MAJOR ARTICLE

Human Papillomavirus Genotype Distribution in External Acuminata Condylomata: A Large French National Study (EDiTH IV)

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Background. External acuminata condylomata (EAC) are among the most common sexually transmitted diseases. Although it is understood that low-risk human papillomavirus (HPV) genotypes 6 and 11 are associated with EAC, there have only been a few, small, published studies reporting the genotype-specific prevalence of HPV. The objective of our study was to assess the prevalence of HPV genotypes for a large number of cases involving both men and women and to evaluate the potential benefit of a quadrivalent (genotypes 6, 11, 16, and 18) HPV vaccine in France.

Methods. A total of 256 women and 260 men who presented with EAC to French gynecologists, dermatologists, and proctologists were prospectively recruited during the period January through April 2007. Specimens were collected with a cytobrush, and the HPV genotype was determined using the INNO-LiPA assay (Innogenetics), which detects 24 HPV genotypes.

Results. Four hundred twenty-three β-globin–positive samples could be analyzed. The median age of patients was 30 years (range, 18–72 years). The overall prevalence of HPV DNA in patients with EAC was 99% (33% of patients were coinfected with another pathogen). Low-risk genotypes predominated, with a prevalence of 89%. The most prevalent genotypes were 6 (69%) and 11 (16%), followed by 16 (9%), 51 (8%), 52 (7%), 66 (6%) 53 (5%), 31 (3%), and 18 (3%). The cumulative prevalence of genotypes 6 and 11 was 83%, and the cumulative prevalence of genotypes 6, 11, 16, and 18 was 88%.

Conclusions. This study is, to our knowledge, the first large, multicenter survey to provide solid data on HPV genotype distribution among patients with EAC. Our results provide strong evidence that, in France, the most prevalent HPV genotypes in persons with EAC are 6 and 11. Because of its 99% efficacy for the prevention of EAC and a vaccine coverage of 100%, the quadrivalent HPV vaccine could prevent 62%–87% of EAC cases in France.

External acuminata condylomata (EAC) are among the most common sexually transmitted diseases worldwide. The incidence of EAC seems to be increasing [1–4], with a peak incidence observed in the 20–24-year-old age group [3, 4]. In the United States, the incidence of genital condyloma increased from 118 cases per 100,000 person-years at risk in 1998 to 205 cases per 100,000 person-years at risk in 2001 [5]. Few studies are available from France. In 2000, Lukasiewicz et al. [6] reported a similar trend, with a yearly incidence of 107 new cases per 100,000 inhabitants, and more recently, Monsonego et al. [7] estimated that the overall incidence was 229 cases per 100,000 female persons aged 15–65 years, corresponding to ~48,000 women per year receiving treatment from gynecologists.

The association between genital warts and presence of human papillomavirus (HPV) infection has been

Received 30 January 2008; accepted 17 April 2008; electronically published 18 July 2008.

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Clinical Infectious Diseases 2008; 47:610–5

1058-4838/2008/4705-0004$15.00
DOI: 10.1086/590560

described elsewhere [8, 9]. HPV transmission usually occurs after epithelial contact with an HPV-infected surface and depends on sexual behavior. Previous studies have reported that, in fact, HPV infection is highly related to the lifetime number of sexual partners [10, 11] and that condoms have a very limited role in preventing the transmission of the virus [12].

Although most EAC cases will spontaneously resolve, therapy is often preferred to avoid long-lasting psychosocial and psychosexual concerns associated with a slow regression process [13]. However, treatment is expensive and painful, and there is a high risk of recurrence [14, 15].

A quadrivalent (HPV genotype 6, 11, 16, and 18) virus-like particle vaccine protecting against the most common HPV infections has been developed and is now licensed [16]. Although it is known that, worldwide, low-risk HPV-6 and HPV-11 are associated with EAC in ~90% of cases [17, 18], data concerning the HPV genotype distribution among patients with EAC are scarce. Because such data are not yet available in France, the objective of this study was to estimate the HPV genotype-specific prevalence in EAC and to evaluate the potential benefit of quadrivalent HPV vaccination in this country.

