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Short Communication

Time trends in incidence and prevalence of human papillomavirus type 6, 11 and 16 infections in Finland

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Human papillomavirus (HPV) type 16 is the major cause of cervical carcinoma, the incidence of which is decreasing in western countries. In Finland the incidence is, however, increasing in women aged <40 years, but possible underlying changes in HPV-16 epidemiology are unknown. To assess incidence trends of HPV infections, paired sera from a random sample of 8000 women with two pregnancies/sera within 5 years, taken from the serum bank of the Finnish Maternity Cohort (1983–98), were analysed for HPV-6, -11 and -16 antibodies. For 23–31-year-old women, HPV-16 incidence increased over the period 1983–97. HPV-16 seroprevalence increased from 17 % in 1983–85 to 24 % in 1995–97, but HPV-6 and HPV-11 prevalence was stable at 9–12 % throughout the study period. Epidemic spread of the oncogenic HPV-16, but not the non-oncogenic HPV-types, throughout the 1980s and 1990s preceded an increase in the incidence of cervical carcinoma in fertile-aged Finnish women.

Human papillomavirus (HPV), most notably type 16, is the major cause of cervical carcinoma (IARC, 1995). The incubation time from infection to carcinoma diagnosis varies from 10 to 20 years. Most of the infected women, however, do not develop cervical carcinoma and the disease may rarely arise in the absence of HPV (Walboomers *et al.*, 1999).

In 1969, the age-adjusted HPV-16 seroprevalence among pregnant women was 16 % in Stockholm, Sweden, and had increased to 21 % by 1989 (af Geijersstam *et al.*, 1998a). In Helsinki, Finland, the age-adjusted HPV-16 seroprevalence was 24 % among primiparous women in both 1983 and 1990 (Kibur *et al.*, 2000a). In Tallinn, Estonia, the comparable HPV-16 seroprevalence was as high as 36 % during 1996–97 (Kibur *et al.*, 2000b). Thus, HPV-16 seroprevalence may vary both by country and by time period, but population-based data on HPV-16 incidence trends are lacking.

As a result of screening programmes, the incidence of squamous cell carcinoma of the uterine cervix, the predominant histological type of cervical carcinoma, decreased from 1973 to 1991 in northern and western Europe (Vizcaino *et al.*, 2000). For instance, in the Nordic countries up to 80 % of the disease burden had been prevented by the early 1990s, even though increased incidence was anticipated due to sexual life-style changes favouring spread of HPVs (Haavio-Mannila *et al.*, 2001; Anttila *et al.*, 1999; Vizcaino *et al.*, 2000). In fact, an increase in the incidence of cervical adenocarcinoma, which is not prevented by the screening, was found among fertile-aged women (Vizcaino *et al.*, 2000).

In Iceland the incidence of cervical carcinoma, however, doubled during an already established screening in the 1980s (Sigurdsson, 1999). Similarly, from 1991 to 1995 the incidence of cervical carcinoma increased among 30–39-year-old women in Finland and the same trend was noted among 40–54-year-old women, who had been screened most systematically (Anttila *et al.*, 1999). Among 30–39-year-old Finnish women the incidence of cervical carcinoma further increased over the next 5 years (1996–2000) (www.cancerregistry.fi) and the trend was seen also among 25–29-year-old women. In Finland screening for cervical carcinoma starts in 25–30-year-old women, but changes in registration and diagnostic practices do not seem to explain the observed increase (Anttila *et al.*, 1999).

We assessed trends of age-specific incidence and prevalence of oncogenic HPV-16 and non-oncogenic HPV-6 and

HPV-11 infections among fertile-aged Finnish women in 1974 and from 1983 to 1997 to identify possible HPV-16 epidemics preceding the increase in incidence of cervical carcinoma.

Over 98 % of pregnant Finnish women participate in serological screening for syphilis, human immunodeficiency virus and hepatitis B virus infections at municipal maternity clinics. Following informed consent, serum samples are drawn at the first trimester of each pregnancy. The Finnish Maternity Cohort (FMC) of the National Public Health Institute (NPHI) has collected, analysed and stored the serum samples (at $-25\,°C$) since 1983. About 50 % of women who had previously participated became pregnant again within 5 years. Currently, the FMC contains more than 1 200 000 samples donated by 650 000 women.

To identify HPV seroconversions, all women with a minimum of two pregnancies within 5 years were identified in the FMC. The estimated time of possible seroconversion was calculated as the mean of the two serum sampling dates. All eligible women, whose age at the estimated time of possible seroconversion was under 32 years, were divided into 25 strata according to the age (five 3-year age bands) and calendar time (five 3-year time bands) of the possible seroconversion (Table 1). In each stratum, a subsample of 200 or 400 women was selected randomly. Four hundred 23–31-year-old women per stratum were selected because their HPV incidence was expected to be low (Kibur et al., 2000a). Paired sera (mean sampling interval 26·7 months, median 23·9, quartiles 17·9 and 33·5 months) were finally available for 7862 women (Table 1).

