or ≥25 years), medical history (normal/abnormal cervical pathology), current smoking status, age at sexual debut (≤16 or >16 years), and number of sexual partners in the past 12 months (≥2 or 0–1). Odds ratio (OR) and 95% confidence intervals (CI) for having HPV infection were calculated for each potential risk factor, adjusted for other potential confounders. Associations between specific HR types and the risk of cervical intraepithelial neoplasia 3 or worse (CIN3+; i.e. CIN3, adenocarcinoma in situ, carcinoma in situ, or invasive cancer) were analyzed by logistic regression. Any factors that were statistically significant were retained in the model. Each HPV type was a separate variable. The risk for CIN3+ was calculated for HPV groupings: (i) any of the eight HR types (16, 18, 31, 33, 35, 45, 52, or 58), (ii) none of the eight types but at ≥1 of the other HR types, or (iii) no HR types.

3. Results

3.1. Population

A total of 5002 women (10.3% were <25 years and 89.7% ≥25 years) were included (Supplementary Table S1). Women ≥25 years reported a higher number of pregnancies, later onset of sexual activity, lower number of recent sexual partners, and lower use of oral contraceptives or hormone replacement therapy, and were less likely to be smokers than women <25 years old.

Most women (82.6–89.9%) had no history of cervical abnormalities (Supplementary Table S1). A history of CIN 1–3 was more common among women >25 (17.3%) than in those <25 years old (10.1%). In the ≥25-year old group, 3 women had a history of adenocarcinoma in situ and one had invasive cervical cancer.

3.2. Overall and type-specific HPV prevalence

LBC samples from 755 women (15.1%) were HPV+ based on HC2 (Table 1). HPV prevalence was 16.1% and 10.1% according to HPV genotyping and AHPV, respectively (Fig. 1 and Table 1). Age-specific prevalence of HPV infection (HC2) was 23.5% and 22.2% in women aged <25 and 25–34 years, respectively, and 8.8% in women aged 45–54 and ≥55 years (Fig. 1).

Prevalence of multiple-type infections (genotyping assay) was 9.3% in women <25, and 5.2% in those ≥25. Few women (≤1.0%) in either age group were infected with more than three HPV types.

HPV-42 was the most common HPV genotype among women <25 years (5.6%), followed by HPV-51 (4.9%), and 16 (4.3%) (Fig. 2). Among women ≥25 years, HPV-16 (2.3%) was the most common, followed by HPV-51 (2.1%), 42 (1.9%), and 53 (1.9%). Most HPV genotypes including HR types were more prevalent in women <25 years than in older women.

The prevalence of infection with ≥1 of HPV-16/18/6/11 was 5.8% in women <25 and 3.3% in women ≥25 years. Prevalence of infection with ≥1 of HPV-31/33/45/52/58 was 3.7% in women <25 and 3.2% in women ≥25 years (Table 1).

3.3. Risk factors

The risk factors associated with HPV infection (HC2 assay) were (Table 2): a higher number of recent sexual partners (OR = 3.9 ≥2 vs. 0–1 sexual partners, $P < 0.001$), a past history of cervical abnormality (OR = 1.7, $P < 0.001$), young age (OR = 1.6 <25 vs. ≥25 years, $P < 0.001$), and a history of smoking (OR = 1.4, $P < 0.001$); results were similar with AHPV (Table 2).

3.4. Type-specific HPV prevalence by cytology

The highest prevalence of ASC-US+ was observed in women <35 years (Fig. 1). In general, the prevalence of any type of HPV infection, HR-type infection, multiple HPV infections, and HPV 16/18 increased with the severity of cytological abnormality (Supplemental Table 2).

Overall HPV prevalence by genotyping in women with normal cytology was higher among women <25 (20.7%) than those ≥25 years (11.7%) (Supplemental Table 2), with lower positivity rates observed with AHPV compared with the HC2. In women ≥25 years, 15.0% of low-grade squamous intraepithelial lesions (LSIL) and 44.2% of high-grade squamous intraepithelial lesions (HSIL) included ≥1 HPV-16/18/6/11 type infection, but

Table 1
Prevalence of HPV infection with specific types (genotyping assay[a]) and HC2 positivity, stratified by age group.