PATIENTS, MATERIALS, AND METHODS

Patients. This French prospective, multicenter, national study was based on clinical reports from physicians involved in the treatment of patients with EAC. A total of 102 gynecologists, 96 dermatologists, and 24 proctologists participated in the survey. For patients to be included, they had to be ⩾18 years of age and to have had EAC diagnosed during clinical examination. All patients had to provide written informed consent. Enrollment continued until 250 men and 250 women had been enrolled. Patients with immunodeficiency due to HIV infection or receipt of any kind of immunosuppressive therapy were excluded. Patient data (e.g., age at diagnosis, area of residence, date of sample collection, presence of lesions, and sampling sites) were extracted from medical records.

Sample collection. Biological samples were obtained atraumatically from the most typical EAC lesions using a cytobrush (DNAPAP Cervical Sampler; Digene). A standardized sampling protocol (mandating three 360° rotations counterclockwise) was provided to each physician. The brush was then placed in Cervical Specimen Transport Medium (Digene) and sent to the Department of Cellular and Molecular Biology (Besançon, France) for DNA extraction and genotype assessment. Prior to study initiation, the technique had been tested on 9 patients with EAC, with a 100% success rate for detection of HPV.

DNA extraction and HPV genotype assessment. DNA extraction was performed with the MagNA Pure Compact robot (Roche Diagnostics) and the MagNA Pure Compact NA Isolation kit I (Roche Diagnostics), in accordance with the manufacturer's instructions. HPV genotypes were determined using the INNO-LiPA HPV Genotyping v2 test (Innogenetics) after amplification with specific biotinylated SF10 primers. After denaturation, PCR products were incubated with HPV-specific oligonucleotide probes immobilized on nylon strips. The INNO-LiPA kit allows the detection of 24 HPV genotypes (13 high-risk genotypes and 11 low-risk genotypes), as follows: high-risk HPV genotypes, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68; and low-risk HPV genotypes, 6, 11, 40, 42, 43, 44, 53, 54, 66, 70, and 74.

A detailed procedure using this method is described elsewhere [19]. Positive and negative controls, consisting of DNA from CaSki cells (harboring HPV-16) and molecular biology grade water, respectively, were systematically used in parallel with DNA from the EAC specimen for each run.

DNA quality was assessed in HPV-negative samples using a β-globin PCR. β-Globin–negative samples were excluded from analysis.

Ethics consideration. In accordance with French law (Public Health Code, modified by the law n° 2004–806, 9 August 2004; and the Huriet-Sérusclat act 88–1138, 20 December 1988), because this study was conducted during patients' routine clinical follow-up, without any modification, no ethics committee approval was necessary. This study complies with the Declaration of Helsinki, and written informed consent was obtained from each patient.

Statistical analysis. The sample size had to be large enough to accurately estimate the prevalence of specific HPV genotypes. The number of subjects was thus maximized, using a prevalence of 50% and precision of 5%, yielding a total of 385 patients. This number was increased by 20% to compensate for possible drop-outs, reaching a total of ~500 cases. The overall prevalence of HPV genotypes was calculated. The distribution of specific HPV genotypes was expressed as the proportion of HPV DNA–positive specimens among all cases of EAC. Qualitative variables were studied using the 2-sided χ^2 test or Fisher's exact test, as appropriate. Quantitative data are expressed as mean ($\pm$SD) and range. Data analysis was conducted using SAS software, version 8.2 (SAS Institute). P values $<.05$ were considered to be statistically significant.

