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Depot-medroxyprogesterone Acetate and Combined Oral Contraceptive Use and Cervical Neoplasia among Women with Oncogenic Human Papillomavirus Infection

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Abstract

Objective—Examine the relationship of depot-medroxyprogesterone acetate (DMPA) and combined oral contraceptive (COC) use with cervical intraepithelial neoplasia (CIN).

Study Design—Two case-control studies of women who presented for gynecological care and underwent cytologic and human papillomavirus (HPV) testing were performed. The first included oncogenic HPV-positive women grouped based on histology: negative(n=152), CIN1(n=133), and ≥CIN2-3(n=173). For the second, two groups were identified: negative HPV/negative histology (n=107) and positive oncogenic HPV/negative histology(n=152).

Results—Among oncogenic HPV-positive women, DMPA use was inversely associated with ≥CIN2-3 (adjusted odds ratio[OR_{adj}]=0.4;95% confidence interval[CI]=0.2–1.1) and CIN1 (OR_{adj}=0.1;95% CI=0.01–0.6); COC use was not associated with either. Among histologically negative women, DMPA use was associated with oncogenic HPV (OR_{adj}=4.7;95% CI=1.4–15.8).

Conclusions—Among women with oncogenic HPV, hormonal contraceptive use was not associated with an increased risk of ≥CIN2-3. Longer-term DMPA use may attenuate the colposcopic and histologic features of CIN as women reporting such use were more likely than others to have cervical oncogenic HPV without evidence of CIN.

Keywords

CIN; hormonal contraception; DMPA; Oncogenic HPV infection

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Introduction

Hormonal contraceptives are used by millions of women worldwide to prevent pregnancy. Many studies have evaluated the relationship between oral contraceptives and cervical cancer and have found the highest risk of cervical cancer was associated with long-term (≥10 years) use.[1, 2] Studies evaluating the association with HPV infection have mixed findings.[3–9] Limitations with many of these previous studies include 1) no measure of HPV status; 2) confounding by history of cytologic screening; and 3) disease status in the cases and controls was determined by different methods (histology vs. cytology). Additionally, because different formulations and doses are being used in the United States (US) today, the results may not be applicable to current methods. Few studies have evaluated the relationship between depot-medroxyprogesterone acetate (DMPA;Depo-Provera, Pfizer, Inc., New York, NY), a progestin only injectable contraceptive, and cervical neoplasia. A recent meta-analysis found only a slight increase in cervical neoplasia risk associated with long-term DMPA use (≥5 years).[1]

The present study was designed to determine whether DMPA and COC use increase the risk for 1) cervical intraepithelial neoplasia grade 2–3 or greater (≥CIN2-3) or CIN1 among oncogenic HPV-positive women or 2) acquisition or detection of HPV among women with no histologic evidence of cervical neoplasia. Unlike previous studies, disease status for both cases and controls was based on histology.

Material and Methods

Study subjects and data collection

The University of Washington Human Subjects Division approved all protocols and consent forms. Women presenting from December 1997 through August 2002 for routine gynecological care at three Planned Parenthood Clinics who met the following criteria were eligible for cytologic and HPV screening with the study: 18–50 years old; no history of treatment for cervical neoplasia or hysterectomy; not planning to continue a current pregnancy; and did not report being HIV-positive or having another immunosuppressive condition.[10–12] During this time period, 4975 women were enrolled and after providing written, informed consent, participants completed a brief questionnaire that included demographic, reproductive, and sexual history questions. A pelvic exam was performed and a cervical specimen was collected using a cytobrush and a plastic spatula for liquid cytology (ThinPrep, Cytyc Corporation, Boxborough, MA). A Dacron-tipped swab sample from the endo-and ecto-cervix was obtained for HPV DNA testing by PCR.

Women with 1) atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL) on Pap test; 2) negative Pap test and a positive oncogenic HPV test; and 3) a random sample of women with negative Pap and negative HPV tests were contacted and offered colposcopy and biopsy with the study (median time between screening and colposcopy-biopsy: 60 days).[10, 11]

At the colposcopy-biopsy visit a detailed questionnaire regarding demographic, reproductive/gynecologic, sexual history, and general medical information was administered. The brand, the duration, and the month and year of last use for the four most recent hormonal contraception methods was obtained via the questionnaire without the use of recall aids. Very few women reported four hormonal contraceptive methods. A pelvic exam was performed and cervical specimens were collected as described for the screening visit. A colposcopic examination of the cervix was performed using acetic acid and punch biopsies were taken from the most abnormal appearing areas. If none were seen, a cervical biopsy was taken at the 12 o'clock position. Women with lesions that extended into the endocervical canal or women with SIL

on screening cytology and no colposcopically visible lesions also underwent endocervical curettage (ECC).

