MAJOR ARTICLE

Proximity of First Sexual Intercourse to Menarche and Risk of High-Grade Cervical Disease

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Background. We assessed if risk of developing cervical intraepithelial neoplasia grade 2/3 (CIN2/3) or adenocarcinoma in situ (AIS) is associated with a short interval between menarche and first sexual intercourse (FSI).

Methods. A total of 1009 Colombian and 1012 Finnish females, aged 16–23, who were enrolled in the phase 3 trials of a quadrivalent human papillomavirus (HPV) 6/11/16/18 vaccine had nonmissing data for age of menarche and FSI. The impact of menarche interval on the odds of developing CIN2-3/AIS was evaluated in placebo recipients who were DNA negative to HPV 6/11/16/18/31/33/35/39/45/51/52/56/58/59 and seronegative to HPV 6/11/16/18 at day 1, and had a normal Pap result at day 1 and month 7, thus approximating sexually naive adolescents (n = 504).

Results. The mean age of menarche and FSI was 12.4 and 16.0 years, respectively. Among the women approximating sexually naive adolescents, 18 developed CIN2-3/AIS. Compared with women who postponed FSI beyond 3 years of menarche, those with FSI within 3 years of menarche had a greater risk of cytologic abnormalities (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.02–2.68; $P = .04$) and CIN2-3/AIS (OR, 3.56; 95% CI, 1.02–12.47; $P = .05$).

Conclusions. A short interval between menarche and FSI was a risk factor for cytologic abnormalities and high-grade cervical disease. These data emphasize the importance of primary prevention through education and vaccination.

Clinical Trials Registration. NCT00092521 and NCT00092534.

High-risk human papillomavirus (HPV) is considered a necessary cause of cervical cancer [1]. A meta-analysis of 85 studies comprised of 10 058 cervical cancer cases found that the 10 most common HPV types in cervical cancer are, in order of prevalence, HPV 16, 18, 33, 45, 31, 58, 52, 35, 59, and 56 [2]. HPV infection is common, with a lifetime risk of infection of 50%–85% [3]. However, most HPV infections and low-grade cervical intraepithelia1 neoplasia grade 1 (CIN1) resolve as a consequence of cell-mediated immunity [4]. Women who are persistently infected with high-risk HPV are at risk for development of high-grade disease (ie, CIN2-3) and cervical cancer [4].

The role that other cofactors play in the development of cervical cancer may facilitate the understanding of why only a small percentage of women infected with HPV will develop cervical cancer. Cofactors for HPV infection and associated lesions have been extensively studied and include [5] early age at first sexual intercourse (FSI), lifetime number of sexual partners (LNSP), nonuse of condoms, and modifiers of (immune)

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surveillance of the HPV-transformed cells, such as smoking [6] and concurrent infection with *Chlamydia trachomatis* [7].

It has been proposed that the interval between menarche and FSI may represent a risk factor for HPV acquisition and development of disease [8–11]. Adolescent cervical tissue is considered to be particularly susceptible to HPV infection. The role of age at menarche as a risk predictor of either HPV infection or CIN has remained a controversial issue. Most studies to date have examined the proximity of FSI to menarche and risk of HPV infection but have not considered progression to disease (ie, cytologic abnormalities or CIN) [8–10]. In a study that examined the role of age at menarche as a potential predictor of development of high-risk HPV infection and high-grade CIN, the time from menarche to FSI was a predictor of high-risk HPV infection, but not high-grade CIN, in a univariate analysis [11].

The large, randomized, placebo-controlled clinical trials of the quadrivalent HPV 6/11/16/18 vaccine included >17 000 women aged 16–26 and included Papanicolaou (Pap) testing and triage to colposcopy and biopsy at 6- to 12-month intervals for up to 4 years [12, 13]. The placebo arms of these trials present a unique opportunity to explore the relationship between the interval of menarche and FSI and the risk of HPV infection and disease. Such information may help to better address the objective of reducing the burden of HPV-associated conditions through timely introduction of effective preventive interventions in the most vulnerable populations.

METHODS

Objectives

The primary objective of this post hoc analysis was to determine if the risk of developing CIN2-3 or AIS is associated with the interval between menarche and FSI in Colombian and Finnish women enrolled in the phase 3 trials of a quadrivalent HPV 6/11/16/18 vaccine (Gardasil, Merck).

Study Design and Populations

Between December 2001 and May 2003, 17 622 women, the majority aged 16–26, were enrolled in 1 of 2 randomized, double-blind, placebo-controlled trials of the quadrivalent HPV 6/11/16/18 vaccine (Protocol 013, n = 5455 [FUTURE I] and Protocol 015, n = 12 167 [FUTURE II]) [12, 13]. The study designs and the results of the primary hypotheses have been described, following the CONSORT guidelines [12, 13].

The trials recruited women who, at enrollment (day 1), reported having had between 0–4 LNSP, with the exception of Finland (872 vaccine; 873 placebo), which enrolled women aged 16–18 with no restrictions on LNSP. Participants with a history of an abnormal Pap test, a history of genital warts, or detection of genital warts at enrollment were excluded. Neither study included a screening phase for HPV infection or abnormal cytology; thus, the trials allowed the enrollment of women with undiagnosed CIN or abnormal cytology, or who were previously or currently infected with HPV, including vaccine HPV types.

