BMJ Open

Is the risk of cervical atypia associated with the interval between menarche and the start of sexual activity? A population-based cohort study

Indira Adhikari,[1] Tiina Eriksson,[1] Tapio Luostarinen,[2] Dan Apter,[3] Matti Lehtinen[1]

To cite: Adhikari I, Eriksson T, Luostarinen T, *et al*. Is the risk of cervical atypia associated with the interval between menarche and the start of sexual activity? A population-based cohort study. *BMJ Open* 2019;**9**:e030091. doi:10.1136/bmjopen-2019-030091

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-030091).

Received 26 February 2019
Revised 17 August 2019
Accepted 20 August 2019

[1]Department of Health Sciences, Tampere University, Tampere, Finland
[2]Institute for Statistical and Epidemiological Cancer Research, Finnish Cancer Registry, Helsinki, Finland
[3]VL-Medi, Helsinki, Finland

Correspondence to
Indira Adhikari;
indira.adhikari@tuni.fi

ABSTRACT

Objective We investigated whether the risk of cervical atypia is associated with a short interval between the age at first sexual intercourse (FSI) or age at the start of oral contraceptive (OC) use and menarche.

Design A population-based cohort study.

Setting Finnish women in the age range of 16–17 years old were enrolled in the PATRICIA trial of human papillomavirus (HPV) 16/18 vaccine efficacy.

Participants The association of cervical atypia with the interval between FSI or start of OC use and menarche was assessed in the control arm (hepatitis A vaccinated) who had participated in biannual clinical follow-up visits for 4 years. Altogether, 913 women had normal baseline cervical cytology and answered behavioural questionnaires at enrolment and end of the follow-up.

Main outcome measure ORs with 95% CIs using univariate and multivariable logistic regression were used to assess the association between cervical atypia and the interval between FSI or the start of OC use and menarche.

Results The mean ages at menarche, FSI and the start of OC use were 12.4, 16.0 and 16.4. *Chlamydia trachomatis* infection was associated with an increased risk of cervical atypia in women with a short (<3 years) interval between menarche and FSI/start of OC use (OR 1.8, 95% CI 1.0 to 3.6 and OR 2.2, 95% CI 1.0 to 5.1). Whereas HPV 16/18 infection was associated with increased atypia risk estimates in women with a longer (≥3 years) interval (OR 1.8, 95% CI 1.1 to 2.7 and OR 1.4, 95% CI 1.0 to 2.1). In women with a short interval between menarche and FSI, early age at the start of OC use was not associated with an increased risk of cervical atypia in the univariate (OR 0.7) nor multivariable analyses.

Conclusion Short interval between menarche and the age at start of sexual activity does not increase the risk of HPV-associated cervical atypia.

Trial registration number NCT00122681.

Strengths and limitations of this study

- ► A large human papillomavirusHPV vaccination trial cohort with standardised clinical and laboratory procedures.
- ► The repeated self-reported study questionnaires were comprehensive and less subject to recall bias.
- ► Use of the overall cervical atypia endpoint increases study power but may have diluted the effects.

INTRODUCTION

Sexually transmitted human papillomavirus (HPV) infections cause both cytological and histological cervical abnormalities.[1 2] Clinical manifestations of persistent infection with oncogenic HPV types and squamous intraepithelial lesions (SILs) of the cervix, also known as cervical intraepithelial neoplasia (CIN), are the precursors of invasive cervical cancer (ICC).[3–5] In addition to HPV, other risk factors which may play a role in the pathogenesis of ICC are smoking,[6] *Chlamydia trachomatis*,[7] lifetime number of sexual partners (LNSPs),[8] age at first sexual intercourse (FSI),[9] parity[10] and the use of oral contraceptives (OCs).[11]

Both early age at FSI and early age at the start of OC use are associated with an increased risk of SIL and CIN.[9 12–14] Furthermore, a short lag between menarche and FSI is a risk factor of SIL/CIN.[9 12 14] This is probably due to exposure of immature cervical cells to infection with HPV, as persistent infections with oncogenic HPV types are established more readily in an immature cervix.[13 15] However, whether or not early start of OC use has an independent role here is unknown. The interplay of the time interval between age at the start of OC use or FSI and menarche in cervical carcinogenesis has not been studied.

