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Hormonal and Barrier Methods of Contraception, Oncogenic Human Papillomaviruses, and Cervical Squamous Intraepithelial Lesion Development

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ABSTRACT

We assessed the influence of hormonal (oral, injectable, or levonorgestrel [Norplant, Wyeth-Ayerst, Philadelphia, PA]) and barrier methods of contraception on the risk of cervical squamous intraepithelial lesions (SIL), while adjusting for high-risk (HR) HPV infection. Subjects were women receiving family planning services through the state health department clinics from 1995 to 1998. We selected 60 cases with high-grade cervical/SIL (HSIL) and 316 with low-grade cervical/SIL (LSIL) and controls (427 women with normal cervical cytology) and analyzed cervical DNA for HR-HPV, using Hybrid Capture I (Digene; Gaithersburg, MD). When assessing ever use, duration, recency, latency, and age at first use, neither oral contraceptives (OC), Norplant, nor injectable use was associated with an increased risk of SIL development after adjusting for age, age at first sexual intercourse, and HR-HPV positivity. Among HR-HPV-positive women, longer duration barrier method use was associated with a reduced risk of SIL. This finding has important clinical implications for SIL prevention among HR-HPV-infected women.

INTRODUCTION

UNDERSTANDING THE ROLE of contraception in cervical neoplasia development is a methodological challenge.[1–3] Risk of disease differs by type of contraceptive used. Barrier methods may reduce the risk of cervical squamous intraepithelial lesions (SIL), whereas hormonal methods may increase SIL risk. Selection bias may be important in studies of preinvasive disease if, for example, oral contraceptive (OC) users are more likely to be screened and potentially detected as having SIL than are nonusers. Additionally, if controls are sampled from demographically different populations than are cases, selection bias may further affect the internal study validity. Investigators must assess the potentially confounding effect of high-risk human papillomavirus (HR-HPV) positivity[4–12] when evaluating the role of contraception in cervical neoplasia development. Other confounding factors include smoking, sexual behavior of the woman and her partner, and parity.

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Several epidemiological studies have addressed the role of OC in SIL,[9,13–20] cervical carcinoma *in situ* (CIS),[3,17,21–25] and invasive cervical cancer (ICC) development.[7,17,26–36] The majority of such studies find an increased risk of ICC[7,16,28,30–32,34,36,37] and CIS[3,21,23–25] associated with long-term (>5 years) and with recent OC use. OC have not been consistently linked with lower-grade cervical lesions.[9,13–20] Because of the potential for detection and confounding bias in explaining study results, Grimes[38] suggests that making the case for a causal role of OC in cervical neoplasia is difficult. Further, only the more recent studies were able to assess HPV positivity, a major etiological agent in cervical neoplasia, which may confound or modify the association between contraceptive use and cervical neoplasia development.

Barrier methods have been linked to a reduced risk of low-grade SIL (LSIL),[9,13,20,39] high-grade SIL (HSIL),[40,41] CIS,[22] and ICC.[24,25,41–43] Three large case-control studies of injectable hormonal contraceptive use, reviewed by LaVecchia,[44] found no strong evidence of an association with cervical neoplasia.[13,45–47] Levonorgestrel implants (Norplant, Wyeth-Ayerst, Philadelphia, PA) have only recently be widely available, and three follow-up studies of users have found no increased risk of cervical SIL.[48-50]

The purpose of this case-control study, nested in a cohort of young, low-income women seeking family planning services in a rural state, was to examine whether hormonal or barrier contraceptives were associated with cervical SIL, controlling for HR-HPV types and risk taking behaviors.

MATERIALS AND METHODS

Subjects

Cases and controls for this study were women receiving family planning services through South Carolina health department clinics from 1995 to 1998. At the time the Pap smear was collected, an additional cervical sample was collected and stored for subsequent evaluation. We conducted HPV typing on a subset of stored cervical samples depending on the women's cervical cytology. We sampled as cases all those whose Pap smear indicated SIL; 60 women had HSIL and 316 women had LSIL. For this analysis, we excluded as cases and controls women with ASCUS or AGCUS on their Pap smear. We included as controls women who had normal cervical cytology on the index Pap smear and no history of treatment for an abnormal Pap smear. Because many women had normal Pap smears (eligible controls), we selected a subsample from this control pool, approximately equal to the number of SIL cases, for interview and HPV typing ($n = 427$). We excluded women with a history of treatment for cervical neoplasia. The age range of subjects was 16–45 years. This case-control study is part of a larger cohort study of HR-HPV and SIL development. Subjects were interviewed to obtain data on medical, reproductive, and sexual history, specifically contraceptive use, alcohol and tobacco use, and physical activity.