Of the 17 622, enrolled women, 1009 women from Colombia and 1012 women from Finland had data available for age of menarche and FSI. This post hoc analysis was approved by the institutional review boards (ethical review committees) at the participating centers.

Clinical Follow-up and Endpoints

Participants returned to the study sites at months 3, 7, 12, 18, 24, 30, 36, 42, and 48 in FUTURE I and at months 7, 12, 24, 36, and 48 in FUTURE II. Comprehensive anogenital examinations were conducted at each scheduled visit whereby an endo/ectocervical swab (1 specimen) and a combined labial/vulvar/perineal plus a perianal swab (pooled to become second specimen) were collected. ThinPrep Pap cervical cytology (Cytyc, Boxborough, Massachusetts) was also performed during scheduled visits. Cytology specimens were classified using the 2001 Bethesda System [14].

During examination, all genital lesions that were, in the opinion of the investigator, possibly, probably, or definitely HPV-related, or whose etiology was unknown, were to be biopsied. All biopsy samples, regardless of location, were processed and adjacent histological sections of each biopsy were first read for clinical management by pathologists at a central laboratory (Diagnostic Cytology Laboratories, Indianapolis, Indiana) and then read for endpoint determination by a panel of up to 4 pathologists who were blinded to central laboratory and clinical diagnoses, treatment group, and HPV status.

Protocol-specified guidelines were used to triage participants with Pap abnormalities to colposcopy [12, 13]. Colposcopists were trained to locate and biopsy all discrete abnormal areas on the cervix. Women with CIN2, CIN3, or AIS (abbreviated as CIN2-3/AIS) or persistent CIN1 were referred for definitive therapy. Cervical biopsies and specimens from excision procedures obtained at any time during the studies were tested for the 4 types in the vaccine (6/11/16/18) and 10 other oncogenic HPV types (31/33/35/39/45/51/52/56/58/59) using a polymerase chain reaction (PCR)–based assay [15–17]. The swabs obtained at day 1 were also tested for the 14 HPV types.

For each participant, blood samples were obtained at enrollment and at defined intervals throughout the study for anti-HPV serology testing [18]. All participants were tested for *C. trachomatis* at baseline and 12-monthly intervals for immediate treatment. *Chlamydia trachomatis* serology was not performed.

Statistical Methods

For each endpoint, summaries are provided for Colombia, Finland, and both countries combined.

Prevalence of High-Risk HPV Infection and Cytologic Abnormalities

Subjects in vaccine and placebo arms were categorized into whether they were PCR positive (based on the cervical swab) at day 1 to at least 1 of the 12 high-risk HPV types and categorized into whether they had a Pap result of atypical squamous cells of undetermined significance (ASC-US) or worse at day 1 or normal cytology at day 1. A total of 2014 subjects had nonmissing PCR status at day 1 (Figure 1). Of the 2015 subjects with nonmissing Pap results at day 1, 35 (1.7%) had an unsatisfactory Pap result and were excluded. The odds of testing positive to at least 1 of the high-risk types at day 1 and of having abnormal cytology (ASC-US or worse) at day 1 were evaluated in relationship to the interval between menarche and FSI (<3 vs ≥3 years) after adjustment for baseline factors of interest, including age, age at FSI, LNSP, new partner in 6 months prior to study start, condom use, oral contraceptive use, and PCR detection of *C. trachomatis*. Odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values based on the Wald χ^2 test were calculated based on estimates from a multivariate logistic regression model [19].

Incidence of Abnormal Cytology and CIN2-3/AIS

In this report, the impact of baseline factors on risk of developing abnormal cytology (ASC-US High risk (HR) positive, LSIL or worse) or CIN2-3/AIS was conducted in a population that approximated sexually naive adolescents. This population was restricted to placebo subjects who, at enrollment, were seronegative [18, 20, 21] and negative [15–17] for HPV 6/11/16 and 18 DNA; were negative for DNA for all 10 nonvaccine high-risk HPV types for which PCR testing was available (HPV 31/33/35/39/45/51/52/56/58/59); and had a normal Pap test result. It should be noted that this is not a per-protocol analysis and that, because more than 40 HPV types are known to infect the anogenital tract, we imposed an additional restriction that these women also have a normal Pap test result at month 7. Follow-up for endpoint ascertainment started after month 7.