	Age of women					
	All		<25 years		≥25 years	
	n	(%)	*n*	(%)	*n*	(%)
Number of women	5002	(100.0)	515	(100.0)	4487	(100.0)
HPV type[a]						
HPV negative	4000	(80.0)	368	(71.5)	3632	(80.9)
Any HPV type	804	(16.1)	129	(25.0)	675	(15.0)
1 HPV type only	521	(10.4)	81	(15.7)	440	(9.8)
More than 1 HPV type	283	(5.7)	48	(9.3)	235	(5.2)
More than 3 HPV types	30	(0.6)	5	(1.0)	25	(0.6)
≥1 low-risk type[b]	266	(5.3)	53	(10.3)	213	(4.7)
≥1 high-risk type[c]	648	(13.0)	102	(19.8)	546	(12.2)
≥1 of HPV 16, 18, 6, or 11[d]	177	(3.5)	30	(5.8)	147	(3.3)
HPV 6 and/or 11[d]	33	(0.7)	5	(1.0)	28	(0.6)
HPV 16 and/or 18[d]	149	(3.0)	27	(5.2)	122	(2.7)
HPV 16 or 18 alone	80	(1.6)	13	(2.5)	67	(1.5)
HPV positive but not HPV 16	655	(13.1)	102	(19.8)	553	(12.3)
≥1 of HPV 31, 33, 45, 52, or 58[d]	164	(3.3)	19	(3.7)	145	(3.2)
No genotyping result[a,e]	198	(4.0)	18	(3.5)	180	(4.0)
HC2 positive	755	(15.1)	121	(23.5)	634	(14.1)
No HC2 result[e]	53	(1.1)	3	(0.6)	50	(1.1)

HC2, Hybrid Capture 2.
[a] HPV genotyping was performed using the PapilloCheck assay.
[b] Alone or with coinfection with high-risk types.
[c] Alone or with coinfection with low-risk types.
[d] Alone or with coinfection with other types.
[e] No result due to lack of material or withdrawal of consent.

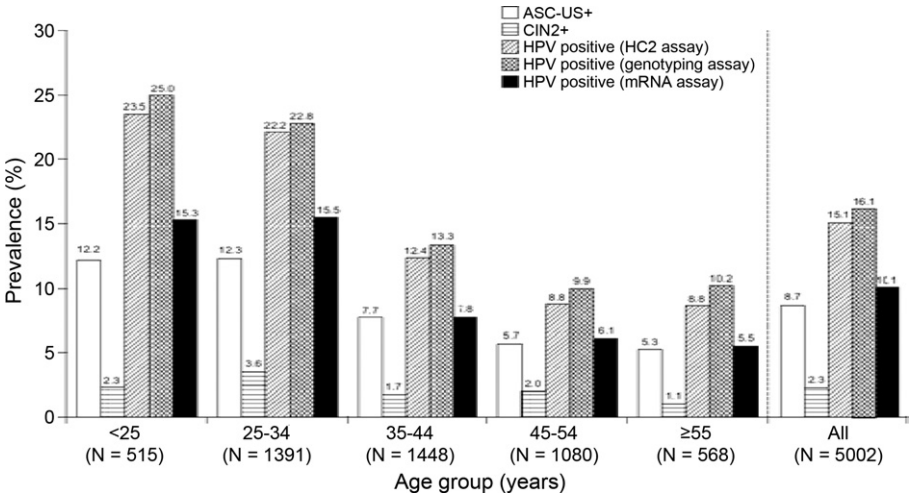

Fig. 1. Prevalence of cervical disease (ASC-US+ and CIN2+) and HPV infection stratified by age. HPV infection was determined using HPV DNA detection (HC2 assay), genotyping (PapilloCheck assay), or mRNA detection (AHPV assay). Age range: 20–80 years. ASC-US+, atypical squamous cells of undetermined significance or higher; CIN2+, cervical intraepithelial neoplasia of grade 2 or higher; HC2, Hybrid Capture 2.

