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The Association of Current Hormonal Contraceptive Use with Type-Specific HPV Detection

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Abstract

Background—Increasing duration of hormonal contraceptive (HC) use may be positively associated with risk of invasive cervical cancer.

Methods—This is a secondary analysis from the HPV Sentinel Surveillance Study. We examined the association between type-specific human papillomavirus (HPV) detection and current HC use among 7718 women attending 26 sexually transmitted diseases, family planning, and primary care clinics in the U.S.

Results—There was an association between HC use and HPV-16 detection [adjusted prevalence rate ratio 1.34; (95%CI: 1.05–1.71) for oral contraceptive users and 1.41; (1.01–2.04) for depo-medroxyprogesterone acetate users]; there was no association between HC use and detection of other HPV types or any HPV overall.

Conclusions—Longitudinal studies are needed to better define this type-specific association and its clinical significance.

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Authors' Contributions

All authors were involved in patient recruitment for the parent HPV Sentinel Surveillance Study and in revising the current manuscript. K.G.G. performed the statistical analyses.

All authors have seen and approved this version of the manuscript

Competing Interests

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Keywords

Hormonal contraception; HPV; human Papillomavirus; Papanicolaou smear

Introduction

Increasing duration of hormonal contraceptive (HC) use may be positively associated with risk of invasive cervical cancer.[1, 2] Reports of an association between HC use and detection of human papillomavirus (HPV) DNA, however, have been inconsistent.[3–7] Some of these inconsistencies may be explained by differences in study design (for example, detection of incident vs. prevalent infection). Most studies, however, did not report any HPV type-specific associations with HC use. Our goal was to examine the association between type-specific HPV detection and HC use.

Materials & Methods

This is a secondary analysis from the cross-sectional HPV Sentinel Surveillance Study (HSS) whose details have been described elsewhere. [8] Briefly, women from 26 clinics in 6 cities were enrolled in this cross sectional study between January 2003 and December 2005. The primary goal of the study was to measure the burden of HPV infection and abnormal Papanicolaou (Pap) test results in the U.S. cervical screening population by using broad sampling and a standardized protocol. Women aged 14 to 65 years were invited to participate if they were eligible for routine Pap screening. Exclusion criteria included a previous hysterectomy, a Pap test in the past 12 months, treatment of the cervix in the past 12 months, active menstruation, and pregnancy. An administered questionnaire was used to collect data on demographics, sexual behaviors, and other behaviors. Data on medical diagnoses (for example, other sexually transmitted infections) and Pap test results were abstracted from medical records.

Clinicians collected cervical specimens (either conventional or liquid-based) for Pap testing. Cytopathologists at each of the 6 cities interpreted all cytology specimens by using the 2001 Bethesda Guidelines. An additional sample using the Digene Cervical Sampler (Digene, Gaithersburg, Maryland) was collected and tested for HPV DNA using the prototype Roche Line probe assay (reagents provided by Roche Molecular Diagnostics, Alameda, CA) and sequencing as previously described. The line probe detected high risk (HR) types [16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39] and low risk (LR) types [6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, 89] [9]. We assessed the association of HC use with any HPV detection overall, with detection of only HR or LR types, with detection of two HPV clades which contain common HR HPV types [clade A7 which includes HPV types 18, 39, 45, 59, and 68 and clade A9 which includes HPV types 16, 31, 33, 35, 52, and 58] [10], and with four of the more common types associated with cervical cancer: HPV 16, 18, 31, and 45[11]. The study was approved by human subjects committees at each of the participating sites and the Centers for Disease Control and Prevention (CDC). Funding for the study was provided by the CDC which was involved in the conduct, design, and reporting of the study. For this analysis, we only included women who had documented information as reported on an interviewer-administered questionnaire about current use of HC, either oral contraceptive pills (OCP) or depo-medroxyprogesterone acetate (DMPA), and those with valid HPV DNA test results.