RESULTS

Patient characteristics. Two hundred fifty-six women and 260 men were prospectively recruited during the period January 2007 through April 2007. Patients were recruited after presenting to 102 gynecologists (220 patients), 96 dermatologists (231 patients), and 24 proctologists (65 patients) scattered throughout the country. Among recruited patients, 6 did not meet the inclusion criteria (3 were receiving immunosuppressive therapy, and 3 had HIV infection) and were thus excluded from the analysis. Moreover, 87 patients (17%) who tested negative for both HPV and β-globin, suggesting the absence

of HPV DNA suitable for PCR, were also excluded. These DNA-negative samples were equally distributed among participating centers (data not shown). For women, these samples were collected from lesions mainly located in the perineum (34%) and the perianal region (29%), whereas DNA-negative samples obtained from men were most often collected from the penis (59%). The remaining 423 samples were analyzed for the presence of HPV by genotype analysis; their characteristics are presented in table 1. The median age of patients was 30 years (range, 18–72 years) for the entire group, but the median age varied slightly between men and women (32 vs. 28 years; $P = .01$).

Thirty-seven percent of all EAC cases were recurrent cases. This percentage varied from 29% for women to 45% for men ($P < .001$) and increased with increasing age at enrollment in the study ($P = .04$, by χ^2 for trend analysis). At the time of diagnosis, 8% of women with EAC were pregnant. The rate of recurrence appeared to be higher for pregnant women (41%) than for nonpregnant women (28%), although this difference was not statistically significant ($P = .27$).

In women, EAC lesions were often located on the vulva (68% of cases), perineum (43%), and perianal region (30%), whereas, for men, the penis (42%) and perianal region (37%) were the most frequent sites (table 1).

HPV prevalence. DNA was detected in 418 of 423 EAC cases, yielding an overall prevalence of 98.8%. Only 5 samples tested negative for DNA. Presence of 1 HPV genotype only was observed in 266 (63%) of 423 cases, whereas 137 cases (32%) involved infection with ⩾2 genotypes. Fifteen other cases (3.5%) tested positive for HPV but could not be further characterized using this genotyping method (so-called undetermined HPV).

On the basis of the Lipa low-risk/high-risk genotype classification, presence of ⩾1 low-risk HPV genotype was found in 381 (90%) of 423 cases, and presence of ⩾1 high-risk genotype was found in 139 cases (33%). These proportions varied significantly with sex; the presence of ⩾1 low-risk genotype was more common among men than among women (93.8% vs. 86.4%; $P = .011$). In contrast, presence of ⩾1 high-risk genotype was more common among women (40.7%) than among men (24.9%; $P < .001$). Two hundred sixty-four (62%) of 423 EAC samples demonstrated infection with ⩾1 low-risk genotype (without high-risk genotypes); 22 (5%) demonstrated infection ⩾1 high-risk genotype (without low-risk genotypes), whereas 117 (28%) demonstrated coinfection with low-risk and high-risk genotypes (table 2). The presence of ⩾1 high-risk genotype occurred as frequently in new cases as in recurrent cases (32%; $P = .69$) and did not vary on the basis of age ($P = .57$). However, the proportion of high-risk genotypes seemed to be higher among pregnant women (53%) than among nonpregnant women (36%), although this difference was not statistically significant ($P = .17$).

Table 1. Characteristics of 423 French patients with external acuminata condylomata.

Characteristic	Value
Sex[a]	
Male	209 (49.4)
Female	214 (50.6)
Age, median years (range)	30 (18–72)
Age group years	
18–24 years	88 (20.8)
24–30 years	127 (30.0)
30–40 years	125 (29.6)
40–50 years	62 (14.7)
50–60 years	16 (3.8)
>60 years	5 (1.2)
Pregnant at time of diagnosis (n = 214)	
Yes	17 (8.0)
No	196 (92.0)
Data not available	1
Area of residence at diagnosis	
Paris area	85 (20.4)
Western or central France	66 (15.9)
Northern or northeastern France	103 (24.8)
Southeastern France or Corsica	99 (23.8)
Southwestern France	62 (14.9)
Other	1 (0.2)
Data not available	7
Type of EAC diagnosis	
New diagnosis	266 (63.2)
Recurrent disease	155 (36.8)
Data not available	2
Location of lesions[b]	
Women (n = 214)	
Vulva	146 (68.2)
Perineum	91 (42.5)
Labia minora	39 (18.2)
Labia majora	24 (11.2)
Perianal region	64 (29.9)
Other	27 (12.6)
Men (n = 209)	
Penis	87 (41.6)
Prepuce	57 (27.3)
Glans	18 (8.6)
Preputial furrow	24 (11.5)
Coronna	9 (4.3)
Meatus	9 (4.3)
Perianal region	78 (37.3)
Other	51 (24.4)