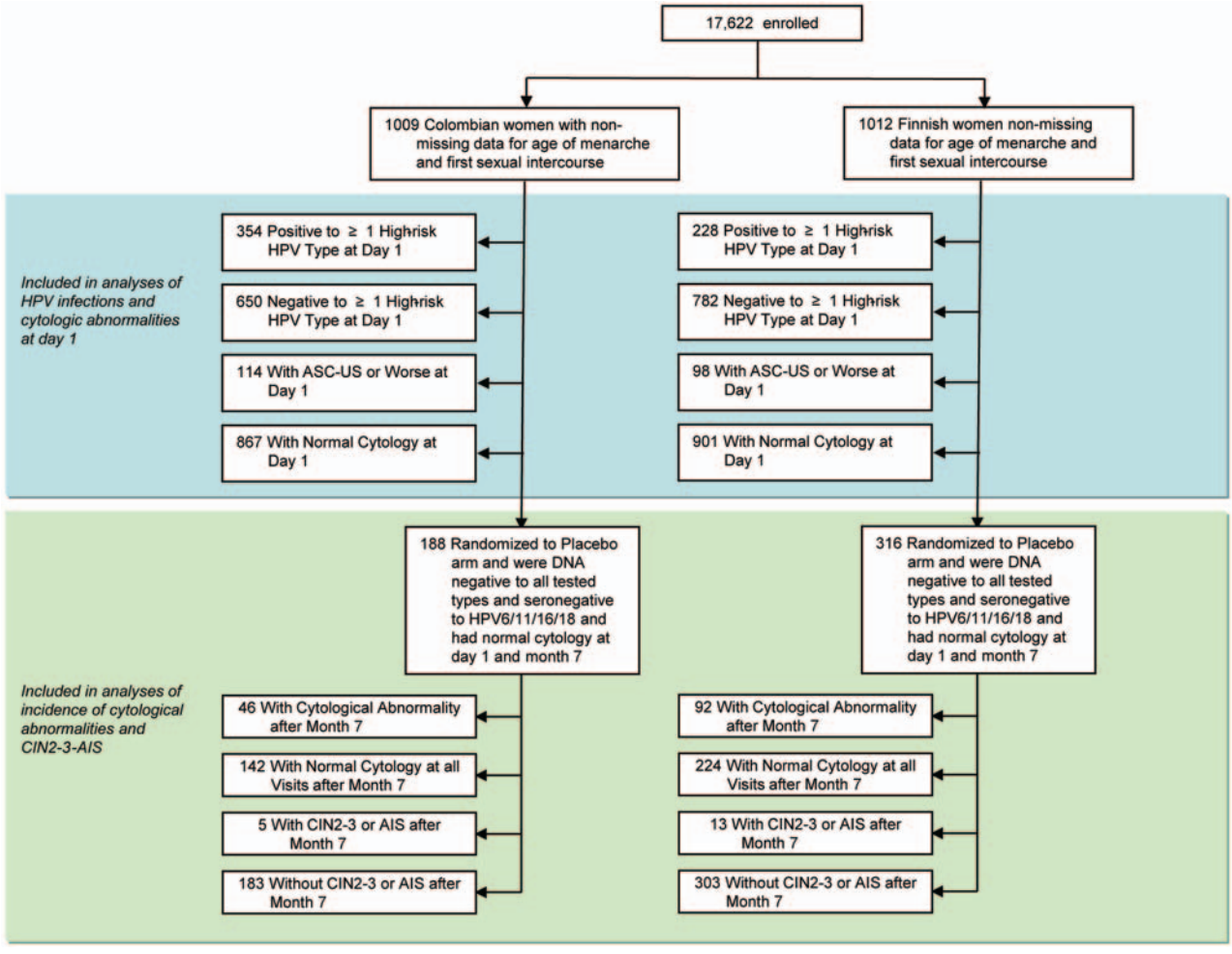

Figure 1. Study flowchart. ASC-US, atypical squamous cells of undetermined significance; AIS, adenocarcinoma in situ; CIN2-3, cervical intraepithelial neoplasia grade 2/3; HPV, human papillomavirus.

As only a subset of women enrolled in FUTURE I had the cervical swabs tested for high-risk HPV DNA after month 7 ($n < 100$), the impact of baseline factors on incident HPV infection was not assessed in this post hoc analysis.

The odds of developing cytologic abnormalities or CIN2-3/AIS was evaluated in relationship to the above baseline factors, with the exception of PCR detection of *C. trachomatis*, owing to the small number of women with *C. trachomatis* infection (9 Colombian, 2 Finnish women). ORs with 95% CI and *P* values based on the Wald χ^2 test were calculated on the basis of estimates from a multivariate logistic regression model.

RESULTS

Baseline Characteristics

Table 1 summaries the baseline characteristics for all subjects (vaccine and placebo arms combined) by the interval between menarche and FSI (<3 vs ≥3 years) for Colombia, Finland, and the combined cohorts. For both cohorts, the baseline characteristics for women who postponed FSI beyond 3 years of menarche to those who had first had intercourse within 3 years of menarche were similar, with the exception of LNSP at enrollment, where approximately 55% of women with an interval ≥3 years had at least 2 LNSP, compared with approximately 73% for those with an interval <3 years. As expected, the mean age of the Colombian women (20.6 years) was nominally higher than that of Finland (16.6 years); however, the mean age at menarche was similar (12.5 vs 12.4 years). Compared with Colombian women, a nominally higher proportion of Finnish women were current smokers (49.8% vs 29.5%) and used hormonal contraception (50.6% vs 28.0%), and a lower proportion had *C. trachomatis* detected at day 1 (2.3% vs 7.7%).

Detection of high-risk HPV DNA in the cervical swab specimen and abnormal cytology were similar based on the interval between menarche and FSI for the Colombian cohort (Table 2). For the Finnish cohort, those with an interval <3 years had a significantly higher baseline prevalence of HPV DNA (26.2% vs 19.1%, $P = .008$). For the Colombian cohort, the overall prevalence of high-risk HPV DNA was significantly higher than that of the Finnish cohort (35.1% vs 22.5%, $P < .001$), and there were some differences in the 5 most common high-risk HPV types detected in Colombia (HPV 16 [7.5%], HPV 52 [7.4%], HPV 56 [7.1%], HPV 51 [6.5%], and HPV 58 [6.4%] vs Finland: HPV 16 [6.8%], HPV 51 [6.8%], HPV 56 [5.4%], HPV 18 [4.6%], and HPV 31 [3.8%]). At baseline, the Colombian cohort was twice as likely as the Finnish cohort to show evidence of HPV 6/11/16 or 18 antibodies (22.3% vs 10.7%). The rates of abnormal cytology were slightly higher among the Colombian cohort compared with the Finnish cohort (11.6% vs 9.8%).