The sample size calculation was based on the primary objectives of the parent study.[8] Ninety five percent confidence intervals are provided as a measure of the uncertainty surrounding each point estimate. The chi squared test was used to compare independent

proportions. Because the outcomes of interest occurred frequently, we calculated the prevalence rate ratios instead of the odds ratios. Associations were assessed using log binomial regression models to generate prevalence rate ratios (PRR). Models were adjusted for following variables: age, race, clinic type, age at first intercourse, total number of children, current pregnancy, lifetime number of sex partners, new partners in past 6 months, current tobacco use, past tobacco use, HIV status, condom use, and reproductive tract infection (only for the Pap smear analysis). We assessed for a statistical interaction between age and HC use as a proxy for duration of HC use.

Results

Of the 9657 women included in the original study, 7718 (80%) had HC data available: 1490 (20.1%) were current OCP users and 478 (6.4%) currently used DMPA. No single variable had >5% missing data except for number of children (Table 1). The majority of women on HC were recruited from family planning clinics. Women taking HC were, in general, younger and more likely to be white; they reported less tobacco use, fewer sexual partners, older age at sexual debut, less condom use, and fewer children. The demographic and clinical characteristics, stratified by HC use, are summarized in Table 1.

The overall prevalence of any HPV type in this subset of women was 32.5%. There was no association between HC use (either OCP, or DMPA) and the detection of any HPV DNA, any HR HPV DNA, any LR HPV DNA, and any clade A7 or A9 HPV DNA (Table 2). There was a significant association between HPV-16 detection and OCP [aPRR 1.34; 95% CI: 1.05–1.71] and DMPA [1.41; 1.01–2.04] use after adjusting for several known confounders (Table 2). Among women who had normal findings on their Pap smears, the associations between HPV-16 detection and COC use remained significant [aPRR 1.41; 95% CI: 1.05–1.89] but the association between HPV-16 and DMPA lost statistical significance [aPRR 1.44; 95% CI: 0.78–1.96]. There was no significant interaction between age and HC use (a proxy measure for duration of HC use). There was no association between current HC use and dysplastic changes on Pap smear (Table 2), even among the subset of women infected with HPV-16 [for OCP users, the PRR of dysplastic changes among HPV-16-infected persons was 1.13 95% CI: 0.90–1.40; for DMPA users, PRR 0.68 (95% CI 0.44–1.05)]. There was an association between OCP use and the detection of atypical squamous cells of unclear significance (ASCUS) on Pap smear. This association, however, was no longer statistically significant when excluding women with detectable HPV-16 DNA.

Discussion

The lack of an overall association between HC use and HPV detection is in agreement with several other large published studies. [4, 7] In a systematic review that included 19 epidemiological studies, there was no association found between HC use and the detection of any HPV types, including HR or LR HPV types overall. [4] In addition, duration of HC use did not impact the probability of HPV detection. Similarly, in a pooled analysis of HPV surveys among 15,145 women conducted by the International Agency for Research on Cancer (IARC), HPV detection was similar in long term OCP users and non-users[7]. Neither of these studies evaluated specific HPV types. A longitudinal study of incident HPV infections among 1997 women reported an association between current OCP use and the diagnosis of any incident HPV infection. Although no type-specific association with HC use was reported, HPV-16 was the most frequently detected type accounting for 10.3% of all incident infections.[5]

In our study, although there was no overall association between HR or LR HPV types, we found an intriguing type-specific association between HPV-16 and HC use. HPV-16 is the most common HPV type that causes cervical cancer in women. [11] There are several biological mechanisms that could explain an association between HPV-16 detection and HC use. Glucocorticoid-responsive elements (GREs) that regulate HPV viral transcription respond to progesterones by increasing the transcription of *E6* and *E7* genes of certain HPV types- including HPV-16 (reviewed by de Villiers [12]). However, not all HR HPV GREs respond to the same degree. These data suggest type-specificity and provide a biological mechanism to account for the increased detection of HPV-16 and its greater oncogenic potential; they cannot, however, completely explain our findings as GREs from the HR type HPV-18 and low-risk type HPV-11 are also thought to respond to progesterone. In addition to increased viral replication, recent data also suggest that other biological mechanisms may be important. Sex hormones significantly alter the immune responses to HPV-16 virus-like particles.[13] This raises the possibility that HC may also affect the host's susceptibility to HPV-16 infection. Other data suggest the possibility of progesterone-mediated persistence of HPV-16 infection thereby increasing the likelihood of its detection.[14]Of note, there was no association between Clade A9 (which includes HPV type 16) and HC use, suggesting that the association between HPV-16 and HC use is type-specific and not clade-specific. Clade-specificities in GRE hormone-responsiveness, immune responses, and persistence, to our knowledge, have not been studied.