NOTE. Data are no. (%) of patients, unless otherwise indicated. EAC, external acuminata condylomata.

[a] Equal numbers of men and women were recruited, although not all were enrolled.

[b] Several locations were possible for each patient.

Prevalence of specific HPV genotypes. The most frequently encountered HPV genotypes were as follows, by decreasing order of frequency: HPV-6 (68%), HPV-11 (16%), HPV-16

Table 2. Prevalence of human papillomavirus (HPV) infection in external acuminata condylomata lesions, according to the low-risk and high-risk classification.

Variable	No. (%) of cases			P
	Men (n = 209)	Women (n = 214)	Total (n = 423)	
One or several low-risk genotypes (without high-risk genotypes)	152 (72.7)	112 (52.3)	264 (62.4)	<.001
One or several high-risk genotypes (without low-risk genotypes)	8 (3.8)	14 (6.5)	22 (5.2)	.21
Low- and high-risk genotypes	44 (21.0)	73 (34.1)	117 (27.7)	.003
Undetermined genotypes	4 (1.9)	11 (5.1)	15 (3.5)	.11
HPV negative	1 (0.5)	4 (1.9)	5 (1.2)	.37
Samples infected with ⩾1 low-risk genotype (single or multiple HPV infections)	196 (93.8)	185 (86.4)	381 (90.0)	.011
Samples infected with ⩾1 high-risk genotype (associated or not with any type of HPV)	52 (24.9)	87 (40.7)	139 (32.9)	<.001

(9%), HPV-51 (8%), HPV-52 (6.4%), and HPV-66 (5.7%) (table 3). DNA from HPV-6 and/or HPV-11 (alone or in association with each other) was found in 56.7% of cases. DNA from these 2 genotypes was detected in combination with DNA from other HPV types in 26.5% of EAC cases, yielding an overall prevalence of HPV-6 and/or HPV-11 infection of 83.2%. Similarly, DNA from HPV-16 and/or HPV-18 (alone or in association with each other) was observed in 2.8% of specimens. DNA from HPV-16 and/or HPV-18 was further detected in combination with DNA from other HPV genotypes in 8.3% of EAC cases, yielding an overall prevalence of infection with HPV-16 and/or HPV-18 of 11.1%. DNA from HPV-6, HPV-11, HPV-16, and/or HPV-18 (alone or in association with each other) was observed in 63.1% of all cases of EAC. Finally, at least 1 of these 4 genotypes (alone or in combination with other genotypes) was found in 88.2% of cases.

Low-risk HPV genotypes 6 and/or 11 were found more frequently in men than in women (90.4% vs. 76.2%; $P < .001$). Conversely, high-risk HPV genotypes 16 and/or 18 were more common among women than among men (15.4% vs. 6.7%; $P = .004$).