Women with negative results or low-grade disease (atypia or CIN1) were referred back to Planned Parenthood for follow-up. Women with high-grade disease (≥CIN2-3) were offered a loop electrosurgical excision procedure (LEEP). Women with cancer were referred to a gynecologic oncologist. At the clinician's discretion, some women were referred for repeat colposcopies and biopsies and/or ECCs. HPV testing was not performed at these repeat visits.

HPV DNA detection

All HPV DNA testing was performed at the Harborview Medical Center HPV DNA Lab (Seattle, Washington).[10–12] First, the cervical swab sample was digested with proteinase K and the DNA precipitated with ethanol. Then the HPV L1 consensus primer (MY09/MY11 and HMB01) PCR amplification assay and Roche line blot assay were used for amplification and typing of HPV DNA.[13] This system allowed for the detection and typing of oncogenic HPV types 16/18/26/31/33/35/39/45/51/52/55/56/58/59/68/73/82/83 and non-oncogenic HPV types 6/11/40/42/53/54/57/66/84. The primers PC04 and GH20 were used for beta-globin detection (control for DNA quality).[13]

Cytology and histology

All cytology and histology specimens were processed and reviewed at Harborview Medical Center. Cytology slides were screened by a cytotechnologist and reviewed by pathologists without knowledge of colposcopy or HPV results; findings were recorded in terms of the 1991 Bethesda System.[14] A random 10% sample of all slides read as negative was rescreened manually. Histology was classified as negative, atypia, CIN1, CIN2, CIN3, carcinoma in situ (CIS), adenocarcinoma in situ (AIS), microinvasive cancer, or invasive cancer.

Statistical analysis

To evaluate the association between hormonal contraception and CIN, the analysis was restricted to women positive for at least one oncogenic HPV type at colposcopy-biopsy (N=591). Three outcome groups were defined based on the most severe histological diagnosis from either a biopsy, ECC, or LEEP specimen. The first was composed of women who were histologically negative and had negative or ASC-US cytology at both screening and colposcopy-biopsy (n=152). The second group was composed of women with CIN1 (n=133). The third was composed of women with ≥CIN2-3 (including ≥AIS) (n=173). To minimize misclassification by case-control status, women with negative histology whose cytology was abnormal (n=60) or unsatisfactory (n=7) and oncogenic HPV women with atypia on histology (n=66) were excluded.

Women were categorized separately as to their DMPA and COC use (i.e. two separate variables) at colposcopy-biopsy: never user, former user, recent user who had been using that method for <2 years, or recent user who had been using that method for ≥2 years. Former use was defined as having stopped using that method at least one year prior to colposcopy-biopsy and recent use was defined as having used that method within one year of colposcopy-biopsy. The time intervals were chosen based on the observation that at least 50% of CIN develops within two years of detecting cervical HPV infection.[15] Women who had used both DMPA and COC within one year of colposcopy-biopsy were categorized as recent users for both methods. A third variable was created to ascertain the association between use of a COC with higher amounts of estrogen (≥35 mcg) and CIN: never used a COC with ≥35 mcg of estrogen, former ≥35 mcg of estrogen COC user, recent ≥35 mcg of estrogen COC user who had been using for <2 years, and recent ≥35 mcg of estrogen COC user who had been using ≥2 years. For all hormonal contraceptive variables, if the month of last use was missing, it was imputed

as the midpoint of the possible months of use. Seven women's (2 negative, 1 CIN1, 4 ≥CIN2-3) month of last use for former COC use was imputed and 14 women's (6 negative, 5 CIN1, 3 ≥CIN2-3) month of last use for former DMPA use was imputed.

Multinomial logistic regression was used to evaluate the association between hormonal contraception and CIN. The DMPA and COC variables were always included in the same model and all models were adjusted for age (18–19, 20–24, 25–29, ≥30 years), parity (0, 1, ≥2), and lifetime number of male partners (1, 2–4, 5–14, ≥15). Other variables (e.g. smoking, screening history) were not included because they did not confound the association between hormonal contraception and CIN.