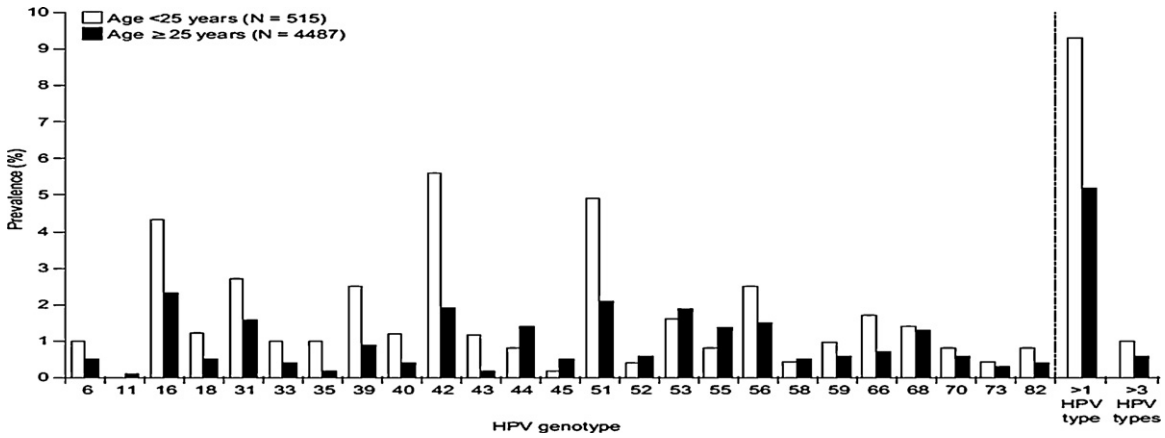

Fig. 2. Overall prevalence of HPV genotypes, stratified by age. HPV genotyping was performed using the PapilloCheck assay.

Table 2
Potential risk factors for HPV infection by type of HPV test (HC2, genotyping[a], and AHPV[b] assays).

Potential risk factor	HC2 assay ($N = 4820$)		Genotyping assay ($N = 4674$)		AHPV assay ($N = 4832$)	
	OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI
Age group						
<25 vs. ≥25 years	1.58	(1.24, 2.00)	1.65	(1.31, 2.08)	1.44	(1.09, 1.90)
Medical history (cervical pathology)[d]						
Abnormal vs. no abnormal pathology	1.74	(1.43, 2.12)	1.70	(1.40, 2.06)	1.40	(1.11, 1.77)
Current smoking status						
Smoker vs. non-smoker	1.42	(1.19, 1.70)	1.35	(1.13, 1.61)	1.55	(1.26, 1.91)
Age at sexual debut						
≤16 vs. >16 years	0.90	(0.69, 1.18)	1.12	(0.87, 1.44)	0.91	(0.66, 1.24)
Number of sexual partners within past 12 months						
≥2 vs. 0 or 1	3.94	(3.13, 4.94)	3.60	(2.86, 4.52)	3.63	(2.82, 4.67)

Women with missing data on potential risk factors were excluded from the analysis, as were women without HPV results due to insufficient material, failed test or withdrawal of consent.
OR, odds ratio; CI, confidence interval; HC2, Hybrid Capture 2.
[a] HPV genotyping was performed using the PapilloCheck assay.
[b] HPV mRNA testing was performed using the AHPV assay.
[c] Odds ratio derived from logistic regression model fitting all terms.
[d] Medical history based on recorded information or spontaneous reports from women.

not 31/33/45/52/58 (Supplemental Table 2). In contrast, 11.2% of LSIL and 20.9% of HSIL involved infection with ≥1 of HPV-31/33/45/52/58 but not 16/18/6/11 (Supplemental Table 2).

3.5. Type-specific HPV prevalence by histology

The highest prevalence rate of CIN2+ was observed in women 25–34 years (3.6%) (Fig. 1). The median age of women with CIN2+ was 33 years. Twenty-nine women (27 aged ≥25 years) had CIN3+ (Table 3).

