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Human papillomavirus prevalence and type distribution in urine samples from Norwegian women aged 17 and 21 years: A nationwide cross-sectional study of three non-vaccinated birth cohorts

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ABSTRACT

Background: The aim of the current study was to assess the HPV prevalence in unscreened and unvaccinated young women living in Norway, to provide important baseline data for early estimation of the impact of the HPV vaccination program.
Methods: A total of 13,129 self-sampled urine samples from two complete birth-cohorts of 17-year old women born in 1994 and 1996 and one third of a birth-cohort of 21-year old women born in 1990, were analysed for the presence of 37 HPV types using PCR and a DNA hybridization technique.
Results: In the two birth cohorts of 17-year old women, HPV was detected in 19.9% (95% CI 18.8–20.9) and 15.4% (95% CI 14.5–16.3), respectively. High-risk HPV types were detected in 11.2% (95% CI 10.3–12.0) and 7.6% (95% CI 6.9–8.2), respectively, while vaccine types were detected in 7.4% (95% CI 6.7–8.1) and 6.0% (95% CI 5.4–6.6), respectively. Among the 21-year old women HPV was detected in 45.4% (95% CI 42.9–47.8), whereas high-risk types were detected in 29.8% (95% CI 27.5–32.0). Vaccine types (HPV 6, 11, 16, 18) were detected in 16.2% (95% CI 14.4–18.1).
Conclusion: This large population based study confirms that HPV testing in urine samples is easy and highly feasible for epidemiological studies and vaccine surveillance in young women. HPV was very common and a broad spectrum of HPV types was identified. Differences in HPV prevalence was seen both between age groups and between the two birth cohorts of 17-year old women.

1. Introduction

Infection with an oncogenic type of human papillomavirus (HPV) is a pre-requisite for developing cervical pre-cancerous lesions and carcinomas. More than 40 HPV types are known to infect the human anogenital tract. At least 12 types are considered carcinogenic and are commonly referred to as high-risk types [1–3].

Vaccination against HPV infection was introduced in the Norwegian childhood immunization program in the school year 2009/2010. All girls born in 1997 and later have been offered the vaccine in the 7th grade at age 11–12 years. No publically funded catch-up vaccination for the older age groups has been introduced. The 4-valent vaccine, Gardasil® is used in the program. The vaccine offers protection against HPV 16 and 18, which cause about 70% of invasive cervical carcinomas [4], as well as the low-risk types 6, 11, the main etiologic agent for external genital warts [5,6].

Knowledge of the baseline HPV prevalence and type distribution in unscreened and unvaccinated birth cohorts is essential for estimating the impact of HPV vaccination. However, few population-based studies have been conducted to assess the prevalence of HPV and type distribution in pre-teens or young adults. Smaller

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studies of unvaccinated women from Scotland and the Netherlands show an HPV prevalence in urine of4.4–32.2% in the age groups of 14–16 and 20–21 years, respectively [7,8]. A few studies have assessed the prevalence of circulating HPV types in Norway, generally focusing on HPV types present in cervical precancerous or cancerous lesions or in women visiting gynaecology clinics [9–15]. Less is known about the HPV prevalence and genotype distribution in women in their late teens or early twenties, who have not yet been invited to participate in the national screening program against cervical cancer. The aim of the current study was to describe the HPV type prevalence in young women in Norway who have not been offered the vaccine against HPV as part of the national childhood immunization program. We were also interested in comparing the HPV prevalence between 17-year olds and 21-year olds and between two birth cohorts of 17-year olds to document natural fluctuations of HPV prevalence.

2. Material and methods

2.1. Enrolment, sample collection, and study sample

Women eligible for the study were identified through the Norwegian Population Register.

In 2011, an invitation letter was sent to all women born in 1994 residing in Norway as of January 1st 2011, except some born at the end of 1994, in total 83.0% of the birth cohort (Fig. 1). In 2013, a total of 99.5% of the women born in 1996 were invited to participate in the study. The invitation was sent the same month the women became 17 years (in 2011 and 2013, respectively). Women born between August and December in 1990 were invited in the period January to May 2012. The HPV prevalence in this age-group was expected to be at least twice the HPV prevalence in the 17-year olds. Therefore, only women born between August and December were invited, in total 30.8% of the birth cohort. From the initial birth cohort list obtained at the beginning of the year of sample collection, some were not invited due to missing address, invalid social security number, death, or emigration.

