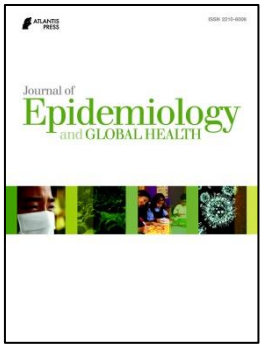

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Prevalence and risk factors of human papillomavirus infection types 16/18/45 in a cohort of French females aged 15—23 years

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Abstract Investigation of the prevalence and risk factors of human papillomavirus (HPV) infection is the basis for developing prophylactic strategies against cervical cancer, especially for young women. This study aimed to assess the prevalence and risk factors of HPV infection among a cohort of sexually active young French women eligible for catch-up vaccination. Between 1997 and 2007, 2163 women aged 15—23 years attending consultations at the department of gynecology in the Hospital of Besançon (France) were screened for high risk HPV (HR HPV) infection. Risk factors were investigated through a questionnaire sent to all participants in 2010. HPV DNA was detected by HC2 and Probe Set assays. The overall prevalence for HR HPV and HPV16, 18 and/or HPV45 was 44.6% (95% CI, 42.5—46.7%) and 19% (95% CI, 17.3—20.7%), respectively. The response rate to the questionnaire was 22.6%. The prevalence of independent risk factors (age older than 19, smoking, and oral contraception) for HPV 16/18/45 infection in this population was less than 20%. Based on this study, HPV vaccination should be offered not only to teenage girls, but also to young women, regardless of their sexual activity.
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1. Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection around the world [1,2]. A large majority of women are usually infected soon after they become sexually active in their teens or early twenties [3,4]. Most infections

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are cleared within two to 3 years [5], but women with persistent infection are at high risk of developing high-grade cervical intraepithelial neoplasia and invasive cancer years later [6]. The main risk factor for cervical cancers is high-risk HPV (HR HPV). Of these viruses, HPV types 16 and 18 are responsible for up to 70% of cervical cancers worldwide [1]. Different co-factors play a role in the persistence of HPV and the risk of development and progression of cervical lesions [7]. They are related to the host (hormones, genetic, immune response) [8], the virus (genotype, multiple infection, viral load and integration) [7] and the environment (high parity and long-term oral contraceptive use [9,10], tobacco smoking and co-infection with other sexually transmitted diseases [11]). However, the key risk factor is sexual behavior especially age at first intercourse and number of life-time partners which reflects exposure to HPV [12,13]. Since 2006, two vaccines have been approved and designed to protect against cervical intraepithelial neoplasia (CIN) grades 2 and 3 and cancers related to HPV 16 and HPV 18 infection in women with no evidence of previous exposure to vaccine-specific HPV types [14]. Until 2013, the French health authorities recommended vaccinating 14-year-old girls before their first sexual intercourse, and proposed a catch-up vaccination for 15- to 23-year-old women only if they have not yet had any sexual activity, or during the first year following their first sexual intercourse [15,16]. In France, there are consistent data documenting HPV prevalence in cervical lesions in women aged over 18 [17], but data from the specific population targeted by the vaccines are scarce [18]. Monitoring HR HPV infections in young women prior to vaccination is necessary to detect early changes in HPV prevalence in vaccine era and to adjust the cervical cancer screening policies.

To give an accurate description of HPV circulation in women who met the criteria of French recommendations for vaccination until December 2012, the prevalence of HPV types 16, 18 and/or 45 was estimated in a cohort of unvaccinated women enrolled between 1997 and 2007. The potential risk factors related to HR HPV, and HPV 16, 18 and/or 45 infection, were also reported.

2. Methods

2.1. Patients and study design

2,163 sexually active women aged 15—23 years living in the geographic region of Franche-Comté, France, who attended a consultation in the gynecology department of the University Hospital of Besançon, France, between January 1, 1997 and December 31, 2007 were included in the study. The Local Medical Ethics Committee (Besançon, France) and the National Committee for the protection of privacy and personal data (Commission Nationale de l'Informatique et des Libertés, CNIL) approved the study. Informed consent was obtained from all participants.

2.2. Specimen collection, cytology and HPV testing

At the time of the gynecology consultation, all women had a pelvic examination and two cervical smears were obtained. The first specimen was collected with a Cytobrush® Plus (Medscand Medical, Malmö, Sweden) for conventional cytology and sent to the pathology laboratory. Pap smear results were reported using the Bethesda system. The second cervical sample was collected with the DNAPAP Cervical Sampler™ (Qiagen, Gaithersburg, MD, USA) for HPV testing. The brush was transferred into a vial containing 1 mL Specimen Transport Medium® (STM) (Qiagen) and the specimen was then processed for routine HR HPV DNA testing with the Hybrid Capture 2 assay (HC2) (Qiagen) according to the manufacturer's instructions. This test permits the detection of the HPV DNA of 13 HR-HPV types, namely HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Samples were then stored at −20 °C.