Of the 1192 women with a colposcopic abnormality that led to biopsy, 661 (55.5%) had a diagnosis of CIN1–3+, of whom 438 (66.3%) were HPV+ by HC2 (Table 4). Of the women who were referred to colposcopy and had normal histological findings, 57.4% of those <25 years, and 46.0% of those ≥25 years were HPV+ (by HC2). Prevalence of HPV infection (any type) and HR-type infection increased with increasing severity of histological diagnosis. HPV detection by HC2 was 96.1–100% in CIN2+ cases. Multiple infection was detected in cervical exfoliated cells in 58.3% of CIN2+ women <25 years and in 33.0% of CIN2+ women ≥25 years, compared with 11.8% and 11.0%, respectively, in women with normal histological findings in these age groups (Table 3).

In women <25 years old, 13.7% of CIN1, 30.0% of CIN2, and 0% of CIN3+ involved infection with ≥1 of HPV-16/18/6/11 but not 31/33/45/52/58, and 8.4% of CIN1, 50.0% of CIN2, and 50.0% of CIN3+ involved infection with ≥1 of HPV-31/33/45/52/58 but not

Table 3
Type-specific HPV prevalence (genotyping assay[a]), and HPV positivity based on the HC2 assay and AHPV assay,[b] stratified by age group and histological diagnosis.

	Normal[c]				CIN1				CIN2				CIN3+[d]			
	<25 years		≥25 years		<25 years		≥25 years		<25 years		≥25 years		<25 years		≥25 years	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Number of women	68	(100.0)	463	(100.0)	95	(100.0)	451	(100.0)	10	(100.0)	76	(100.0)	2	(100.0)	27	(100.0)
Any HPV type by the genotyping assay	28	(41.2)	173	(37.4)	59	(62.1)	222	(49.2)	10	(100.0)	64	(84.2)	2	(100.0)	23	(85.2)
More than 1 HPV type	8	(11.8)	51	(11.0)	26	(27.4)	91	(20.2)	6	(60.0)	27	(35.5)	1	(50.0)	7	(25.9)
Any LR type[e]	10	(14.7)	41	(8.9)	20	(21.1)	62	(13.7)	3	(30.0)	11	(14.5)	1	(50.0)	2	(7.4)
Any HR type[e]	23	(33.8)	152	(32.8)	51	(53.7)	199	(44.1)	10	(100.0)	64	(84.2)	2	(100.0)	23	(85.2)
≥1 of 16, 18, 6, or 11[e]	4	(5.9)	35	(7.6)	16	(16.8)	49	(10.9)	3	(30.0)	23	(30.3)	0	(0.0)	15	(55.6)
6 and/or 11[e]	0	(0.0)	3	(0.6)	1	(1.1)	10	(2.2)	0	(0.0)	3	(3.9)	0	(0.0)	1	(3.7)
16 and/or 18[e]	4	(5.9)	32	(6.9)	16	(16.8)	40	(8.9)	3	(30.0)	21	(27.6)	0	(0.0)	15	(55.6)
16 or 18 alone	2	(2.9)	22	(4.8)	7	(7.4)	16	(3.5)	2	(20.0)	7	(9.2)	0	(0.0)	12	(44.4)
≥1 of 31, 33, 45, 52, or 58[e,f]	1	(1.5)	31	(6.7)	11	(11.6)	60	(13.3)	5	(50.0)	30	(39.5)	1	(50.0)	7	(25.9)
≥1 of 6, 11, 16, 18, 31, 33, 45, 52, or 58[e]	5	(7.4)	64	(13.8)	24	(25.3)	98	(21.7)	8	(80.0)	48	(63.2)	1	(50.0)	22	(81.5)
≥1 of 6, 11, 16, 18[e], none of 31, 33, 45, 52, 58	4	(5.9)	33	(7.1)	13	(13.7)	38	(8.4)	3	(30.0)	18	(23.7)	0	(0.0)	15	(55.6)
≥1 of 31, 33, 45, 52, 58[d], none of 6, 11, 16, 18	1	(1.5)	29	(6.3)	8	(8.4)	49	(10.9)	5	(50.0)	25	(32.9)	1	(50.0)	7	(25.9)
HC2 positive[g]	39	(57.4)	213	(46.0)	62	(65.3)	265	(58.8)	10	(100.0)	73	(96.1)	2	(100.0)	26	(96.3)
AHPV positive[h]	22	(32.4)	127	(27.4)	39	(41.1)	162	(35.9)	10	(100.0)	69	(90.8)	2	(100.0)	26	(96.3)