To evaluate the association between hormonal contraception and oncogenic HPV detection, cases were women who were positive for an oncogenic HPV type at colposcopy-biopsy, were histologically negative, and had normal or ASC-US cytology at both visits (controls from the CIN analysis; n=152). Controls were HPV-negative women with negative histology and cytology at both visits (n=107). Cases were compared to controls using logistic regression and all models were adjusted for age, parity, and lifetime number of male partners. COC use, DMPA use, ≥35 mcg COC use variables were created similarly to that for the CIN analysis, but the time intervals for defining recent use and duration of use were halved because new HPV infections are generally detectable within one year of exposure.[5] One case's month of last use for former DMPA use was imputed as described above.

Results

Hormonal contraception and CIN

Of the 458 subjects in the analysis who were oncogenic HPV-positive at colposcopy-biopsy, 377 (83%) were also oncogenic HPV-positive at screening and of these, 345 (92%) were positive for the same type. At colposcopy-biopsy, HPV16 was detected in specimens from 43 (28%) of the women with negative histology, 27 (20%) of the women with CIN1, and 90 (52%) of the women with ≥CIN2-3. CIN cases were more likely than controls to have two or more oncogenic HPV types detected at colposcopy-biopsy and to have the same type detected at both visits (Table 1). Cases were slightly less likely to have undergone cytologic screening prior to study enrollment. Among those previously screened, ≥CIN2-3 cases were more likely to have a history of an abnormal cytologic result.

Recent use of DMPA for ≥2 years was inversely associated with ≥CIN2-3, although this association was not significant (adjusted odds ratio (OR_{adj})=0.5;95% confidence interval (CI) =0.2–1.4) (Table 2). Recent use of DMPA for ≥2 years was also inversely associated with CIN1 (OR_{adj}=0.1;95% CI=0.01–0.6). However, there was only one woman with CIN1 with this exposure. When both of the recent DMPA use categories were combined, recent use remained inversely associated with CIN1 (OR_{adj}=0.5;95% CI=0.2–1.0;p=0.04). Recent use of a COC for ≥2 years was not associated with ≥CIN2-3 (OR_{adj}=0.9;95% CI=0.4–1.9) or with CIN1 (OR_{adj}=1.1;95% CI=0.5–2.6). When women who had used COCs for ≥5 years were compared to never users, there was no association with ≥CIN2-3 (OR_{adj}=1.0;95% CI=0.4–2.6) or with CIN1 (OR_{adj}=1.1;95% CI=0.4–3.2). Recent use of a ≥35 mcg of estrogen COC for ≥2 years was not associated with ≥CIN2-3 (OR_{adj}=1.1;95% CI=0.5–2.7). The main analysis was repeated separating women with CIN3 from women with CIN2. The estimates for CIN3 were not significantly (all p>0.13) different from those for CIN2 (data not shown). Likewise, when the main analysis was restricted to HPV16-positive women, results were similar (data not shown).

Hormonal contraception and oncogenic HPV

Oncogenic HPV-positive women were younger and more likely to be nulliparous than HPV-negative women (data not shown). Among histologically-negative women, recent use of DMPA for ≥1 year was significantly associated with oncogenic HPV detection (OR_{adj}=4.7;95% CI=1.4–15.8), but recent COC use was not (Table 3). When cases were restricted to HPV16-positive women, the OR for recent DMPA use for ≥1 year increased slightly (OR_{adj}=5.5;95% CI=0.9–34.5).

To further explore the association of DMPA use with oncogenic HPV, two additional analyses were performed. First, among 142 histologically-negative women who were HPV-negative at screening, DMPA use for ≥1 year was associated with being oncogenic HPV-positive at colposcopy-biopsy (OR_{adj}=7.3;95% CI=1.5–35.5). Adjusting for the number of new male partners since screening did not change the estimate to an important degree. Second, among 163 histologically-negative women who were oncogenic HPV-positive at screening and did not have any new male partners between visits (women most likely not acquiring a new HPV infection), DMPA use for ≥1 year was not associated with being positive for the same oncogenic HPV type at colposcopy-biopsy (OR_{adj}=1.1;95% CI=0.3–3.7).