DISCUSSION

This large, national, multicenter, prospective study reports the prevalence of specific HPV genotypes among patients with EAC in France. Because of the large number of participating health care centers and the good coverage of the national territory (all regions of the country were equally represented), our study provides a reasonable representation of EAC cases in France. The median age at inclusion observed in our study is somewhat higher than that reported in the United Kingdom, where a first episode of anogenital warts was most often observed among persons aged 20–24 years [20]. This could be explained by our study's inclusion of recurrent EAC cases and exclusion of patients aged <18 years. Our results are indeed in accordance with a previous French study conducted in 2000 that involved 700 general practitioners who belonged to the Sentinelles network, in which recurrent cases were also included [6]. The difference in the median age observed between men and women (32 and 28 years, respectively) could be partly explained by the higher recurrence rate observed in men (45% vs. 29%). It is also possible that, because women undergo routine screening and follow-up with gynecologists, EAC cases are detected earlier in women than in men, for whom EAC is often diagnosed at sexually transmitted infection clinics or by dermatologists. This difference between men and women in age distribution was previously observed in the United Kingdom [20].

Seventeen percent of the initially included cases could not be analyzed, because no cellular DNA was found (i.e., the cases were β-globin negative). This proportion did not depend on the participating health care center and likely reflects the difficulty in retrieving cells from some EAC-associated samples. Most of the lesions were cutaneous and located in the perineum and perianal region in women and on the penis in men. Difficulties in the correct sampling of external genital organs, especially for men, have been reported elsewhere [11, 21]. We suggest that cutaneous lesions may be less adequate or productive than mucosal lesions for cell retrieval. Although the cytobrush was probably not the best tool for cell collection, it was surely the most appropriate, because it was noninvasive and represented an easy and acceptable sampling method for patients. In a review of genital HPV infection in men [22], the authors reported that, regardless of the type of cytobrush used, the proportion of β-globin–negative samples ranged from 16% to 26%, which is in accordance with our results (17%).

The higher proportion of recurrent EAC cases observed among men may have resulted from the different age distributions for men and women. In fact, in our study population, the recurrence rate increased with age. Another possible explanation for this higher proportion could involve the inclusion of male subjects with at-risk behaviors. For example, having multiple sex partners—a common situation among men who have sex with men—was shown to be associated with an elevated risk of EAC recurrence [23].

Table 3. Prevalence of specific human papillomavirus (HPV) genotypes among 423 cases of external acuminata condylomata, by decreasing order of frequency.

HPV genotype	No. (%) of cases	
	Cases of single infection	All infections (single or multiple)
HPV-6	195 (46.1)	289 (68.3)
HPV-11	42 (9.9)	68 (16.1)
HPV-16	11 (2.6)	38 (9.0)
HPV-51	2 (0.5)	34 (8.0)
HPV-52	1 (0.2)	27 (6.4)
HPV-66	2 (0.5)	24 (5.7)
HPV-53	5 (1.2)	21 (5.0)
HPV-31	1 (0.2)	14 (3.3)
HPV-18	…	11 (2.6)
HPV-40	…	11 (2.6)
HPV-68	2 (0.5)	10 (2.4)
HPV-44	2 (0.5)	9 (2.1)
HPV-54	1 (0.2)	9 (2.1)
HPV-59	…	8 (1.9)
HPV-39	…	7 (1.7)
HPV-45	…	6 (1.4)
HPV-56	…	6 (1.4)
HPV-43	1 (0.2)	5 (1.2)
HPV-58	1 (0.2)	5 (1.2)
HPV-33	…	4 (0.9)
HPV-70	…	4 (0.9)
HPV-35	…	3 (0.7)
HPV-42	…	1 (0.2)
Undetermined	15 (3.5)	34 (8.0)
HPV negative	5 (1.2)	5 (1.2)

The observed overall prevalence of HPV infection of 99% suggests that EAC lesions almost never occur in the absence of HPV infection. In other studies that used the same methodology and genotype analysis method, we have previously shown that the prevalence of HPV infection is similarly high for other genital lesions—namely, those associated with invasive cervical cancer [24] and cervical intraepithelial neoplasia 2/3 [19]—but also in smears evocative of low-grade squamous intraepithelial lesions [25], with a prevalence of ~98%.