In a large cohort study, we have investigated whether the risk of cervical atypia is associated with a short interval between menarche and the age at the start of OC use or FSI.

Table 1 Characteristics of 22-year-old women (n=913) who attended eight biannual follow-up visits and a subgroup of these women (n=197) who developed cervical atypia during 4 years of follow-up

	Attendees		Women with atypia	
Characteristics	**n=913**	**%**	**n=197**	**%**
Age				
22	422	46.2	94	47.7
23	489	53.6	103	52.3
24	2	0.2	0	0
Missing	0	0	0	0
Age at menarche				
≤11	194	21.3	52	26.4
12–14	659	72.2	136	69.0
≥15	52	5.7	6	3.10
Missing	8	0.8	3	1.5
Age at FSI				
12–16	602	65.9	129	65.5
17–22	273	29.9	60	30.5
Missing	38	4.2	8	4.0
LNSPs				
0	3	0.3	1	0.5
1	131	14.3	29	14.7
2–4	283	31.0	57	28.9
5–9	236	25.9	50	25.4
≥10	230	25.2	55	28.0
Missing	30	3.3	5	2.5
OC use				
Non-user	62	6.8	15	7.6
User	842	92.2	179	90.9
Missing	9	1.0	3	1.5
Age at start of OC use				
12–16	504	55.2	104	52.8
17–22	371	40.6	85	43.1
Missing	38	4.2	8	4.1
Condom use				
Non-user	414	45.4	97	49.2
User	406	44.5	83	42.1
Don't know	76	8.3	16	8.1
Missing	17	1.8	1	0.5
Smoking				
Never	525	57.5	108	54.8
Past	93	10.2	16	8.1
Present	291	31.9	73	37.1
Missing	4	0.4	0	0
HPV 16				
Negative	711	77.9	145	73.6
Positive	201	22.0	52	26.4
HPV 18				
Negative	792	86.8	165	83.8
Positive	120	13.1	32	16.2
Chlamydia				
Negative	811	88.8	175	88.8
Positive	102	11.2	22	11.2

FSI, first sexual intercourse; HPV, human papillomavirus; LNSPs, lifetime number of sexual partners; OC, oral contraceptive.

MATERIALS AND METHODS

Study sample

The study population consists of women enrolled in the control arm of a double-blinded, multi-national randomised control PATRICIA trial whose primary aim was to evaluate the vaccine efficacy of the HPV 16/18 vaccine against CIN2+.[16 17] Full description of the trial, details of recruitment and final results on its endpoints have been reported earlier.[18] PATRICIA enrolled only 16–17-year-old women in Finland (2409 received at least one dose of HPV 16/18 vaccine) and 2399 women (received at least one dose of hepatitis A virus (HAV) vaccine). The criteria of having no more than six LNSPs was not applied in Finland, so all women interested and willing to participate in the study were included.[18] Written informed consent was obtained from all the participants.

The present study began after the end of the clinical PATRICIA trial. All 4808 women who were approximately 22 years old when exiting the trial were sent a questionnaire on living conditions, lifestyle habits and sexual health. All the women (913) who had received the HAV vaccine, answered the questionnaires both at enrolment and at the end of the follow-up, and had negative cytology at baseline and before menarche were eligible (table 1). Cytology outcomes were detected at the follow-up visits.