Prevalence of High-Risk HPV Infection and Cytologic Abnormalities

The odds of testing positive to at least 1 of the high-risk HPV types and the odds of having cytologic abnormalities at day 1 are shown in Figure 2 and Supplementary Table 1. For both cohorts, menarche interval was not a significant predictor of prevalent HPV infection or abnormal cytology (Table 3). For both cohorts, a higher LNSP and prevalent *C. trachomatis* infection were significantly associated with high-risk HPV prevalence. Condom use and oral contraceptive use were significantly associated with lower risk of HPV prevalence only when data from the 2 cohorts were combined (condom use, OR = 0.73, $P = .02$; oral contraceptive use, OR = 0.70, $P = .01$). Likewise, mean age (OR = 1.12, $P < .001$) and mean age at FSI (OR = 1.10, $P = .01$) were significantly associated with higher risk of HPV prevalence for the combined cohorts. Having at least 1 new partner in the 6 months prior to study start was significantly associated with increased risk of HPV prevalence for the Colombian cohort (OR = 1.74, $P = .001$), and for the combined cohorts (OR = 1.31, $P = .03$). Prevalence of abnormal cytology was significantly associated with a higher LNSP (both cohorts $P < .01$) and prevalent *C. trachomatis* infection for the Finnish cohort (OR = 2.86, $P < .04$).

Incidence of Abnormal Cytology and CIN2-3/AIS

The odds of developing cytologic abnormalities or high-grade cervical disease was assessed in women who were randomized to the placebo arm and who approximated sexually naive adolescents. This generally HPV-naive population represented 35.9% (188/523) and 62.6% (316/505) of the Colombian and Finnish cohorts, respectively.

Multivariate logistic regression estimates are shown in Figure 2 and Supplementary Table 2. Of the study subjects approximating sexually naive adolescents, 24.5% (46/188) of the Colombian cohort and 29.1% (92/316) of the Finnish cohort had at least 1 abnormal Pap test result after month 7. Of these, 2 had a diagnosis of HSIL. A shorter interval between menarche and FSI was associated with increased risk of developing abnormal cytology, with OR of 1.11 (Colombia) and 1.70 (Finland), but was only significant for the combined cohorts (OR = 1.65, $P = .04$). For the Finnish cohort and for the combined cohorts, risk of developing abnormal cytology was significantly associated with a higher LNSP (Finland, OR = 1.29, $P = .03$; combined cohorts, OR = 1.26, $P = .01$).

Oral contraceptive and condom use were significantly associated with lower risk of developing CIN2-3/AIS for the Finnish cohort (oral contraceptive use, OR = 0.04, $P = .004$; condom use, OR = 0.11, $P = .03$) and oral contraceptive use was significant for the combined cohorts (OR = 0.09, $P = .007$). A shorter interval between menarche and FSI was associated with increased risk of developing CIN2-3/AIS with OR of 6.42 for Finland ($P = .05$), and when the cohorts were