The analysis of the prevalence of specific HPV genotypes provides strong data regarding the distribution of HPV genotypes in EAC. It provides evidence that, in France, the most prevalent HPV genotypes in patients with EAC are HPV-6 and HPV-11. These 2 genotypes, either alone or in combination with other HPV genotypes, occur in 83% of cases. It has been suggested that low-grade lesions due to HPV-6 and HPV-11 have a very low risk of progression to malignancy, because these viruses do not integrate their DNA into the chromosome of the infected cells [26]. Nevertheless, our results indicate that 33% of all patients with EAC harbor high-risk HPV DNA. These lesions represent productive lesions in which high-risk HPV DNA likely remains under episomal form. This allows a careful regulation of viral genes (in particular, E6 and E7 oncogenes are repressed), leading to the production of virions in the most differentiated layer of the epithelium [27]. Most of these infections will be controlled by an effective immune response, resulting in viral clearance. In some cases, however, HPV DNA will integrate into the chromosomes of the infected cells, resulting in cell immortalization. Subsequent cell transformation following expression of the HPV E6 and E7 oncogenes may then occur, leading to malignancy [28]. In our study, the proportion of persons with EAC who harbored high-risk HPV DNA was significantly higher among women than men (41% vs. 25%). This is probably related to the fact that high-risk HPV DNA is frequently encountered in women with cervical HPV infection [19, 24, 29]. Another possible explanation is the lower sampling quality of EAC lesions for men than for women [30, 31].

Low-risk and high-risk HPV genotypes share a common route of transmission. Thus, presence of EAC indicates HPV exposure and a risk of also being exposed to high-risk HPV. It has been reported that cervical cancer and cancer of the vulva, vagina, and penis share common causes and are related to genital warts [32]. Another study showed that men who have sex with men who have anal condylomata had a 50-fold higher risk of developing anal cancer [33]. EAC are typically benign lesions with a low risk of progression to invasive cancer but represent a clinical marker of risk of developing a high-risk HPV genotype–related malign lesion.

Because the incidence of EAC in France is high, and because the costs of treatment are considerable [7], preventing the occurrence of these lesions appears to be essential. Two multivalent HPV-L1 virus-like particle vaccines have been developed. One of the vaccines is directed against the most common cervical cancer–causing genotypes (genotypes 16 and 18) and the most common genital wart–causing genotypes (genotypes 6 and 11) and showed a 99% efficacy for the prevention of EAC [34]. With a 99% efficacy and a vaccine coverage of 100%, such a vaccine could prevent between 62% of EAC cases (i.e., those due to genotype 6, 11, 16, or 18, in the absence of another genotype) and 87% of EAC cases (99% × 88.2%) in France.

A cost-effectiveness analysis conducted in France reported that adding a quadrivalent HPV vaccine (given to girls at age 14 years) to the current screening program was a cost-effective strategy for reducing the burden of cervical cancer, precancerous lesions, and genital warts caused by HPV genotypes 6, 11, 16, and 18 [35]. Another study that attempted to estimate the impact of HPV vaccination on the incidence of genital warts reported that, if quadrivalent HPV vaccine was widely used in both male and female subjects, the incidence of this disease could decrease by as much as 97% [36]. Our results could

support the recommendation of HPV vaccination for persons of both sexes. However, the health benefits and economic impact of such a strategy should be further evaluated.

Acknowledgments

We gratefully thank Rama Kane (Sanofi Pasteur MSD) for her precious help, Ludivine Ragot (THERAPHARM Recherches; Boulogne Billancourt, France) for data management and analysis, Nubia Muñoz for critically commenting the manuscript, and all members of the Etude de la Distribution des Types d'HPV en France (EDiTH) Study Group, including gynecologists, dermatologists and proctologists, who actively participated in EAC collection

Financial support. Région de Franche Comté, the Institut National du Cancer, and Sanofi Pasteur MSD. M.S. is the recipient of a predoctoral scholarship from Région de Franche Comté.

Potential conflicts of interest. J.-L.P., X.C., and D.R. have served as consultants to Sanofi Pasteur MSD. All other authors: no conflicts.

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