From our data, there was no short-term impact of HC use on cervical dysplasia as measured by Pap smear, even in the subset of women who had detectable HPV-16 DNA. This finding mirrors the results of two case control studies which assessed the impact of HC use on cervical intraepithelial neoplasia. [15] Dysplastic changes, however, develop over time so a cross-sectional design is not ideal to study this association. Several other studies, however, including a systematic review [2] and a multicenter case control study [1] suggest an association between HC use and the development of cervical cancer. Whether the increased detection of cervical cancer among HC users may be mediated, in part, by a type-specific interaction between HPV-16 (and possibly other HR HPV types) and HC is not known.

This study has several limitations. The cross-sectional design introduces the potential for selection and information biases. The large number of women recruited and the variety of settings from which they were recruited may help limit some of these. We had limited data on the type, timing and duration of HC use so no causal link between HC use and type-specific HPV detection can be inferred. Despite our large sample size, the low prevalence of some HPV types may have limited the power of this study to detect other type-specific associations with HC use. However, the lack of an overall association between HC use and HR HPV overall, LR HPV overall, and HPV clades (all of which had a higher prevalence than HPV-16) suggests that the type-specific association described with HPV-16 is not due to its higher prevalence. Finally, we cannot completely discount the possibility that our finding is the result of behavioral changes or chance alone.

Over 300 million women worldwide use HC. Defining the impact of HC use on HPV infection is critically important. This study suggests a type-specific association between HPV-16 detection and HC use. Longitudinal studies are needed to better define this association and determine its clinical significance.

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Key Points

1. We detected a cross-sectional type-specific association between HPV-16 and hormonal contraception use
2. There was no cross-sectional association between hormonal contraception use and Papanicolaou smear abnormalities
3. Longitudinal studies are needed to better define these associations and determine their clinical impact

Table 1
Demographic and clinical characteristics of participants stratified by hormonal contraception use

(%)	No HC Use % (N=5750)	Current OCP % (N=1490)	P*	Current DMPA % (N=478)	P**
Clinic Type					
STD	37.7 (2167)	17.8 (265)	<0.001	9.8 (47)	<0.001
Family Planning	31.1 (1804)	52.8 (784)	<0.001	60.3 (313)	<0.001
Primary Care	30.9 (1779)	29.6 (441)	0.33	24.7 (118)	0.004
Race					
Black	26.2 (1506)	13.8 (205)	<0.001	30.5 (146)	0.02
White	39.3 (2260)	63.2 (942)	<0.001	37.2 (178)	0.53
Asian/Pacific Islander	14.5 (831)	6.4 (96)	<0.001	3.1 (15)	<0.001
American Indian/Alaska	1.2 (68)	0.6 (9)	0.002	0.6 (3)	0.30
Multiracial	1.7 (96)	1.0 (15)	0.4	2.3 (11)	0.4
Refused/Unknown	17.2 (989)	15.0 (223)	0.2	26.2 (125)	<0.001
Ethnicity					
Hispanic	29.6 (1700)	27.7 (413)	0.67	41.8 (200)	<0.001
Refused/Unknown	1.4 (81)	1.7 (25)	0.40	1.05 (5)	0.28
Age (years)					
<18	3.7 (213)	3.0 (45)	0.20	10.0 (48)	<0.001
18–25	33.6 (1933)	52.0 (775)	<0.001	49.8 (238)	<0.001
26–45	48.6 (2795)	42.3 (631)	0.01	38.3 (183)	0.008
>45	14.1 (809)	2.6 (39)	<0.001	1.9 (9)	<0.001
Tobacco use					
Current	32.8 (1875)	20.9 (309)	<0.001	28.3 (134)	0.05
Past	18.5 (1065)	21.4 (319)	0.012	15.3 (73)	0.08
Ever	51.7 (2939)	43.5 (627)	<0.001	44.1 (207)	0.002
Condom Use					
	43.3 (2487)	30.9 (461)	<0.001	18.8 (90)	<0.001
Total # lifetime partners					