In total, 1192 women underwent histological evaluation. Percentages are calculated using the total number of women in the relevant histological category as the denominator.
A total of 3688 women (324 aged <25 years; 3364 aged ≥25 years) were not referred for biopsy. According to the protocol, biopsies were taken if cytology or HPV assays were positive and in a random sample of 14% of women with negative cytology and HPV assays.
No histology test result was available for 122 women (16 aged <25 years; 106 aged ≥25 years) due to loss to follow-up, withdrawal from the study, withdrawal of consent, or biopsy performed in a non-investigational institution.
AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HC2, Hybrid Capture 2; HR, high-risk; LR, low-risk.
[a] HPV genotyping was performed using the PapilloCheck assay.
[b] HPV mRNA testing was performed using the AHPV assay.
[c] Among women with abnormal cytology who were referred to a colposcopic examination.
[d] Comprises CIN3, AIS (2 women aged ≥25 years), and invasive cervical cancer (3 women aged ≥25 years).
[e] Alone or with coinfection with other types.
[f] HPV HR 31, 33, 45, 52, and 58 are under evaluation as targets for a new generation of multivalent HPV vaccines, in addition to HPV 16 and 18.
[g] 17 women (2 aged <25 years; 15 aged ≥25 years) had no HC2 result.
[h] 6 Women (1 aged <25 years; 5 aged ≥25 years) had no AHPV result.

Table 4
Risk of CIN3+ associated with high-risk HPV types (16, 18, 31, 33, 35, 45, 52, and 58[a]).

High-risk HPV type	Comparison	No. with CIN3+/total in group	Adjusted OR[b]	95% CI	*P*-value
Other HR types[c]	Other HR types (HPV 39, 45, 51, 56, 59, and 68) vs. no HR types	2/254 vs. 1/622	4.95	(0.45, 54.89)	0.190
	HR (16, 18, 31, 33, 35, 45, 52, and 58) vs. other HR types	22/267 vs. 2/254	10.89	(2.53, 46.86)	0.001
Type 16	16 vs. not 16	13/107 vs. 12/1036	11.64	(5.15, 26.32)	<0.001
Type 18	18 vs. not 18	1/26 vs. 24/1117	1.68	(0.22, 12.98)	0.620
Type 31	31 vs. not 31	4/79 vs. 21/1064	2.62	(0.88, 7.87)	0.085
Type 33	33 vs. not 33	2/16 vs. 23/1127	6.96	(1.48, 32.76)	0.014
Type 35	35[d] vs. not 35	0/14 vs. 25/1129	2.47	(0.00, 15.60)	1.000
Type 45	45 vs. not 45	1/21 vs. 24/1122	2.18	(0.28, 17.00)	0.458
Type 52	52 vs. not 52	1/26 vs. 24/1117	1.47	(0.19, 11.47)	0.714
Type 58	58 vs. not 58	1/20 vs. 24/1123	2.26	(0.29, 17.72)	0.437

CIN3+ comprises CIN3, adenocarcinoma in situ, carcinoma in situ, and invasive cervical cancer.
Women without data on HPV type, histological status, or smoking status were excluded from the analysis. The total number of women included = 1143.
CIN, cervical intraepithelial neoplasia; CI, confidence interval; OR, odds ratio.

[a] HPV 16, 18, 31, 33, 35, 45, 52, and 58 are the eight most common high-risk HPV types found in high-grade cervical lesions and cancers worldwide (12).