Response rate

Of 1052 attempted interviews (458 SIL cases and 594 controls), we were able to complete interviews with 76% of subjects (82% of cases and 72% of controls). We could not locate 17% (13% of cases and 17% of controls), and 7% (5% of cases and 10% of controls) refused. The number of attempted interviews included all eligible women. There were no significant differences in response rates (refusals, could not locate, or completed interview) by race. Among the nonrespondents, 57% were African American and 41% were white. Nonresponders, however, were younger than responders. As our population is very mobile, is relatively young, and has a low income, we believe our response rate is appropriate. The total sample size included in these analyses is 376 SIL cases and 427 controls.

Sampled cases and controls were interviewed by telephone (56.3%) or in person (43.7%). On completion of the 15–20-minute interview, we mailed subjects $10 for their time. The University of South Carolina Institutional Review Board approved this project, and all women included in these analyses provided informed consent for study participation.

Contraceptive history by method, including ever use, duration, latency, and recency

We obtained detailed contraceptive histories in telephone or in-person interviews. For each contraceptive method (OC, Norplant, injectables, intrauterine devices [IUD], and barrier methods, in-

cluding condoms, spermicides, and diaphragms), we asked about consistent use for at least 6 months, age at first use, last use, and total duration of use. We created duration, latency, and recency indices for each method. Recency was defined as current users (within the past year) or those no longer using the method at the time of interview (>1 year since last use). OC method users, in particular, are required to have Pap smears to remain on this method. This linkage of contraceptive exposure with screening for SIL may lead to a detection bias and is the reason we specifically addressed recency of contraceptive method use. Latency was defined as the time since first contraceptive method use (current age minus age at first contraceptive method use). To be etiologically linked to SIL, we hypothesized that contraceptive use must have begun at least 2 years prior to SIL development.

As indicated in Table 1, the majority (85%) of women had ever used OC. We, therefore, could not create mutually exclusive categories of contraceptive use. Instead, we opted to adjust for barrier method use (condoms, spermicides, or diaphragm use) when evaluating hormonal contraceptive use, and vice versa. To illustrate, of 414 barrier method users, 84% had also used OC, of 63 Norplant users, 79% were also OC users, and of 166 injectable contraceptive users, 69% had also used OC. There were too few women who had ever used IUDs to evaluate the risk of SIL associated with IUDs.

Other risk factors assessed in the interview included age, race, employment, education, and current marital status; reproductive history, including number of pregnancies, pregnancy outcomes, mode of delivery, and infertility; sexual history, including age at first sexual intercourse, number of male sex partners, number of sex partners of the current partner; active and passive smoke exposure; and a brief medical history, including sexually transmitted infections by type.

HPV analyses

A cervical sample for subsequent HPV typing using Hybrid Capture I (Digene; Gaithersburg, MD) was collected from each woman before the Pap smear was taken. This sample was collected and stored in a Virapap transport buffer medium developed by Digene. Samples were stored in freezers until case status could be determined. DNA was extracted from cervical smear samples using standard procedures, and PCR amplification for β-globin DNA sequences was performed to determine if sufficient cervical DNA was present in the sample. A unique study number was assigned to each cervical sample. Samples were sent to L.P.'s laboratory for analysis. To minimize differential misclassification, those conducting HPV analyses were blinded to subjects' cervical disease status.

HR-HPV positivity was determined using Hybrid Capture I techniques according to the manufacturer's guidelines. The same person (T.G.) conducted HPV typing for all samples. We assessed high-risk (HPV16, 18, 31, 33, 35, 45, 51, 52, and 56) and low-risk types (HPV6, 11, 42, 43, and 44). For this analysis, we focused solely on HR-HPV positivity. HR-HPV positivity indicates that the case or control had one of the range of oncogenic HPV viral types in her cervix at the time the sample was collected. We do not have prospective measures of HPV positivity for this analysis.

Statistical analysis

All statistical analyses were performed using SAS version 6.12 . We assessed confounding by examining the association between possible confounders and case or control status. Age, age at first sexual intercourse, and HR-HPV status were significantly associated with SIL status and were, therefore, included as confounders in subsequent models. Additionally, because women frequently use more than one method of contraception and barrier methods are thought to reduce SIL risk whereas long-term hormonal use may increase risk, we included as confounders ever use and duration of other methods of contraception in subsequent models. Not adjusting for barrier method use, for example, could bias the resulting relative risk estimate for hormonal contraceptive use away from the null. Multiple logistic regression models[51] were used to estimate the relative risk for contraceptive methods and SIL development, adjusting for these three confounders and other contraceptives (Table 2) and within strata of HR-HPV positivity (Table 3). Contraceptive use is presented as having used the method consistently for at least 6 months. The categories are not mutually exclusive, and we do control for barrier method use when evaluating hormonal contraceptive use, and vice versa.