The invitation was sent by mail and included information about the study, an informed consent form, and a pre-franked envelope for returning the signed informed consent. Women who consented to participate received a sample kit and instructions for obtaining a first void urine sample together with a pre-franked return envelope. The sample device contained a preservative (boric acid), to prevent bacterial growth. The urine samples were shipped by mail to the Norwegian Institute of Public Health (NIPH) where the samples were marked, processed and stored at −80 °C until further analysis. An aliquot was sent to the Norwegian HPV Reference Laboratory (Akershus University Hospital) for isolation of nucleic acids and HPV genotyping. HPV results were not routinely communicated to the participants, but were provided upon request. Participants could withdraw from the study at any time. All participants were rewarded with two cinema tickets for their contribution.

A total of 13,129 women contributed with a urine sample. The participation rates were similar for the northern, middle, western, southern and eastern region of Norway, and ranged from 14.2 to 17.8% for the 21-year olds and 16.9–22.3% for the 17-year olds.

Linkage to the immunization register for individual vaccination status was not performed since the current study population is largely unvaccinated. These young women were not offered vaccine against HPV as part of the national immunization program. According to distribution numbers, very few vaccine doses have been distributed for sale to this group.

The study was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Authority.

2.1.1. Isolation of nucleic acids

Nucleic acids were isolated using Boom's isolation method [16] and the automatic NucliSENS easyMAG extraction device (bioMérieux Corporate, Marcy l'Etoile, France). Total nucleic acids were kept cold and analysed within four hours or stored at −80 °C until analysis.

Validation of sample adequacy and HPV genotyping

Human β-globin quantitative real-time PCR for validation of sample adequacy and HPV genotyping using PCR and DNA hybridization and Luminex based technology was performed as previously described [17,18]. The HPV genotyping method detects 37 HPV types; 12 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), six probable high-risk types (26, 53, 66, 68, 73, 82), and 19 undetermined or low-risk types (6, 11, 30, 40, 42, 43, 54, 61, 67, 69, 70, 74, 81, 83, 86, 87, 89, 90, 91)[1,2].

In order not to compete with the HPV PCR, the β-globin PCR was run in a separate reaction. The PCR products were kept frozen at −20 °C until further analysis.

Upon Luminex detection of values in the range from the cut-off value up to two times the cut-off value for any HPV-type, a re-analysis was performed in duplicate. Individual cut-off values for each HPV-type were calculated for each run based on the level of background noise. Cut-off modification values and factors for cross-hybridization correction used to calculate the cut-off were adapted from the WHO HPV reference laboratory in Sweden. A total of 202 samples (1.5%) did not give a valid result for β-globin or for HPV, and were excluded from the analyses.

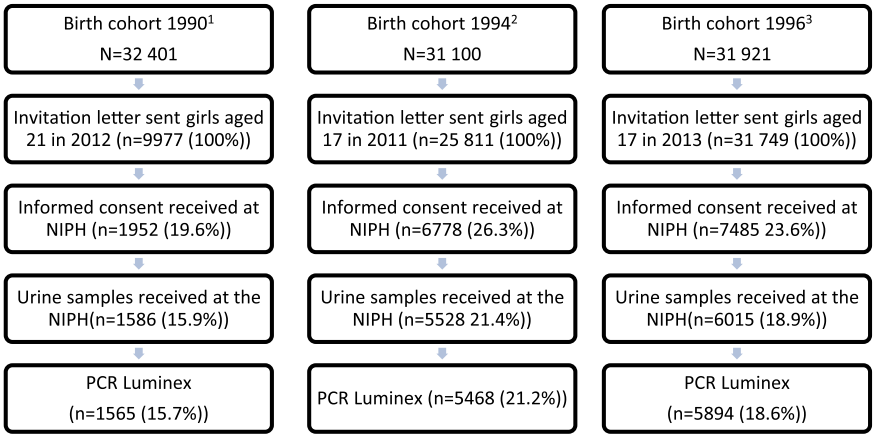

Fig. 1. Flow-chart study population. [1,2,3]Total female birth cohort alive the 1st of January the year of sample collection [29].