[b] Logistic regression analysis identified smokers as more likely to have CIN3+ than non-smokers. Age group (<25 or ≥25 years) did not have a statistically significant effect on outcome and was not retained in the final analysis. Odds ratios were derived from a logistic regression model fitting smoking status, and each type individually.

[c] Other HR types' refers to HR types not specified in this table (HPV 39, 45, 51, 56, 59, and 68).

[d] Exact methods of analysis were used for HPV 35 due to small numbers.

16/18/6/11 (Table 3). HPV types in the two cases of CIN3+ were 31 and 39/42/51/66, respectively. For women ≥25 years, 8.4% of CIN1, 23.7% of CIN2, and 55.6% of CIN3+ involved infection with ≥1 of HPV-16/18/6/11 but not 31/33/45/52/58, and 10.9% of CIN1, 32.9% of CIN2, and 25.9% of CIN3+ involved infection with ≥1 of HPV-31/33/45/52/58 but not 16/18/6/11 (Table 3).

Smokers were more likely to have CIN3+ than non-smokers and, after adjustment for smoking status, the risk of having CIN3+ in women infected with ≥1 of the HPV-16/18/31/33/35/45/52/58 was nearly 11-fold greater that of women infected with other HR types (Table 4). HPV-16 was most strongly associated with CIN3+ (OR = 11.64, $P < 0.001$), followed by HPV-33 (OR = 6.96, $P = 0.014$).

4. Discussion

Overall, the prevalence of HPV infection was 15% using the HC2 assay and 10.1% using the AHPV assay among women undergoing routine gynecological examination in Paris. The 15% prevalence value was similar to that reported in another study for women 15–76 years in France [8], but lower than that found in Portugal (19%) [9]. HPV prevalence increased with cytological and histological severity.

The <25-year old group approximates the target population for prophylactic HPV vaccination (including catch-up) in France. The prevalence of HPV infection observed in women <25 years (23.5% by HC2, 15.3% by AHPV) is relatively high but consistent with that in previous studies [10–13].

The HR types detected most frequently in women <25 years (HPV-16, 31, and 51) are consistent with those reported most frequently in women aged 10–30 in Germany [11]. Multiple HPV infections have been reported to be associated with a higher risk of CIN2+ and HSIL [14]. No formal post hoc analyses of the association between multiple infection with specific HPV types and cytological/histological findings were performed in our study to avoid false positive findings resulting from repeated analyses on correlated data, and given that HPV infection was ascertained in cervical cells rather than biopsy specimens.

HPV prevalence declined with age. HPV prevalence was highest in women <25, and declined to reach a plateau in women ≥45 years. We did not observe a second peak in HPV prevalence in women ≥45 years, consistent with other European studies [12,15,16], but in contrast to studies in some other countries [17,18].

Women with more sexual partners had a higher risk of HPV infection, as shown in other studies [11,19–21]. Women with a history of cervical abnormalities had a higher risk of HPV infection, suggesting that women with past/current cervical abnormalities are more vulnerable to new HPV-associated diseases and should be followed up closely. HPV testing is a valuable screening approach for recurrent cervical disease [22]. HPV vaccination could also benefit some women with past/current cervical abnormalities. The quadrivalent HPV vaccine reduces recurrences of CIN in women previously treated for CIN [23]. Furthermore, both the bivalent and the quadrivalent HPV vaccines protect women who have past HPV infection with HPV vaccine types [24,25].

Infection with HPV-16/18 (targeted by prophylactic HPV vaccines) was more common in women <25 years (5.2%) than in those aged ≥25 years (2.7%), supporting the rationale for the HPV vaccination program in France which targets 14 year-old women, with catch-up vaccination until age 23.

A high proportion of high-grade cervical lesions were associated with non-vaccine HR types, consistent with previous findings [16]. This emphasizes the need for continued screening in vaccinated women to detect CIN2+ that cannot be prevented by vaccination, and provides a rationale for HPV testing as an initial screening tool in HPV-vaccinated women.