Data collection

In addition to collecting information on living conditions and lifehabits, the questionnaires collected information about history of OC use, use of other contraceptives, smoking, menarche and sexual habits. The end of study questionnaire was more complete regarding the initiation of sexual habits, and was therefore used in the analysis. The age at the start of OC use, menarche and age at FSI were the independent variables in this study. Intervals of <3 years, or more than or equal to 3 years were calculated between menarche and the age at the start of OC use, as well as between menarche and FSI. Data on smoking ('never smokers', 'past smokers' and 'present smokers'), LNSPs ('none', '1', '2–4', '5–9' and 'more than 10'), condom use ('non-user', 'user' and 'do not know') and sexually transmitted infections (HPV

Adhikari I, *et al*. *BMJ Open* 2019;**9**:e030091. doi:10.1136/bmjopen-2019-030091

Table 2 Distribution of cervical atypia risk factors by interval between menarche and age at the start of OC use or age at the FSI in young adult women followed up for 4 years

	Interval between menarche and age at the start of OC use		Interval between menarche and the FSI	
	Interval <3 years (n=192)	Interval ≥3 years (n=675)	Interval <3 years (n=302)	Interval ≥3 years (n=566)
Category	n/Mean (%/SD)	n/Mean (%/SD)	n/Mean (%/SD)	n/Mean (%/SD)
Chlamydia trachomatis	39 (20.3)	59 (8.7)	54 (18.0)	44 (7.8)
HPV 16	55 (28.7)	142 (21.1)	97 (32.2)	100 (17.8)
HPV 18	35 (18.2)	83 (12.3)	47 (15.6)	71 (12.5)
HPV 16/18	69 (35.9)	190 (28.2)	115 (38.2)	144 (25.4)
Smoking				
Never	84 (43.8)	405 (60.4)	134 (44.8)	356 (63.0)
Past smoker	22 (11.4)	69 (10.2)	37 (12.4)	54 (9.6)
Present smoker	86 (44.8)	197 (29.4)	128 (42.8)	155 (27.4)
Age at menarche	13.4 (1.2)	12.2 (1.1)	13.1 (1.3)	12.1 (1.1)
Age at FSI	14.7 (1.2)	16.3 (1.9)	14.6 (1.2)	16.7 (1.9)
Age at start of OC use	14.9 (1.2)	16.9 (1.7)	15.3 (1.3)	17.1 (1.7)
Lifetime number of partners				
0	0	1 (0.2)	0	1 (0.2)
1	11 (5.7)	119 (17.6)	14 (4.6)	116 (20.5)
2–4	46 (24.0)	230 (34.1)	73 (24.2)	204 (36.0)
5–9	69 (36.0)	163 (24.2)	98 (32.5)	134 (23.7)
>10	66 (34.4)	162 (24.0)	117 (38.7)	111 (19.6)

FSI, first sexual intercourse; HPV, human papillomavirus; OC, oral contraceptive.

16/18 and *C. trachomatis*) were used as covariables, as they are important factors in cervical carcinogenesis. These covariables were used in both the univariate and multivariable models to evaluate if the short intervals between menarche and FSI or age at the start of OC use are truly associated with or modify the risk of cervical atypia.

Laboratory analysis and endpoints

In the PATRICIA trial, biannual cervical cytological and DNA samples were obtained in conjunction with pelvic examination. PCR analyses for *C. trachomatis* and HPV DNA were performed as described.[18]

At the follow-up visits, the first cytological findings of atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL) were registered as index incident cases for the statistical analysis. Colposcopy-directed biopsy samples were also obtained during the trial. The first histopathological findings of CIN grades 1, 2 and 3 were also listed as the index cases for statistical analysis. SIL and CIN cases were combined together to form a new variable, cervical atypia.

Cervical atypia findings were registered by the interval between menarche and FSI or the start of OC use to form four mutually exclusive different individual outcome variables; (1) cervical atypia with shorter than 3 years lag between menarche and FSI, (2) cervical atypia with equal or longer than 3 years lag between menarche and FSI, (3) cervical atypia with shorter than 3 years lag between menarche and OC use and (4) cervical atypia with equal or longer than 3 years lag between menarche and OC use.

Patient and public involvement

Patient (adolescent study subjects) and public (parental) involvement in the planning and design of the study was noted as their attitudes and willingness to participate in a HPV vaccination trial in a questionnaire sent to households (parents and their adolescent daughter) in one of the major study site communities.[19] No patients with cervical cytological atypia were involved in setting the research questions, the outcome measures or in developing the plans for recruitment, design or implementation of the study.