Table 1. Baseline Participant Demographics

	Colombia		Finland		Total	
	Interval <3 y (n = 181)	Interval ≥3 y (n = 828)	Interval <3 y (n = 484)	Interval ≥3 y (n = 528)	Interval <3 y (n = 665)	Interval ≥3 y (n = 1356)
Age, y, mean (SD)	20.2 (1.7)	20.6 (1.6)	16.5 (0.6)	16.6 (0.6)	17.5 (1.9)	19.1 (2.4)
Age at menarche, y, mean (SD)	13.8 (1.4)	12.2 (1.2)	13.0 (1.0)	11.8 (0.9)	13.2 (1.2)	12.0 (1.1)
Race/ethnicity						
Asian	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.1)
Black	0 (0.0)	3 (0.4)	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.2)
Hispanic	181 (100)	825 (99.6)	0 (0.0)	0 (0.0)	181 (27.2)	825 (60.8)
White	0 (0.0)	0 (0.0)	482 (100)	525 (99.4)	482 (72.5)	525 (38.7)
Other	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.1)
Smoking status						
Current smoker	53 (29.3)	245 (29.6)	268 (55.4)	236 (44.7)	321 (48.3)	481 (35.5)
Ex-smoker	13 (7.2)	63 (7.6)	51 (10.5)	42 (8.0)	64 (9.6)	105 (7.7)
Never smoked	115 (63.5)	520 (62.8)	165 (34.1)	250 (47.3)	280 (42.1)	770 (56.8)
Contraceptive use[a]						
Barrier	66 (36.5)	309 (37.3)	233 (48.1)	283 (53.6)	299 (45.0)	592 (43.7)
Hormonal	50 (27.6)	233 (28.1)	260 (53.7)	252 (47.7)	310 (46.6)	485 (35.8)
Behavior	30 (16.6)	234 (28.3)	12 (2.5)	23 (4.4)	42 (6.3)	257 (19.0)
Other	40 (22.1)	93 (11.2)	0 (0.0)	0 (0.0)	40 (6.0)	93 (6.9)
Missing/unknown	3 (1.7)	5 (0.6)	0 (0.0)	0 (0.0)	3 (0.5)	5 (0.4)
Age at first sexual intercourse, mean (SD)	15.1 (1.5)	17.5 (1.8)	14.4 (1.0)	15.5 (0.9)	14.6 (1.2)	16.7 (1.8)
Lifetime no. of male or female sexual partners at enrollment						
1	52 (28.7)	358 (43.2)	124 (25.6)	256 (48.5)	176 (26.5)	614 (45.3)
2	65 (35.9)	261 (31.5)	84 (17.4)	112 (21.2)	149 (22.4)	373 (27.5)
3	38 (21.0)	163 (19.7)	90 (18.6)	71 (13.4)	128 (19.2)	234 (17.3)
4	26 (14.4)	46 (5.6)	55 (11.4)	35 (6.6)	81 (12.2)	81 (6.0)
>4	0 (0.0)	0 (0.0)	131 (27.1)	54 (10.2)	131 (19.7)	54 (4.0)
Median	2	2	3	2	3	2
No. of new male or female sexual partners in the 6 mo prior to study start						
0	144 (79.6)	637 (76.9)	162 (33.5)	186 (35.2)	306 (46.0)	823 (60.7)
1	35 (19.3)	183 (22.1)	213 (44.0)	257 (48.7)	248 (37.3)	440 (32.4)
2	2 (1.1)	7 (0.8)	71 (14.7)	50 (9.5)	73 (11.0)	57 (4.2)
3	0 (0.0)	1 (0.1)	23 (4.8)	21 (4.0)	23 (3.5)	22 (1.6)
4	0 (0.0)	0 (0.0)	7 (1.4)	9 (1.7)	7 (1.1)	9 (0.7)
>4	0 (0.0)	0 (0.0)	8 (1.7)	5 (0.9)	8 (1.2)	5 (0.4)
Chlamydia trachomatis, m/n[b] (%)	19/180 (10.6)	59/827 (7.1)	14/484 (2.9)	9/527 (1.7)	33/664 (5.0)	68/1354 (5.0)

All data are presented as no. (%) unless otherwise specified.

[a] A woman may have reported >1 form of contraceptive use.

[b] Mandatory test at enrollment. Percentage is n/m × 100, where n = number of subjects tested and m = number of subjects with *C. trachomatis* at day 1.

combined (OR = 3.56, $P = .05$). Shorter menarche to FSI interval remained a significant predictor of risk of developing high-grade cervical disease when the interval between menarche and FSI was entered into the model as a continuous variable ($P = .02$, combined cohorts, results not shown). The risk of developing CIN2-3/AIS was also associated with a shorter interval between menarche and FSI when the interval was categorized into the groups <2 years, 2–4 years, and ≥4 years ($P = .002$, combined countries, based on Cochran-Armitage test for trend). The odds of developing high-grade cervical disease was also assessed using stepwise regression analyses for the combined countries. Menarche interval remained a significant predictor of risk of developing CIN2-3/AIS ($P = .003$) and oral contraceptive use remained significantly associated with lower risk of developing CIN2-3/AIS ($P = .03$). None of the other baseline factors were found to be significant at $P = .05$.