(%)	No HC Use % (N=5750)	Current OCP % (N=1490)	P*	Current DMPA % (N=478)	P**
1-3	38.7 (2227)	43.1 (642)	0.05	50.2 (240)	0.002
4-10	36.2 (2081)	40.0 (596)	0.01	33.5 (160)	0.18
>10	23.8 (1371)	16.3 (243)	<0.001	16.1 (77)	0.002
# Partners last 6 months					
0-3	93.4 (5340)	95.3 (1414)	0.01	96.4 (448)	0.01
4-10	2.1 (123)	1.1 (17)	0.01	0.6 (3)	0.001
>10	3.3 (187)	3.0 (45)	0.70	4.0 (19)	0.76
# New partners last 6m					
0	61.7 (3545)	66.0 (984)	0.002	70.1 (335)	<0.001
1-3	31.2 (1795)	28.9 (430)	0.08	23.6 (113)	0.01
4-10	2.1 (123)	1.1 (17)	0.01	0.6 (3)	0.03
>10	3.3 (187)	3.0 (45)	0.74	4.0 (19)	0.34
Age at sexual debut					
14	19.3 (1109)	13.1 (194)	<0.001	20.8 (99)	0.47
15-18	50.2 (2885)	61.2 (912)	<0.001	58.4 (279)	0.001
>18	29.5 (1697)	25.0 (373)	0.01	20.7 (99)	0.002
#of children					
0	21.4 (1229)	21.1 (315)	0.9	21.3 (102)	0.9
1-2	36.6 (2102)	28.1 (418)	<0.001	49.6 (237)	<0.001
>2	20.7 (1188)	8.3 (123)	<0.001	12.3 (59)	<0.001
Missing/unknown	21.4 (1231)	42.6 (634)	<0.001	16.7 (80)	0.02
Concomitant Infections***					
HIV	0.1 (2)	0 (0)	<0.001	0 (0)	0.84
GC	2.7 (110)	0.7 (6)	<0.001	0.6 (2)	0.02
CT	7.1 (303)	4.1 (41)	0.001	8.2 (29)	0.39
Trichomonas	4.5 (254)	1.0 (14)	<0.001	2.4 (11)	0.03
BV	21.2 (1201)	9.6 (140)	<0.001	8.39 (39)	<0.001
Candidiasis	10.2 (577)	11.3 (164)	0.25	7.1 (33)	0.001

(%)	No HC Use % (N=5750)	Current OCP % (N=1490)	P*	Current DMPA % (N=478)	P**
HPV ***					
Any	33.4 (1841)	34.2 (494)	0.58	37.2 (171)	0.10
LR ^f	18.7 (1030)	17.7 (256)	0.39	19.6 (90)	0.64
HR ^f	24.2 (1335)	25.7 (371)	0.26	28.9 (133)	0.03
Clade A7 [^]	9.7 (535)	9.8 (142)	0.9	12.1 (56)	0.09
Clade A9 ^{^^}	11.1 (613)	13.1 (189)	0.8	15 (69)	0.01
16	4.8 (265)	7.1 (102)	0.001	8.0 (37)	0.002
18	2.2 (122)	2.1 (30)	0.75	2.8 (13)	0.40
45	1.8 (99)	1.4 (20)	0.28	3.0 (14)	0.06
31	1.8 (101)	1.7 (25)	0.79	2.0 (9)	0.84
Pap Results					
Normal	80.9 (4651)	78.4 (1169)	0.05	80.3 (384)	0.76
ASC-US	7.9 (456)	9.9 (148)	0.01	9.2 (44)	0.24
ASC-H/ AGC	0.9 (49)	0.8 (12)	1.0	0.2 (1)	0.18
LSIL/HSIL/AIS	6.1 (351)	7.3 (108)	0.12	4.8 (23)	0.31
Missing	4.2 (243)	3.6 (53)	0.30	5.4 (26)	0.24

OCP= oral contraceptive pill; DMPA= depo-medroxyprogesterone acetate; NS= not statistically significant; LR= low risk; HR= high risk; GC= gonorrhea; CT= chlamydia; BV= bacterial vaginosis; ASCUS= atypical squamous cells of unclear significance; LSIL=low-grade squamous intraepithelial lesion; HSIL= high-grade squamous epithelial lesion; AIS= adenocarcinoma in situ.