There are no plans to directly disseminate the results of the research to study participants; however, the results have and will be disseminated to a wider audience, including members of the public, patients, health professionals and experts through written communication, events and conferences, networks and social media.

Table 3 Relative risk (ORs with 95% CI) of cervical atypia (cytological SIL and/or CIN grade 1 or worse, CIN1+) associated with different covariables in analyses stratified by the interval between menarche and age at FSI (category 1), or between menarche and the age at start of OC (category 2) use in young adult women followed up for 4 years

	Frequency and relative risk of cytological atypia: SIL or CIN1 in the different categories by interval from menarche							
	Category 1				Category 2			
	Menarche to FSI <3 years SIL/CIN1+		Menarche to FSI ≥3 years SIL/CIN1+		Menarche to start of OCs <3 years SIL/CIN1+		Menarche to start of OCs ≥3 years SIL/CIN1+	
Variable	**n/N**	**OR (95% CI)**	**n/N**	**OR (95% CI)**	**n/N**	**OR (95% CI)**	**n/N**	**OR (95% CI)**
HPV 16/18								
Positive	21/115	1.0 (0.6 to 2.0)	45/144	1.8 (1.1 to 2.7)	13/69	1.4 (0.6 to 3.0)	53/190	1.4 (1.0 to 2.1)
Negative	33/186	1	87/422	1	18/123	1	102/484	1
Chlamydia								
Positive	14/54	1.8 (1.0 to 3.6)	8/44	0.7 (0.3 to 1.6)	10/39	2.2 (1.0 to 5.1)	12/59	0.8 (0.4 to 1.6)
Negative	40/248	1	124/522	1	21/153	1	143/616	1
Smoking								
Yes	34/165	1.5 (0.8 to 2.7)	52/209	1.1 (0.8 to 1.7)	22/108	2.1 (1.0 to 5.0)	64/266	1.1 (0.8 to 1.6)
No	20/134	1	80/356	1	9/84	1	91/405	1
Condom use								
Yes	22/146	0.7 (0.4 to 1.2)	59/256	0.9 (0.6 to 1.3)	15/102	0.6 (0.3 to 1.3)	66/300	0.9 (0.6 to 1.3)
No	29/139	1	61/251	1	16/80	1	74/309	1
LNSPs								
High	39/215	1.1 (0.6 to 2.0)	64/245	1.3 (0.9 to 2.0)	24/135	1.5 (0.6 to 3.8)	79/325	1.2 (0.8 to 1.7)
Low	15/87	1	68/321	1	7/57	1	76/350	1

*Five or more.
CIN, cervical intraepithelial neoplasia; FSI, first sexual intercourse; LNSPs, lifetime number of sexual partners; OC, oral contraceptive; SIL, squamous intraepithelial lesion.

Table 4 Relative risk (ORs with 95% CI) of cervical atypia (cytological SIL and/or CIN grade 1 or worse, CIN1+) stratified by the interval between menarche and age at FSI or between menarche and the age at start of OC use in young adult women followed up for 4 years

Frequency and relative risk of cytological atypia: SIL or CIN1 in the different categories by interval from menarche						
	Category 1			Category 2		
	Menarche to FSI <3 years SIL/CIN1+			Menarche to start of OCs ≥3 years SIL/CIN1+		
Variable	n/N	OR (95% CI)		n/N	OR (95% CI)	
Lag between FSI and menarche						
<3 years.	53/301	NA		23/110	0.9 (0.5 to 1.4)	0.9 (0.8 to 1.0)
≥3 years	NA	NA		132/565	1	*Interval (cont.)
Lag between start of OCs and menarche						
<3 years.	30/191	0.7 (0.4 to 1.3)	0.9 (0.9 to 1.0)	NA	NA	
≥3 years	23/110	1	*Interval (cont.)	155/675	NA	

CIN, cervical intraepithelial neoplasia; FSI, first sexual intercourse; OC, oral contraceptive; SIL, squamous intraepithelial lesion.