Table 2. Prevalence of Human Papillomavirus by DNA or Serology

	Colombia		Finland		Total	
	Interval <3 y (n = 181)	Interval ≥3 y (n = 828)	Interval <3 y (n = 484)	Interval ≥3 y (n = 528)	Interval <3 y (n = 665)	Interval ≥3 y (n = 1356)
Positive to ≥1 of 12 high-risk HPV types by PCR[a]	67 (37.0)	287 (34.7)	127 (26.2)	101 (19.1)	194 (29.2)	388 (28.6)
By HPV type						
HPV 16	14 (7.7)	62 (7.5)	32 (6.6)	37 (7.0)	46 (6.9)	99 (7.3)
HPV 18	2 (1.1)	20 (2.4)	25 (5.2)	22 (4.2)	27 (4.1)	42 (3.1)
HPV 31	10 (5.5)	34 (4.1)	26 (5.4)	12 (2.3)	36 (5.4)	46 (3.4)
HPV 33	5 (2.8)	6 (0.7)	13 (2.7)	9 (1.7)	18 (2.7)	15 (1.1)
HPV 35	4 (2.2)	21 (2.5)	9 (1.9)	6 (1.1)	13 (2.0)	27 (2.0)
HPV 39	5 (2.8)	48 (5.8)	13 (2.7)	13 (2.5)	18 (2.7)	61 (4.5)
HPV 45	8 (4.4)	15 (1.8)	6 (1.2)	9 (1.7)	14 (2.1)	24 (1.8)
HPV 51	12 (6.6)	54 (6.5)	42 (8.7)	27 (5.1)	54 (8.1)	81 (6.0)
HPV 52	16 (8.8)	59 (7.1)	22 (4.5)	9 (1.7)	38 (5.7)	68 (5.0)
HPV 56	11 (6.1)	61 (7.4)	36 (7.4)	19 (3.6)	47 (7.1)	80 (5.9)
HPV 58	15 (8.3)	50 (6.0)	18 (3.7)	7 (1.3)	33 (5.0)	57 (4.2)
HPV 59	10 (5.5)	24 (2.9)	18 (3.7)	6 (1.1)	28 (4.2)	30 (2.2)
Positive to ≥1 of HPV 6/11/16 or 18 by serology	52 (28.7)	173 (20.9)	57 (11.8)	51 (9.7)	109 (16.4)	224 (16.5)
By HPV type						
HPV 6	20 (11.0)	53 (6.4)	27 (5.6)	23 (4.4)	47 (7.1)	76 (5.6)
HPV 11	3 (1.7)	18 (2.2)	8 (1.7)	5 (0.9)	11 (1.7)	23 (1.7)
HPV 16	33 (18.2)	101 (12.2)	25 (5.2)	30 (5.7)	58 (8.7)	131 (9.7)
HPV 18	9 (5.0)	31 (3.7)	13 (2.7)	11 (2.1)	22 (3.3)	42 (3.1)
Pap test result[b]						
Satisfactory	174 (96.7)	807 (97.6)	479 (99.6)	520 (98.7)	653 (98.8)	1327 (98.0)
ASC-US or worse	26 (14.9)	88 (10.9)	48 (10.0)	50 (9.6)	74 (11.3)	138 (10.4)
ASC-US	5 (2.9)	31 (3.8)	13 (2.7)	24 (4.6)	18 (2.8)	55 (4.1)
LSIL	19 (10.9)	56 (6.9)	31 (6.5)	25 (4.8)	50 (7.7)	81 (6.1)
ASC-H	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
HSIL	2 (1.1)	0 (0.0)	3 (0.6)	1 (0.2)	5 (0.8)	1 (0.1)
AGC	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Data are presented as no, (%) unless otherwise specified.

Abbreviations: AGC, atypical glandular cells; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot rule out high grade squamous intraepithelial; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; PCR, polymerase chain reaction.

[a] Positive by PCR in the endo/ectocervical swab.

[b] Percentages for Pap diagnoses computed as 100 × (n/no. with satisfactory Pap test result).

DISCUSSION

Among women approximating sexually naive adolescents, the risk of CIN2-3/AIS was associated with a shorter interval from menarche to FSI, when analyzed both as a continuous variable or when stratified by intervals ≥3 years or <3 years, after adjusting for common risk factors for HPV acquisition. It was also associated with an increased risk for incident cytological abnormalities in the 2 cohorts that were studied. Risk factors related with sexual behavior such as mean age at FSI (only for the combined cohorts), mean LNSP, PCR detection of *C. trachomatis*, and number of new sexual partners in the previous 6 months were found to be significantly associated with baseline prevalence of high-risk HPV infection while condom and oral contraceptive use were associated with a lower risk of baseline prevalence of high-risk HPV infection.

Importantly, this study was performed in a young population recruited within a few years from their menarche and their FSI, which presumably may have reduced the risk of a memory bias with regard to these 2 variables. The sample size, the homogeneity of the population, the standardization of the clinical and laboratory follow-up, and procedures that are inherent in the design of these clinical trials also minimized