Comment

Among women with oncogenic HPV, those with CIN were slightly less likely than women with negative histology to report ever use of DMPA in the previous year (borderline statistical significance for ≥CIN2-3). COC use was not associated with ≥CIN2-3 or with CIN1. Recent use of DMPA for ≥1 year was positively associated with detection of oncogenic HPV. The association was attenuated, but remained elevated when women with CIN were included as cases indicating that the association was likely not solely due to difficulty with lesion detection. This relationship did not appear to be due to HPV persistence as measured by type-specific repeat oncogenic HPV positivity, however, DMPA was associated with new HPV infection. COC use was not associated with oncogenic HPV detection.

One study that specifically addressed the risk of cervical cancer associated with DMPA among oncogenic HPV-positive women found no association,[16] but Castle et al. found a small increased risk of CIN2 and CIN3 with current injectable contraceptive use.[8] This is in contrast to our findings of an inverse association between DMPA use and both CIN1 and ≥CIN2-3 among oncogenic HPV-positive women. Unlike our study, neither of these previous studies used a control group free of cervical disease, which would lead to associations that are spuriously weakened.

Several recent studies,[1–3, 17–21] but not all,[16] among HPV-positive women have found an increased risk of cervical neoplasia for longer durations (≥10 years) of OC use. We did not find a positive association between ≥2 or ≥5 years of COC use and cervical neoplasia, though the estimates from recent meta-analyses by Smith et al.[1] (medium-duration use OR=1.3) and Appleby et al.[2] (≥5 years of use risk ratio=1.45) are well inside our confidence interval. However, these results were largely driven by studies conducted outside of the US and subjects likely used very different hormonal contraceptive formulations than those used by women in the US in recent years. Previous studies among HPV-positive women conducted in the US and other industrialized countries did not find an association.[3, 17, 18, 21] We found no association between COC use and HPV detection, which is similar to other studies.[3, 6, 9]

There are a number of mechanisms through which use of hormonal contraceptives might affect the development of HPV infection and risk of cervical neoplasia. First, hormones may inhibit the immune response to HPV infection.[22, 23] Our findings that HPV persistence and ≥CIN2-3 were not positively associated with DMPA or COC use do not support this mechanism,

however, the interactions between HPV, hormones, and the immune system are not completely understood.

Second, HPV gene expression and cellular proliferation is increased by estrogen and progestin *in vitro*.[24–26] Our preliminary work assessing levels of HPV16 E7 DNA using quantitative PCR suggests that DMPA users have slightly higher levels than non-DMPA users (personal communication, Long Fu Xi). Upregulation of HPV gene expression by hormones may be an early stage event that occurs prior to viral integration[27, 28] and other evidence suggests that once HPV is integrated hormones may have various effects depending on the placement of the hormone response elements.[29] The fact that we did not find a positive association between hormonal contraception and ≥CIN2-3 could be explained, in part, by the fact that women enrolled in our study were relatively young and the duration of use was relatively short.

And third, hormones influence cervical epithelial differentiation and maturation.[30–32] DMPA decreases cell maturation and promotes the appearance of atrophic epithelium[30, 32], which could make histologic features of CIN more difficult to detect among DMPA users because the loss of glycogen and hydration will shrink the cytoplasm lessening the effect of acetic acid.[33] If the colposcopist cannot see the acetowhite lesions then she/he cannot do a directed biopsy. This may explain why among women with oncogenic HPV infection, DMPA use was inversely associated with CIN detection. However, this may not translate into an increased risk of developing invasive cervical cancer because the inverse association between DMPA and CIN was strongest for CIN1 lesions and most CIN1 lesions regress spontaneously. We have found that DMPA use did result in thinning of the vaginal epithelium perhaps reflecting the loss of glycogen.[34] However, this association was not found in other studies.[35–37]

A limitation of this analysis is the use of self-reported data on hormonal contraceptive use, but there is no reason to suspect that accuracy differed between women with and without CIN because these data were obtained prior to colposcopy-biopsy. Additionally, studies comparing self-reported information to data from other sources have found good agreement for the current method and for total duration of use.[38] We did not have information on the number of DMPA injections or if COC use was continuous during the time interval women reported using the method. Because of the young age of our population and their fewer years of contraceptive use, we had limited power to assess the association between long-term (≥10 years) hormonal contraceptive use and CIN and for several of the sub-analyses. Because women mostly used two similar types of COCs, we were also unable to look at the risk associated with specific formulations. Additionally, we did not have complete information on barrier contraception use. However, use of barrier contraception has not been consistently associated with protection from HPV infection.[39, 40]

There are several strengths of the current analysis. All subjects were ascertained from the same clinic population, and misclassification of disease status was minimized by 1) cases and controls being diagnosed in the same manner (by cytology and histology) and 2) requiring that the oncogenic HPV-positive/histologically negative group have negative and/or ASC-US cytology at both screening and colposcopy-biopsy. Lastly, we collected detailed information (brand/type, duration, date of last use) on the four most recent hormonal contraceptive methods. Only five women reported four methods so we are fairly confident that we sufficiently captured usage.