Statistical analysis

The outcome variables were analysed in the univariate and multivariable logistic regression models along with the independent variables and above listed covariates. The risks are reported as the ORs with 95% CI. The statistical analysis was performed using Stata V.14.0 (Stata Corp LP, Statistical Software: Release 14).

RESULTS

Baseline characteristics of our study cohort attending biannual follow-up visits for 4 years are materially homogeneous with little variation (table 1).

Age at menarche was between 12 and 14 years for 659 (72.2%) participants. Age at the FSI and age at the start of OC use were between 12 and 16 years for 602 (65.9%) and 504 (55.2%) participants, respectively. No cervical atypia cases were found before the menarche, age at the FSI or the age at the start of OC use. One cervical atypia case occurring concomitantly with the start of OC use was removed from the analyses.

By the end of the follow-up period, out of 913 women, 156 (17.1%) had ASCUS, 189 (20.7%) had LSIL, 5 (0.6%) had HSIL, 40 (4.4%) had CIN1, 22 (2.41%) had CIN2 and 8 (0.9%) had CIN3. 197 (21.6%) of 913 women were identified with cervical atypia (table 1). Almost one-third of the women with cervical atypia (55 (28.0%) of 197) had more than 10 LNSPs. Half of the women with or without cervical atypia, 49.2% and 45.4% respectively, did not regularly use condoms. Most of the women (179 (90.9%) of 197) with cervical atypia had used OCs. Age at the start of OC use for the majority of these women (104 (52.8%) of 197) was between 12 and 16 years (table 1). During the 4 year follow-up, 201 (22%) of all women were tested positive for HPV 16 and 120 (13.1%) were tested positive for HPV 18 (table 1). One-third of women with either HPV 16 or HPV 18, or both were diagnosed with cervical atypia during the follow-up. The number of women who tested positive for *C. trachomatis* was 102 (11.2%), and the number of *C. trachomatis* positive women with cervical atypia was 22 (11.2%) (table 1).

We categorised the risk factors of cervical atypia according to the interval between menarche and age at the start of OC use, or between menarche and age at FSI using a stratification of <3 years and ≥3 years (table 2).

The mean ages at menarche, at FSI and at the start of OC use were similar in the corresponding categories (table 2). Women in the <3 years interval categories were more often HPV 16 positive than women in the ≥3 years interval categories (table 2). The percentages of women with multiple (>5) LNSPs were also higher in the short interval categories (table 2).

In the univariate analysis, the risk of cervical atypia associated with its known risk factors was evaluated separately in the short and long interval categories (table 3).

Cervical atypia risk estimates associated with HPV 16/18 were increased (OR 1.8, 95% CI 1.1 to 2.7 and OR 1.4, 95% CI 1.0 to 2.1) in the longer (≥3 years) interval categories. On the contrary, the cervical atypia risk associated with *C. trachomatis* was increased (OR 1.8, 95% CI 1.0 to 3.6 and OR 2.2, 95% CI 1.0 to 5.1) in the short (<3 years) interval categories. Condom use was not associated with a significantly decreased risk of cervical atypia in any of the interval categories (table 3).

In univariate analyses, the risk of cervical atypia associated with the short interval between menarche and age at the start of OC use appeared to be somewhat decreased (OR 0.7, 95% CI 0.4 to 1.3) when the interval between menarche and age at the FSI was short (table 4).

The risk estimate, however, approached unity (OR 0.9) when the interval was estimated as a continuous variable. There was no risk of atypia associated with the long-term interval between menarche and the start of OC use (table 4).

In multivariable analyses, stepwise exclusion of one variable at a time from the multivariable model was performed to check the interdependency of the interval between menarche, age at the start of OC use and age at FSI in this context. Exclusion of any of the abovementioned variables did not affect significance of the estimates (data not shown).