All cervical specimens positive for HR HPV and from which enough material was available were retested in 2008 using the HPV 16/18/45 Probe Set Test (Qiagen). This test is also based on liquid hybridization with specific probes that make it possible to confirm the presence of HPV16 and/or HPV18 and/or HPV45 DNA in the samples without identifying the specific type. The HPV 16/18/45 Probe Set Test has an analytical sensitivity (1 pg/mL) similar to that of the HC2 test.

2.3. Questionnaire investigating risk factors for HPV infection

In June 2010, a questionnaire was sent with an explanatory letter to all females enrolled in the study between 1997 and 2007, to the postal address indicated in their medical file. Questions were regarding socio-demographic characteristics (educational level, smoking) at the time of HPV testing performed between 1997 and 2007, gynecological history (age at first HPV test, age at first menstruation, age at first pregnancy, number of children at HPV test, previous sexually transmitted diseases), and sexual behavior (age at first intercourse, duration between age at first intercourse and age at

HPV test, contraceptive use). Due to privacy legislation, the CNIL authorized to ask the question regarding the number of sexual partners at the time of the questionnaire, but not at the time of the HPV test. A reminder was sent by post four weeks later if the questionnaire was not returned.

2.4. Statistical analysis

The number of females enrolled in the cohort ($n = 2{,}163$) allowed the study team to estimate the overall prevalence of HR HPV and HPV 16/18/45 with a precision of 5% and 10%, respectively.

Continuous data are presented as mean (range) and categorical (qualitative) variables as number and percentage. A Mac Nemar test was performed to test the association between HPV and cytology results.

Prevalence was defined as number of women positive for HPV infection at the time of the first gynecology consultation between 1997 and 2007/total number of women screened by HPV test. Further analysis was performed to verify the representativeness of the sample of women who responded to the questionnaire in 2010 in comparison with the overall cohort of women included between 1997 and 2007.

To assess the association between HPV infection and the characteristics of women at the time of the HPV test, a crude odds ratio (OR) with exact 95% confidence interval (CI) was calculated. The number of subjects to be included in the risk factors analysis was based on the detection of a minimum OR of predictors using logistic regression. For an OR = 1.5, with an alpha risk of 5% and a power of 80%, 450 subjects are sufficient.

Continuous variables such as age at HPV test and the period of inclusion were categorized and tested by the Wald χ^2 test. When potential risk factors were found to be associated with infection with a p value <0.10 by univariate analysis, they were subsequently entered into the multivariate logistic regression model (stepwise selection) to identify factors independently associated with HR HPV infection or 16/18/45 HPV infection. Goodness of fit for the final model was assessed using the Hosmer—Lemeshow test. The multivariate models tested were adjusted for the period. All tests were two-sided and a p-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.2. (SAS Institute, Cary, NC, USA).

3. Results

From 1997 to 2007, 2163 females aged 15—23 years who attended a consultation in the gynecology department were enrolled in the study. The average age of the cohort was 21.1 years (median: 21.4, standard error 2.0). The questionnaire investigating retrospectively the potential risk factors was returned by 511 women, of whom 491 had completed the questionnaire, and 20 refused to respond (Fig. 1).

3.1. Prevalence of high risk HPV and HPV types 16/18/45 according to age

Out of the 2163 specimens collected, 44.6% (95% CI: 42.5—46.7%) were positive for HR HPV. The results from ProbeSet test showed that out of the 2038 analyzable specimens, 19% (95% CI: 17.3—20.7%) were positive for HPV 16/18/45 (Table 1).

The overall prevalence by age is reported in Table 1 and Fig. 2. There was an overall significant increase in HR HPV prevalence with age until 22 years (29.4—49.1%, $p = 0.0013$, $\beta = 2.29$). Women over 20 years of age were at a significantly higher risk of being infected by HR HPV ($p = 0.006$) in comparison with women under 20 (46.4% and 39.7%, respectively). However, prevalence of HPV 16/18/45 showed an almost similar age-distribution around 18%.

Of the 2,163 cervical swabs, cytology was available for 63% (1377/2163) of the samples at the time of the study. Among those samples 68.8% (948/1377) were within normal limits (WNL), whereas 8.4% (116/1377) showed atypical squamous cells of undetermined significance (ASCUS), 19.0% (262/1377) low-grade squamous intraepithelial lesion (LSIL) and 3.7% (51/1377) high-grade squamous intraepithelial lesion (HSIL). Over the 1377 samples, 558 (40.5%) were HR HPV-positive. This proportion increased significantly according to cytological diagnosis severity from 24% in normal specimens to 59% in ASCUS, 81% in LSIL and 92% in HSIL ($p < 0.0001$). Among 948 women with normal cytology the overall HR HPV prevalence varied according to age from 19% below 19 years to 25.2% above 19 years ($p < 0.0001$).

As for HPV 16/18/45, they were detected in 9.9% of WNL samples, 25.2% of ASCUS, 33.6% of LSIL and 59.1% of HSIL.

3.2. Risk factors associated with HR HPV and HPV 16/18/45 infection

The response rate to the questionnaire was 22.6% and the mean age of responders was 27.3 years in 2010.

Table 2 shows the number of young women enrolled every year (starting from 1997) and the number of women who completed the questionnaire.