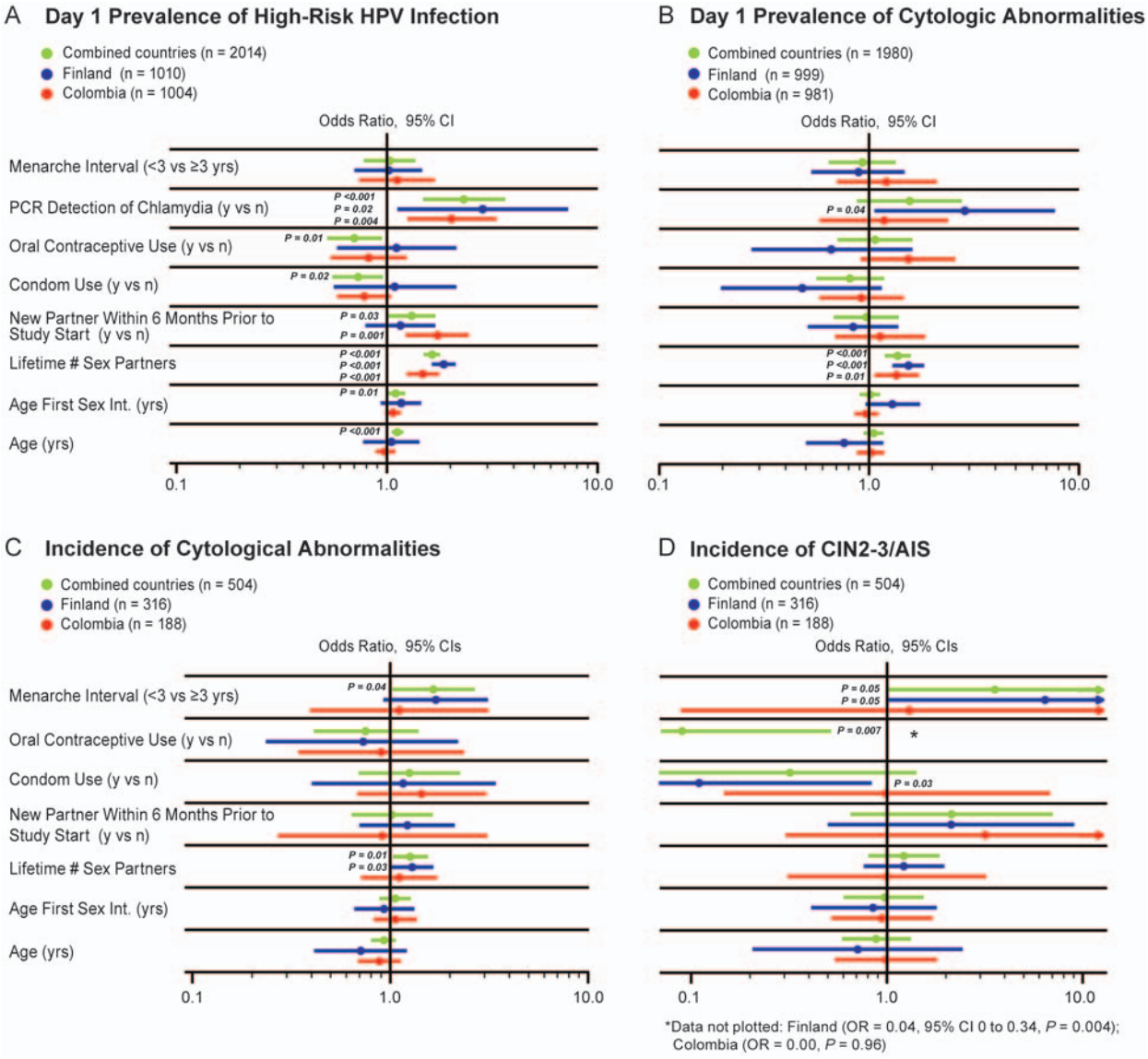

Figure 2. The association of the interval between menarche and age at first sexual intercourse with adjustment for baseline factors for (*A*) day 1 prevalence of high-risk HPV infection; (*B*) day 1 prevalence of cytologic abnormalities; (*C*) incidence of cytological abnormalities after month 7; and (*D*) incidence of CIN2-3/AIS after month 7. AIS, adenocarcinoma in situ; CI, confidence interval; CIN2-3, cervical intraepithelial neoplasia grade 2/3; HPV, human papillomavirus; OR, odds ratio; PCR, polymerase chain reaction.

confounding and other possible biases. The study is also accompanied by some limitations. The trials were not designed or powered to evaluate the effect of age of menarche and FSI and risk of developing cervical disease. In addition, FUTURE I had more aggressive colposcopy triage for suspected disease compared with FUTURE II, which followed a clinical protocol that was based on Pap screening intervals and management algorithms that constituted the standard of care in different communities. A histologic diagnosis of CIN2 is less reproducible and spontaneous regression is more common than for CIN3; however, the trials did not examine disease regression or lesion size, so it is unknown whether some of the disease detected in these young women would have regressed.

Several risk factors have been associated with the possibility of progression from high-risk HPV infection to high-grade CIN and invasive cervical cancer. Behavioral factors have been clearly identified in several studies such as age at FSI, LNSP, partner's number of sexual partners, smoking, and condom use [5]. Other factors related to reproductive characteristics have been also explored including parity, age at first delivery, menopause, and age at menarche.

Table 3. Impact of the Interval Between Menarche and First Sexual Intercourse on Infection and Disease Endpoints

	Colombia			Finland			Total		
	No.	Interval <3 y	Interval ≥3 y	No.	Interval <3 y	Interval ≥3 y	No.	Interval <3 y	Interval ≥3 y
Positive to ≥1 high-risk HPV type at day 1	354	67 (18.9)	112 (17.2)	228	127 (55.7)	357 (45.7)	582	194 (33.3)	469 (32.8)
Negative to all high-risk HPV types at day 1	650	287 (81.1)	538 (82.8)	782	101 (44.3)	425 (54.3)	1432	388 (66.7)	963 (67.2)
OR (95% CI), *P* value		1.12 (.75–1.66), *P* = .5861			1.01 (.70–1.47), *P* = .9556			1.03 (.79–1.34), *P* = .8333	
With ASC-US or worse at day 1	114	26 (22.8)	148 (17.1)	98	48 (49.0)	431 (47.8)	212	74 (34.9)	579 (32.7)
With normal cytology at day 1	867	88 (77.2)	719 (82.9)	901	50 (51.0)	470 (52.2)	1768	138 (65.1)	1189 (67.3)
OR (95% CI), *P* value		1.21 (.70–2.11), *P* = .4954			0.89 (.54–1.45), *P* = .6310			0.93 (.64–1.34), *P* = .6799	
With cytological abnormality after month 7	46	8 (17.4)	24 (16.9)	92	54 (58.7)	88 (39.3)	138	62 (44.9)	112 (30.6)
With normal cytology at all visits after month 7	142	38 (82.6)	118 (83.1)	224	38 (41.3)	136 (60.7)	366	76 (55.1)	254 (69.4)
OR (95% CI), *P* value		1.11 (.40–3.08), *P* = .8414			1.70 (.94–3.06), *P* = .0774			1.65 (1.02–2.68), *P* = .0416	
With CIN2-3 or AIS after month 7	5	1 (20.0)	31 (16.9)	13	11 (84.6)	131 (43.2)	18	12 (66.7)	162 (33.3)
Without CIN2-3 or AIS after month 7	183	4 (80.0)	152 (83.1)	303	2 (15.4)	172 (56.8)	486	6 (33.3)	324 (66.7)
OR (95% CI), *P* value		1.30 (.09–18.19), *P* = .8459			6.42 (1.02–40.38), *P* = .0474			3.56 (1.02–12.47), *P* = .0468	