DISCUSSION

We found that cervical atypia was not associated with early start of sexual activity after menarche. The risk of cervical atypia associated with *C. trachomatis* was increased shortly after start of sexual activity following menarche, whereas the risk of cervical atypia was associated with HPV 16/18 infections more than 3years after the start of sexual activity following menarche.

Our large HPV-vaccination-trial-derived population of young adult women, with uniform ethnicity (97% Caucasian Finnish women), and the standardised clinical and laboratory procedures are noteworthy strengths of the study. In young Finnish women, HIV infection has been and is extremely rare (www.thl.fi). Furthermore, over the entire follow-up period the trial participants received regular sexual health counselling which probably helped in retaining the participants and reduced possible confounding and bias in our study. To the best of our knowledge, the association between interval between menarche and the age at the start of OC use with cervical atypia has now been assessed for the first time.

Some limitations of our study are as follows. The use of the overall cervical atypia endpoint, which was necessary to retain the statistical power of the study strata. The study questionnaires used were self-reported at the ages of 18 and 22 years, the latter of which is subject to recall bias. The endpoint questionnaire (at age 22) was, however, in line with the enrolment questionnaire (at age 18), for example, for menarche. Moreover, questionnaire-based information regarding sexual behaviour is supposed to have adequate validity and reliability.[20 21] It gave the most comprehensive information about sexual risk-taking characteristics of the study subjects over time. This was important when assessing the longitudinal effects of OC use on prospective development of cervical atypia following the exposures. Free contraceptives were distributed to the participants during the trial period, which might have increased the proportions of OC and condom users in our study.

The absence of HPV 16/18 associated risk of cervical atypia in women with short lag between menarche and the start of sexual activity appears to defy the assumption that the immature cervical transformation zone is especially prone to persistent HPV infection.[15] Our observation is in line with Collins *et al*, who reported that the increased interval between menarche and the age at the FSI increases the risk of HPV infection.[22] Overall cervical atypia, the most common clinical manifestation of genital HPV infection, needs some time to develop.

On the other hand, our findings seem to contradict a study by Ruiz *et al* who first reported that short interval between menarche and age at the FSI is a predictor of cervical cytological abnormalities and CIN.[9] While our homogeneous study population had ampler power to detect a threefold increased risk (see online supplementary appendix), their study population was heterogeneous and had only baseline sexual risk-taking behaviour questionnaire data, which could not elaborate (possible changes in) the risk-taking behaviour during the follow-up. Furthermore, we found a lack of association between short interval of menarche and two different measures of the start of sexual activity (age at FSI and age at the start of OC use). However, these different observations on the interval between menarche and start of sexual activity, and the risk of cervical atypia,[9 12–14] may also reflect limited sample sizes.

Our group has earlier reported that when *C. trachomatis* infection precedes or cooccurs with HPV infection the risk of high-grade cervical neoplasia associated with the joint infection is very high.[23] Our results on the increased risk of *C. trachomatis* infection with cervical atypia especially in women with a short lag between menarche and the start of sexual activity emphasise the need to identify, treat and follow-up adolescent females with *C. trachomatis*.

In conclusion, while our study does not support the hypothesis that a short interval between menarche and age at the start of sexual activity always increases the risk of cervical atypia, early age of acquiring *C. trachomatis* infections may set the stage for cervical carcinogenesis and should be identified and treated.

Contributors IA developed the research protocol, analysed the data and prepared the manuscript. TE contributed in data acquisition and data interpretation. TL contributed in the analysis plan, commented on the drafts of the paper and helped in the revision of paper. DA commented on the tables and drafts of the paper. ML helped in data acquisition, contributed in the development of research plan, analysis plan, commented on the draft of the paper and the revision of the paper.

Funding Academy of Finland.

Competing interests ML and DA have grants from Merck & Co. Inc. and GSK for HPV vaccination trials through their employers (Tampere University, ML; Family Federation Finland, DA).

Patient consent for publication Not required.