Peak prevalence of CIN2+ at age 25–34 confirms the importance of screening in this age group. The declining prevalence of CIN2+ with age was probably due to regular cervical screening and treatment of detected abnormalities over time. HPV DNA testing has a higher sensitivity but lower specificity than cytology for detecting high-grade cervical lesions [6,26–30], supporting the use of HPV testing for primary screening, with referral to cytology for women positive for HR types [31,32]. In a screening setting, AHPV has a high sensitivity for CIN2+ detection (similar to HC2) and a similar specificity to LBC [6]. AHPV testing may therefore have potential value for primary screening of women starting in their mid-20s and older.

In women ≥30 years with normal cytology, the presence of HPV-16 or 18 predicts a risk of approximately 10% for CIN2+. Therefore, women with normal cytology who are HPV-16 and/or 18 positive require immediate referral for colposcopy. The high PPV of HPV-16 for CIN3 [16] suggests that HPV genotyping may be a valuable primary screening approach in women >30–35 years.

The potential impact of vaccination on the prevalence of cervical pathology may be estimated by examining the proportion of abnormalities related to HPV-16/18. Based on our findings, HPV vaccination may prevent up to 2.4% of ASC-US, 12.8% of LSIL, 20.0% of ASC-H, 46.5% of HSIL, and 40.0% of AGC in the ≥25-year old group. In this age group, HPV vaccination has the potential to prevent up to 27.6% of CIN2 and 55.6% of CIN3+ associated with HPV-16/18. This is

consistent with an estimate that catch-up vaccination in sexually active women would reduce the incidence of moderate or worse cytology by 45% and borderline or mild cytology by 7% [33].

Cross-protection against cervical lesions associated with non-vaccine HR types has been reported and may contribute to the efficacy of HPV vaccines in the short term [34–41]. Because the extent and duration of this cross-protection is unknown, new multivalent HPV vaccines targeting a wider range of HR types should be developed. Our study shows that non-vaccine HPV types cause a considerable proportion of high-grade cervical lesions. A new generation of multivalent vaccines targeting HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58 is under development. The absence of HPV-16/18 in the two CIN3+ women <25 years suggests that vaccines targeting a wider range of HR types may provide more benefit than current HPV vaccines when administered before sexual debut. Our study suggests that a substantial amount (up to one-third) of high-grade cervical disease may be prevented by new vaccines targeting HPV-31, 33, 45, 52, and 58, in addition to 16/18.

Most detected HPV infections are transient and not expected to cause future high-grade cervical disease. A study in women aged 18–22 showed that most HPV infections became undetectable within 2 years, and that CIN1 was not associated with persistent HPV infection [42]. Associations between high-grade abnormalities and HPV genotypes should be viewed with caution given the small number of CIN2+ detected in the present study. Furthermore, although the clinical performance of the PapilloCheck assay in detecting high-grade CIN has acceptable agreement with a well-established PCR assay [43], it needs further validation before it can be utilized systematically in screening settings. Another study limitation is that HPV DNA detection was performed in cervical exfoliated cells rather than in biopsy specimens with laser dissection, which limits our ability to make causal determinations between specific HPV types and CIN2+. Moreover, the association between HPV types and CIN2+ lesions does not necessarily imply causality.

Our findings support HPV vaccination and HPV/cytological screening programs in France targeting females aged 14 years (with catch-up to 23 years), and screening programs targeting women ≥25 years for cytology and ≥35 years for HPV. Although HPV testing is not approved for primary screening in France, our findings suggest including HPV testing in screening programs for non-vaccinated and vaccinated women.

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Conflict of interest statement: J. Monsonego has received funding to conduct studies related to the FASE study from Gen-Probe and Greiner, and related to HPV vaccines from Merck and Glaxo-SmithKline. He has participated in Steering Committees at Merck, and in Advisory Boards for Sanofi Pasteur MSD, Gen-Probe and Roche Diagnostics. J. Smith has received research grants or contracts, honoraria and consulting fees during the last 3 years from Merck, GSK, Hologic, Qiagen and Gen-Probe. K. Syrjänen, P. Halfon, L. Zerat, and J.C. Zerat have no conflicts of interest to report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2012.06.013.

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