The HPV-6, HPV-11 and HPV-16 IgG antibody analyses were carried out by standard ELISAs (Dillner et al., 1996). Highly purified, yeast-expressed HPV-6, HPV-11 and HPV-16 virus-like particles comprising the L1 proteins kindly supplied by Kathrin Jansen (Merck Research Laboratories, USA) were used. Cut-off levels were determined as mean + 3 standard deviations of sera from 40 virginal women. Incident cases were defined as seroconversions, i.e. an initially antibody negative person becoming antibody positive in her second sample. Internal control sera were included on each plate and intra-assay variation was low for all the assays, being 8·3 for HPV-6, 9·4 for HPV-11 and 8·4 for HPV-16 ELISA. In addition, all serum samples of a given age group over the different time periods were analysed simultaneously. In the following, the HPV-6 and HPV-11 results were combined (either both negative or one/both positive).

Because the numbers of seroconversions were lower than expected, the two youngest and the three oldest age groups were combined for the statistical analyses according to previous observations on the characteristics of the age group-specific HPV-16 seroconversion rates (Kibur et al., 2000a). The HPV-16 and HPV-6 and HPV-11 incidence rates among susceptibles (i.e. seronegative at the time of first pregnancy) were calculated per 1000 person years. For both incidence sets, we fitted a Poisson regression model with age at the time of possible seroconversion (0 = under 23 and 1 = 23–31 years), linear calendar-time term (-6 = 1983–85, -3 = 1986–88, 0 = 1989–91, 3 = 1992–94 and 6 = 1995–97), quadratic calendar-time term and interaction terms between age and both calendar-time terms to evaluate possible time trends and their statistical significance. In addition, we fitted the Poisson regression model with linear (first-degree), quadratic (second-degree) and cubic (third-degree) calendar-time terms for HPV-6, HPV-11 and HPV-16 incidence in the younger age groups. The models were fitted by the method of maximum likelihood using the Genmod procedure of the SAS program (version 8.2).

From 1966 to 1972, the Finnish Social Insurance Institution's Mobile Clinic Health Examination Survey (MC) carried out a multiphasic health examination in various parts of Finland. Re-examinations were performed from 1973 to 1976. During the baseline study, serum samples from 19 000 women were stored frozen and during the re-examination study samples from 9000 women were stored (Knekt, 1990). In the MC, paired sera (mean sampling interval 49·2 months, median 48·7, quartiles 48·1 and 50·6 months) were available for a total of 159 women. Their estimated mean year of possible seroconversion was 1974. The subsample included a total of 45 women whose age

Table 1. Size (n) of random subsamples and absolute numbers (N) of women belonging to the Finnish Maternity Cohort by estimated age and calendar time of possible seroconversion

The women had had two pregnancies within 5 years during 1983–97.

| Age (yrs) | 1983–85 | | 1986–88 | | 1989–91 | | 1992–94 | | 1995–97 | | Total |
	n	N	n	N	n	N	n	N	n	N	(n)
<20	197	1 046	192	2 285	200	2 189	193	2 063	200	218	982
20–22	195	4 249	195	8 870	193	9 267	199	7 899	200	717	982
23–25	390	7 020	392	16 177	388	18 298	394	16 169	399	1 153	1 963
26–28	394	7 848	397	19 300	385	24 483	390	22 758	399	1 549	1 965
29–31	396	5 342	392	14 001	393	18 396	389	18 461	400	1 240	970
Total (n)	1 572		1 568		1 559		1 565		1 598		7 862

at the time of possible seroconversion was under 23 years and 114 women between 23 and 31 years. Due to the small size of the MC subsample, the year 1974 incidence was left out from the Poisson regression models, but the data are given in the text for comparison.

To estimate the relative proportions of susceptible women and to determine the spread of the epidemics, HPV-16 and HPV-6 and HPV-11 prevalence at the time of the first pregnancy/serum sampling was calculated for the two age groups at six different calendar-time periods. In incidence calculations age and calendar time are fixed on the mean of the two serum sampling dates and median sampling interval is about 2 years. The prevalence was calculated from the first serum samples; therefore prevalence rates apply to women who are about 1 year younger and refer to a calendar-time period about 1 year earlier than the incidence rates.