Ethics approval Finnish national ethics committee (TUKIJA 1174/04).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

REFERENCES

1. Brinton LA, Fraumeni JF. Epidemiology of uterine cervical cancer. *J Chronic Dis* 1986;39:1051–65.
2. Campion MJ, McCance DJ, Cuzick J, *et al*. Progressive potential of mild cervical atypia:prospective cytological, colposcopic, and virological study. *Lancet* 1986;8501:237–40.

3. Koutsky LA, Holmes KK, Critchlow CW, *et al*. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992;327:1272–8.
4. GY H, Burk RD, Klein S, *et al*. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst* 1995;81:1365–71.
5. Liaw KL, Glass AG, Manos MM, *et al*. Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst* 1999;91:954–60.
6. Kapeu AS, Luostarinen T, Jellum E, *et al*. Is smoking an independent risk factor for invasive cervical cancer? A nested case-control study within Nordic biobanks. *Am J Epidemiol* 2009;169:480–8.
7. Lehtinen M, Ault KA, Lyytikainen E, *et al*. *Chlamydia trachomatis* infection and risk of cervical intraepithelial neoplasia. *Sex Transm Infect* 2011;87:372–6.
8. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and sexual behavior: collaborative reanalysis of individual data on 15,461 women with cervical carcinoma and 29,164 women without cervical carcinoma from 21 epidemiological studies. *Cancer Epidemiol Biomarkers Prev* 2009;18:1060–9.
9. Ruiz Ángela María, Ruiz JE, Gavilanes AV, *et al*. Proximity of first sexual intercourse to menarche and risk of high-grade cervical disease. *J Infect Dis* 2012;206:1887–96.
10. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *Int J Cancer* 2006;119:1108–24.
11. Appleby P, Beral V, Berrington de González A, *et al*. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007;370:1609–21.
12. Shew ML, Fortenberry JD, Miles P, *et al*. Interval between menarche and first sexual intercourse, related to risk of human papillomavirus infection. *J Pediatr* 1994;125:661–6.
13. Daling JR, Madeleine MM, McKnight B, *et al*. The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. *Cancer Epidemiol Biomarkers Prev* 1996;7:541–8.
14. Kahn JA, Rosenthal SL, Succop PA, *et al*. The interval between menarche and age of first sexual intercourse as a risk factor for subsequent HPV infection in adolescent and young adult women. *J Pediatr* 2002;141:718–23.
15. Ho GY, Bierman R, Beardsley L, *et al*. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338:423–8.
16. Adhikari I, Eriksson T, Luostarinen T, *et al*. The risk of cervical atypia in oral contraceptive users. *Eur J Contracept Reprod Health Care* 2018;23:12–17.
17. LehtinenM, PaavonenJ W*et al*. Overall efficacy of HPV-16/18 vaccine against the most stringent cervical pre-cancer end-points: end-of study report of a double blind, randomized trial. *Lancet Oncol* 2012;13:89–99.
18. Paavonen J, Jenkins D, Bosch FX, *et al*. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet* 2007;369:2161–70.
19. Woodhall SC, Lehtinen M, Verho T, *et al*. Anticipated acceptance of HPV vaccination at the baseline of implementation: a survey of parental and adolescent knowledge and attitudes in Finland. *J Adolesc Health* 2007;40:466–9.
20. Kahn JA, Goodman E, Kaplowitz RA, *et al*. Validity of adolescent and young adult self-report of Papanicolaou smear results. *Obstet Gynecol* 2000;96:625–31.
21. Brener ND, Collins JL, Kann L, *et al*. Reliability of the youth risk behavior survey questionnaire. *Am J Epidemiol* 1995;141:575–80.
22. Collins SI, Mazloomzadeh S, Winter H, *et al*. Proximity of first intercourse to menarche and the risk of human papillomavirus infection: a longitudinal study. *Int J Cancer* 2005;114:498–500.
23. Luostarinen T, Lehtinen M, Bjørge T, *et al*. Joint effects of different human papillomaviruses and *Chlamydia trachomatis* infections on risk of squamous cell carcinoma of the cervix uteri. *Eur J Cancer* 2004;40:1058–65.