* Chi-squared p-values comparing 'No HC' group to 'Current OCP' group;

** Chi-squared p-values comparing 'No HC' group to 'Current DMPA' group

*** Of specimens tested

^f Women with concomitant detection of both LR and HR types were excluded from this analysis

[^] Clade A7 includes HPV types 18, 39, 45, 59, and 68

^{^^} Clade A9 includes HPV types 16, 31, 33, 35, 52, and 58

Table 2

Univariable and multivariable associations of HC use, HPV detection, and Pap smear abnormalities.

	Current OCP		Current DMPA	
	PRR (95%CI)	aPRR* (95%CI)	PRR (95%CI)	aPRR* (95%CI)
HPV: Any type	1.02 (0.93–1.13)	1.01 (0.91–1.12)	1.11 (0.95–1.30)	1.11 (0.94–1.30)
HPV: LR* (any)	0.95 (0.83–1.09)	0.99 (0.85–1.14)	1.05 (0.84–1.30)	1.07 (0.85–1.14)
HPV: HR* (any)	1.06 (0.94–1.19)	1.02 (0.90–1.16)	1.19 (1.00–1.43)	1.18 (0.98–1.42)
HPV: Clade A7 [^]	1.01 (0.84–1.22)	0.97 (0.80–1.19)	1.25 (0.95–1.65)	1.28 (0.96–1.70)
HPV Clade A9 ^{^^}	1.18 (1.00–1.38)	1.13 (0.95–1.35)	1.21 (0.93–1.58)	1.19 (0.89–1.58)
HPV: Type 16	1.47 (1.17–1.84)	1.34 (1.05–1.71)	1.67 (1.19–2.36)	1.41 (1.01–2.04)
HPV: Type 18	0.94 (0.63–1.40)	0.88 (0.57–1.34)	1.28 (0.72–2.30)	1.19 (0.65–2.15)
HPV: Type 45	0.77 (0.48–1.25)	0.74 (0.44–1.24)	1.69 (0.97–2.97)	1.90 (0.98–3.43)
HPV: Type 31	0.94 (0.61–1.47)	0.92 (0.57–1.47)	1.07 (0.54–2.11)	1.05 (0.52–2.14)
ASCUS	1.26 (1.06–1.50)	1.31 (1.06–1.61)	1.17 (1.04–1.33)	0.84 (0.68–1.05)
ASC-H/AGC/LSIL/HSIL/AIS	1.18 (0.97–1.43)	1.13 (0.90–1.40)	0.74 (0.50–1.10)	0.68 (0.44–1.05)

Adjusted for the following variables (all variables are categorical; the categories are listed in Table 1): age, race, age at first intercourse, total number of children, current pregnancy, lifetime number of sex partners, new partners in past 6 months, current tobacco use, past tobacco use, HIV status, condom use, clinic type, and reproductive tract infection (only for ASCUS). PRR= prevalence rate ratio; aPRR= adjusted PRR; OCP= oral contraceptive pill; DMPA= depo-medroxyprogesterone acetate; aOR= adjusted odds ratio; CI= confidence intervals; LR= low risk; HR= high risk ASCUS= atypical squamous cells of unclear significance; LSIL=low-grade squamous intraepithelial lesion; HSIL= high-grade squamous epithelial lesion; AIS= adenocarcinoma in situ.

* Women with concomitant detection of both LR and HR types were excluded from this analysis.

[^] Clade A7 includes HPV types 18, 39, 45, 59, and 68

^{^^} Clade A9 includes HPV types 16, 31, 33, 35, 52, and 58

The PRR reflects the prevalence risk ratio of that association among OCP or DMPA users compared to non-HC users