The HPV-16 prevalence among women under 23 years of age was stable, ranging from 17 to 18 % during 1983–97 (Fig. 1A). In 1974, the HPV-16 prevalence was 13 %. For women between 23 and 31 years of age, the HPV-16 prevalence was approximately within the same range from 1974 (18 %) to 1989–91 (15–17 %), but increased thereafter to 24 % in 1995–97.

The HPV-16 incidence was 1·4- to 5-fold higher among women under 23 years of age compared with women between 23 and 31 years of age (Fig. 1C). In the younger age group the HPV-16 incidence per 1000 person years was 26 (four cases) in 1974. It was lowest at 13 in 1992–94 and highest at 31 in 1995–97. There was insufficient evidence of either quadratic or linear trend. In the older age group, a gradually increasing linear trend ($P=0·007$) of HPV-16 incidence was seen during 1983–97. The incidence in 1995–97 was 13, i.e. 2·6-fold higher than in 1983–85. In 1974, however, the HPV-16 incidence was 16 (six cases).

The combined HPV-6 and HPV-11 prevalence in both age strata varied from 9 to 12 % during 1983–97 (Fig. 1B). In 1974, the HPV-6 and HPV-11 prevalence was comparable: 9 % and 14 % for women under 23 and between 23 and 31 years of age, respectively.
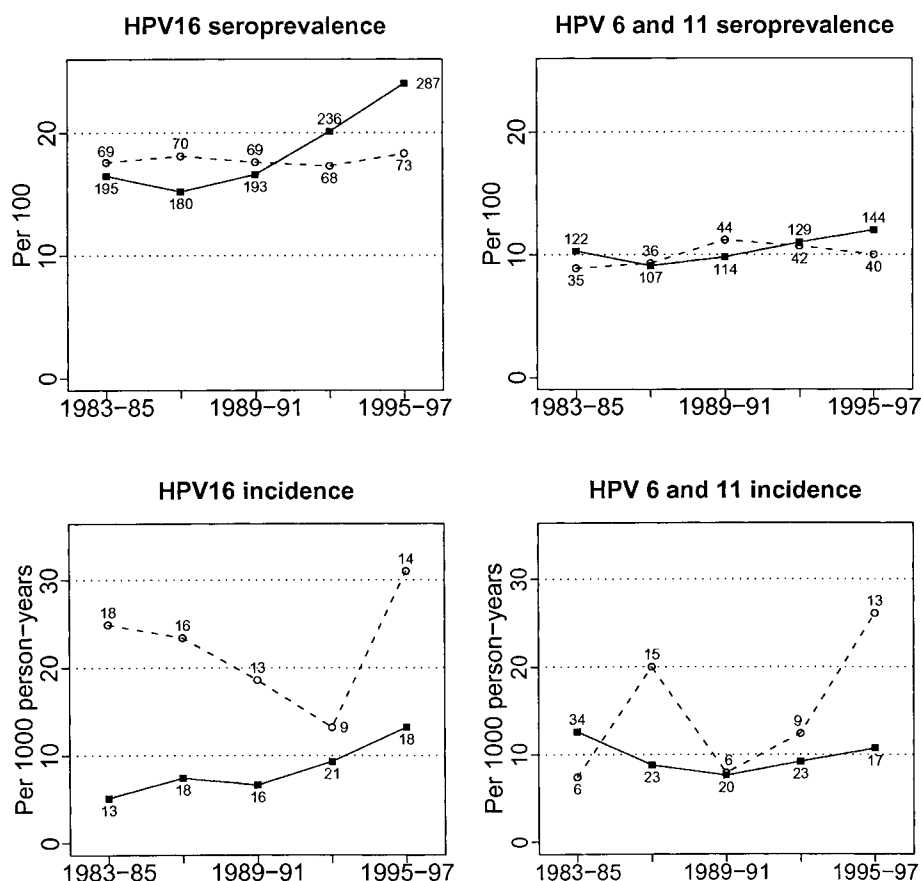

Fig. 1. HPV-6 and -11 and -16 seroprevalence (%) and incidence (per 1000 person years) in women belonging to the Finnish Maternity Cohort by estimated age and calendar time of possible seroconversion. The women had had two pregnancies within 5 years during 1983–97. Numbers of prevalent and incident cases are shown for the different time periods (----, ⩽22 years; ——, 23–31 years).

The HPV-6 and HPV-11 incidence fluctuated considerably among women under 23 years of age. In 1974 it was 18 (three cases) per 1000 person years and in 1995–97 it peaked at 26 per 1000 person years (Fig. 1D). Neither linear nor quadratic term of calendar time improved the fit of the Poisson regression model, but adding the cubic term essentially reduced the residual deviance. In the older age group the incidence was 15 (six cases) in 1974 and 8 (three cases) in 1989–91 and then became steady at about 10 per 1000 person years. There was insufficient evidence of cubic, quadratic or linear trends.