In summary, the hormonal contraception formulations used by women in this study do not appear to increase risk of ≥CIN2-3 or CIN1. Although women who use DMPA may be at an increased risk for HPV acquisition, neither the risk for persistent infection nor CIN was increased. Due to the tendency of DMPA to promote the appearance of an atrophic epithelium, it is also possible that the colposcopic and histologic features of HPV-related cervical lesions

are less pronounced among women who use DMPA. If DMPA use makes lesions less visible, then this will be important for clinicians to take into account when performing colposcopies in women using this contraceptive method. Additionally, it will be important for future studies to evaluate the effects of long-term DMPA use and the current formulations of COC on HPV infection and cervical neoplasia.

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TABLE 1

Distribution of demographic, gynecological, sexual behavior, and HPV characteristics for oncogenic HPV DNA positive women with negative, CIN1, and ≥CIN2-3 histology.

Characteristic	HPV+, Negative Histology (n=152) No. (%)	HPV+, CIN1 Histology (n=133) No. (%)	*p**	HPV+, ≥CIN2-3 Histology (n=173) No. (%)	*p**
Age (years)			0.10		0.88
18–19	23 (15)	34 (26)		24 (14)	
20–24	74 (49)	64 (48)		79 (46)	
25–29	37 (24)	25 (19)		46 (26)	
30–50	18 (12)	10 (7)		24 (14)	
Race/Ethnicity			0.36		0.47
White	99 (65)	97 (73)		123 (71)	
Black	20 (13)	14 (10)		21 (12)	
Other	33 (22)	22 (17)		29 (17)	
Education			0.86		0.34
<12th grade	17 (11)	14 (11)		14 (8)	
≥12th grade	135 (89)	119 (89)		159 (92)	
Ever Had a Cytologic Test Prior to Study			0.02		0.03
No	1 (1)	7 (5)		8 (5)	
Yes	151 (99)	126 (95)		165 (95)	
History of Abnormal Cytology‡			0.81		<0.001
No	98 (65)	80 (63)		66 (40)	
Yes	53 (35)	46 (37)		99 (60)	
Parity			0.06		0.15
0	100 (66)	87 (65)		96 (55)	
1	29 (19)	36 (27)		46 (27)	
≥2	23 (15)	10 (8)		31 (18)	
Age at First Sexual Intercourse (years)			0.23		0.50
≤13	20 (13)	21 (16)		19 (12)	
14–17	104 (70)	79 (60)		108 (66)	
≥18	26 (17)	32 (24)		37 (22)	

Characteristic	HPV+, Negative Histology (n=152) No. (%)	HPV+, CIN1 Histology (n=133) No. (%)	p*	HPV+, ≥CIN2-3 Histology (n=173) No. (%)	p*
Lifetime Number of Male Partners§			0.13		0.48
1	5 (3)	12 (9)		5 (3)	
2–4	37 (25)	29 (22)		32 (19)	
5–14	76 (50)	71 (53)		101 (58)	
≥15	33 (22)	21 (16)		35 (20)	
Cigarette Smoking Status			0.11		0.35
Never smoker	53 (35)	34 (25)		50 (29)	
Former smoker	26 (17)	34 (26)		39 (22)	
Current smoker	73 (48)	65 (49)		84 (49)	
Number of Oncogenic HPV Types at Colposcopy-Biopsy			0.04		<0.001
1	122 (80)	93 (70)		108 (62)	
2+	30 (20)	40 (30)		65 (38)	
Type-specific Oncogenic HPV Repeat Positivity‖			0.01		<0.001
No	56 (38)	31 (23)		20 (12)	
Yes	92 (62)	102 (77)		151 (88)	

*p value (two-sided) for Pearson's chi-square test of the null hypothesis that the CIN1 histology group and ≥CIN2-3 histology group are different than the negative histology group with respect to the distribution of the listed characteristics.

†Among those who had at least one cytologic test and does not include cytologic result from study screening visit.