Results from the multiple logistic regression models. Data for all variables entered into the model are shown in Supplementary Tables 1 and 2. Odds ratios are from multivariate logistic regression estimates after adjusting for the following variables in the model: age, age at first sexual intercourse, menarche interval, lifetime number of sexual partners, new partner in 6 mo prior to study start, use of condom, use of oral contraceptives, and polymerase chain reaction detection of *C. trachomatis* (for prevalent HPV infection and prevalent cytologic abnormalities endpoints only).

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; AIS, adenocarcinoma in situ; CI, confidence interval; CIN2-3, cervical intraepithelial neoplasia grade 2/3; HPV, human papillomavirus; OR, odds ratio.

Previous observations have suggested that the interval between menarche and FSI may be a risk factor for HPV infection [9–11, 22]. Several explanations support those findings: (1) anovulatory cycles are common in the first years after menarche and are associated with a decreased production of progesterone with the consequent decreased production of cervical mucus that normally acts as a barrier to sexually transmitted infections including HPV infection [11]; and (2) elevated levels of estrogens after puberty contribute to change the vaginal pH and to redefine the squamous-columnar junction, which may contribute to increased susceptibility to sexually transmitted infections [8]. Several theories also support the probability of a higher risk of progression to disease in women exposed to HPV infection immediately after menarche. These theories include greater areas of ectopy, a very active maturation process (active metaplasia), and higher affinity of high-risk HPV types for areas of metaplasia associated to changes in the local immune response of an immature cervix. The immature cervix with increased areas of metaplastic epithelium may have a greater vulnerability to HPV infection, and more importantly, to neoplastic change [23–25]. Moscicki found larger areas of cervical ectopy measured by colpophotography in teenagers with CIN compared to those without CIN [26]. However, subsequent studies by the same author have suggested that, more than the size of the ectopia, it is the rapid rate of metaplastic change within the transformation zone (measured as the percent change in the area of immaturity over a defined period) that has been associated with increased risk of LSIL [27].

Studies that had focused on the association between the interval of menarche and FSI and risk of HPV infection have yielded conflicting results. Shew et al [8] found a significantly different interval between menarche and FSI in women with HPV infection (26.6 months) compared with those not infected (35.7 months, $P = .02$). When analyzed in a multivariate model, FSI within 12, 18, and 36 months of menarche was found to significantly increase the risk of HPV infection. According to the authors, this relation appears to weaken after 2 years, when other important risk factors, such as LNSP, become more important predictors of infection [8]. In a study of 504 female university studies, Kahn et al found that women with an interval <4 years had a significant higher risk of HPV infection than women with a longer interval, and a decrease in the interval by 1 year was associated with a 12% increase in the odds of subsequent HPV infection [9].

Conversely, longer intervals between menarche and FSI have also been associated with risk of HPV infection. In a longitudinal study of 474 women aged 15–19 who were recruited within 12 months of FSI and prior to the acquisition of a second partner, Collins et al [10] found an increase in the hazard ratio of 12.9% for every year of increase in this interval (median duration of follow-up, 22 months). In a multivariate analysis, when women were stratified by an interval of ≥3 years and <3 years, those who postponed FSI beyond 3 years had a greater risk of infection after controlling for age and sexual experience of partner. A possible explanation was that basal cells are most accessible in the transformation zone, which is known to increase in size after menarche because of hormonal stimulation. The fact that women who postpone FSI had a tendency to have older and more experienced partners may represent a confounding factor in these findings [10]. Discrepancies between studies can in part be due to differences mainly related to study populations and study designs.

Beyond the risk of HPV infection associated with the characteristics of the cervix of postpubertal women, the present study explored the association between interval from menarche to FSI and CIN2-3/AIS. To our knowledge, only 1 previous study has explored the relation between interval from menarche to FSI and risk of developing CIN. In contrast to our findings, Syrjanen et al reported no association between time from menarche to FSI and high grade CIN when women were divided according to age at menarche (<13 years, between 13–14 and 15 years) [11]. This study was, however, conducted on a population of women with a mean age of 32.6.

Our findings, that a short interval between menarche and FSI represents a risk factor for cytologic abnormalities and high-grade cervical disease, favor the relevance of a "window of vulnerability" in postpubertal adolescents. Furthermore, the fact that this association was most significant in the Finnish population in which mean age at FSI was 15 years and mean interval was 2.6 years, but not in the Colombian population where the corresponding values were 17.1 and 4.6 years, supports this theory. It is possible to speculate that an interval of <3 years between menarche and FSI, when most of the adolescents have anovulatory cycle, immature local immunity, and very active process of metaplasia, may represent an important time window for establishing persistent HPV infection and subsequent development of precancerous lesions in the adolescent women. These data emphasize the importance of primary prevention through education and vaccination of early adolescents.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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