A steady annual increase of 0·7 % in the HPV-16 incidence took place in Finland from 1983 to 1997 among a random sample of women with at least two pregnancies between 23 and 31 years of age. These women represented one-third of fertile-aged Finnish women and our data are the first evidence to suggest that significantly increasing incidence of HPV-16 infections precedes the increase in cervical carcinoma incidence (Anttila et al., 1999) in Finland. Since the sensitivity of HPV-16 serology is not more than 50–65 % (Carter et al., 1996; Dillner et al., 1996) the observed rates represent an underestimate of the epidemic. The rates of HPV seroreversions have been negligible (af Geijersstam et al., 1998b) and were also low in the present study: 0·7 % for HPV-6, 0·7 % for HPV-11 and 1·4 % for HPV-16. However, it is noteworthy that previous occurrence of HPV infections in the population has an effect on the HPV incidence at each subsequent time point and cannot be controlled for by, for example, confidence intervals. This is due to contacts between adjacent birth cohorts and is further modified, for example, by assortative risk-taking sexual behaviour not controlled for in the Poisson regression model either.

Increasing HPV-16 prevalence was not observed in an earlier Finnish study among women with two pregnancies in the Helsinki metropolitan area in 1983 and 1990 (Kibur et al., 2000a). The HPV-16 prevalence was 24 %, similar to our 1995 observations, but remarkably higher than the 15–17 % observed for our 1983–90 samples, which represent the entire country. Calendar-time period, geographic and life-style differences may well explain the observed differences. Swedish data from Stockholm show a comparable, albeit earlier, increase in the HPV-16 seroprevalence from 16 to 21 % between 1969 and 1980 (af Geijersstam et al., 1998a). In the early 1970s HPV-16 seroprevalence in the 40–50-year-old women was less than 5 % (Lehtinen et al., 1996), but was 18 % among the 23–31-year-old women in 1974. Thus, among the fertile-aged Finnish women, a major increase in the HPV-16 prevalence had already taken place before the mid-1970s. Also, the HPV-16 incidence in 1974 was higher than in the 1980s and 1990s, which suggests that in the early 1970s the epidemic was a recent one.

A series of detailed questionnaire studies has revealed that sexual behaviour of 18–34-year-old Finnish women changed considerably from 1971 to 1999 (Haavio-Mannila et al., 2001). The number of lifetime sexual partners increased from 2·6 to 7·7 and the age of sexual debut decreased from 18·9 to 16·6 years, increasing the impact of oncogenic HPV infections due to earlier exposure. In the youngest age groups, the changes have probably been even more pronounced. If the first HPV-16 epidemic had already occurred in the 1970s throughout Finland, the resulting relatively high proportion of immune individuals in the fertile-aged population might explain the observed relatively low increase of HPV-16 incidence until the late 1980s. An increase in risk-taking sexual behaviour probably exposed more and more susceptible adolescent individuals to the virus and eventually resulted in the considerable increase of HPV-16 seroprevalence in the new sexually active birth cohorts in the 1990s.

HPV-6 and HPV-11 prevalence showed no material changes during the study period, which suggests an epidemic steady state. This presumably implies different transmission modes and dynamics for HPV-6, HPV-11 and HPV-16 infections. HPV-16 is predominantly transmitted by mucosal contacts, while HPV-6 and HPV-11 are also transmitted via the skin (Wen et al., 1999). Finally, possible competitive advantages favouring the spread of HPV-16 over HPV-6 and HPV-11 or chance cannot be ruled out as explanations for the observed differences between the oncogenic and non-oncogenic HPV types.

For the observed peaks in the HPV-6 and HPV-11 incidence in 1986–88 and 1995–97 in women under 23 years of age, borderline significance of the cubic (third-degree) term might indicate epidemic outbreaks. We also found a sharp peak in the HPV-16 incidence among women under 23 years of age in 1995–97, but not among the older women. The former may represent chance findings, but on the other hand the epidemic situation may indeed be different among the very young pregnant women as compared with the older women (Lehtinen et al., 2002) and outbreaks of HPV infections are likely to occur in the young.

While it is not possible to conclude from these data that increased cervical carcinoma incidence results from increased HPV-16 incidence, our data indicate that an increase in the background exposure to HPV-16 precedes the increase of cervical carcinoma incidence in Finland. In conclusion, both naturally occurring and vaccination-induced dynamics of background exposure to the oncogenic HPVs should be considered when national HPV vaccination and cervical cancer screening programmes are being contemplated.

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