‡Two women in the negative histology group, one woman in the CIN1 histology group, and nine women in the ≥CIN2-3 histology group were missing information on age at first sexual intercourse.

§One woman in the negative histology group was missing information on lifetime number of male partners.

‖Four women in the negative histology group and two women in the ≥CIN2-3 histology group had insufficient PCR results from screening and therefore type-specific oncogenic HPV repeat positivity could not be determined.

Table 2

Odds ratios (OR) and 95% confidence intervals (CI) for the associations between hormonal contraception and CIN among oncogenic HPV DNA positive women.

	HPV+, Negative (n=151)*	HPV+, CIN1 (n=133)	HPV+, CIN1 vs. HPV+, Negative		HPV+, CIN2-3 (n=173)	HPV+, ≥CIN2-3 vs. HPV+, Negative	
Contraceptive Type	**No. (%)**	**No. (%)**	**OR_{adj}†**	**95% CI**	**No. (%)**	**OR_{adj}†**	**95% CI**
DMPA							
Recent user‡	35 (23)	16 (12)	0.5	0.2, 0.98	35 (20)	0.7	0.4, 1.3
≥2 years of use	15 (10)	1 (1)	0.1	0.01, 0.6	13 (8)	0.4	0.2, 1.1
<2 years of use	20 (13)	15 (11)	0.6	0.3, 1.5	22 (12)	0.7	0.4, 1.6
Former user	18 (12)	17 (13)	0.8	0.4, 1.8	19 (11)	0.7	0.4, 1.5
Never user	98 (65)	100 (75)	1.0		119 (69)	1.0	
COC							
Recent user‡	94 (62)	101 (76)	1.5	0.7, 3.1	105 (60)	0.9	0.5, 1.7
≥2 years of use	37 (24)	31 (23)	1.1	0.5, 2.6	44 (25)	0.9	0.4, 1.9
<2 years of use	57 (38)	70 (53)	1.4	0.7, 3.0	61 (35)	0.8	0.4, 1.6
Former user	26 (17)	14 (10)	1.1	0.4, 2.8	32 (19)	1.0	0.5, 2.1
Never user	31 (21)	18 (14)	1.0		36 (21)	1.0	

*One woman in the negative histology group was excluded from the analysis because of missing information on lifetime number of male partners.

†Adjusted for age at colposcopy-biopsy (18–19, 20–24, 25–29, 30–50), lifetime number of male partners (1, 2–4, 5–14, ≥15), and parity (0, 1, ≥2).

‡Recent use was defined as using that method within one year of the colposcopy-biopsy visit. The most recent COC brand reported was Ortho tri-cyclen (38%) followed by Ortho cyclen (19%) and Ortho-novum 7/7/7 (10%); 6% could not recall the brand of combined oral contraceptive they most recently used.

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for the associations between hormonal contraception and oncogenic HPV DNA positivity.

	Negative (n=107)*	Positive (n=151)*		
Contraceptive Type	**n (%)**	**n (%)**	**OR_{adj}†**	**95% CI**
DMPA				
Recent user‡	17 (16)	32 (21)	1.6	0.7, 3.7
≥1 years of use	5 (5)	20 (13)	4.7	1.4, 15.8
<1 years of use	12 (11)	12 (8)	0.7	0.3, 2.1
Former user	12 (11)	21 (14)	1.5	0., 3.6
Never user	77 (73)	98 (65)	1.0	
COC				
Recent user‡	66 (62)	87 (58)	0.6	0.3, 1.5
≥1 years of use	32 (30)	48 (32)	0.8	0.3, 2.0
<1 years of use	34 (32)	39 (26)	0.5	0.2, 1.2
Former user	23 (22)	33 (22)	0.9	0.3, 2.3
Never user	17 (16)	31 (20)	1.0	

* One woman in the negative histology group was excluded from the analysis because of missing information on lifetime number of male partners.

† Adjusted for age at colposcopy-biopsy (18–19, 20–24, 25–29, 30–50), lifetime number of male partners (1, 2–4, 5–14, ≥15), and parity (0, 1, ≥2).

‡ Recent use was defined as using that method within six months of the colposcopy-biopsy visit. The most recent COC brand reported was Ortho tri-cyclen (39%) followed by Ortho cyclen (19%) and Ortho-novum 7/7/7 (11%); 4% could not recall the brand of combined oral contraceptive the most recently used.