RESULTS

Table 1 shows the demographic profile of clinic clients. Only low-income women are eligible to receive family planning services through health department clinics. Thus, all these women have low incomes. Sixty-one percent of the women were African American, and the rest were white, not Hispanic. The mean age at interview was 26.1 years (standard deviation [SD] 6.1 years). SIL cases were significantly younger than controls. Cases had an earlier age at first sexual intercourse and were more likely to have had any type of sexually transmitted infection, specifically to have

TABLE 1. DEMOGRAPHIC AND RISK FACTOR PROFILE OF SIL CASES AND CONTROLS RECRUITED FROM SOUTH CAROLINA HEALTH DEPARTMENT CLINICS, 1995–1998 (n = 803)

	HSIL (n = *60*)	*LSIL* (n = *316*)	*Controls* (n = *427*)
Age, years	24.5 ± 5.7[a],**	25.4 ± 6.2**	28.1 ± 6.5
Number of pregnancies	1.3 ± 1.3***	1.5 ± 1.4***	1.7 ± 1.6
Age at first sexual intercourse	15.8 ± 2.4*	16.0 ± 2.6***	16.7 ± 3.0
Lifetime number of male sex partners	5.8 ± 5.0	6.5 ± 6.5	6.1 ± 6.6
	% (n)	% (n)	% (n)
Marital status			
Divorced/separated	15.0 (9)	17.7 (56)	13.1 (56)
Married	30.0 (18)	25.0 (79)**	35.1 (150)
Single[b]	55.0 (33)	57.2 (181)	51.8 (221)
Ever pregnant	70.0 (42)	69.6 (220)	74.7 (319)
Never pregnant[b]	30.0 (18)	30.4 (96)	25.3 (108)
Race			
African American	58.3 (35)	62.3 (197)	59.5 (254)
White[b]	41.7 (25)	37.7 (119)	40.5 (173)
Education			
≤High school	55.0 (33)	63.9 (202)	57.4 (245)
>High school[b]	45.0 (27)	36.1 (114)	42.6 (182)
Unemployed	28.3 (17)	31.6 (100)	29.3 (125)
Employed or student[b]	71.7 (43)	68.4 (216)	70.7 (302)
Partner infidelity	76.7 (46)*	63.6 (201)	63.0 (269)
No known partner infidelity[b]	23.3 (14)	36.4 (115)	37.0 (158)
Self-reported history of a sexually transmitted infection by type			
Any	48.3 (29)*	40.8 (129)*	34.9 (149)
Genital warts	13.3 (8)*	10.8 (34)*	6.6 (28)
Gonorrhea	13.3 (8)	10.4 (33)	9.1 (39)
Pelvic inflammatory disease	6.7 (4)	9.2 (29)	8.0 (34)
Human immunodeficiency virus (HIV)	0.0 (0)	0.9 (3)	1.6 (7)
High-risk HPV positive	65.0 (39)**	44.9 (142)**	18.3 (79)
Smoking status			
Ever smoker	35.0 (21)	32.6 (103)	32.1 (137)
Never smoker[b]	65.0 (39)	67.4 (213)	67.9 (290)
Current smoker	30.0 (18)	24.1 (76)	23.9 (102)
Ever used contraceptives regularly for 6 months or longer by type			
Oral contraceptives (OC)	78.3 (47)	85.4 (270)	85.2 (364)
Intrauterine device (IUD)	1.7 (1)	1.9 (6)	2.8 (12)
Injectables	26.7 (16)	18.7 (59)	21.5 (92)
Norplant	3.3 (2)	9.5 (30)	7.5 (32)
Barrier methods	48.3 (29)	57.9 (184)	47.5 (203)
Condoms/spermicides	45.0 (27)	49.7 (157)	44.5 (190)
Diaphragm	1.7 (1)	2.5 (8)	3.7 (16)

[a]Mean ± SD.
*p = 0.01–0.05.
**p = 0.01
***p = 0.06–0.1.
[b]Comparison group.

ever had genital warts, and were more likely to have been positive for HR-HPV. HSIL cases were more likely than LSIL cases and controls to report infidelity by their male partner. Neither ever smokers nor current smokers were at increased risk of SIL in these data.

As anticipated in this study of family planning clients, more than 80% had ever used OC. Less than 3% had ever used IUDs, 21% had used injectables, 8% had used Norplant, and 52% had ever used barrier methods regularly for 6 months or longer. The majority of barrier methods used were condoms and spermicide, and 3% of all subjects had ever used a diaphragm. SIL development was not significantly associated with ever use of any specific contraceptive (Table 1).

Table 2 presents our more detailed evaluation of SIL risk associated with contraceptive use by type, duration, age at first use, and recency (OC use only), adjusting for HPV, age, age at first sexual intercourse, and other contraceptives. Neither duration of OC use, recency, nor age at first use was associated with HSIL or LSIL risk. Similarly, no attribute of injectables or Norplant use was associated with HSIL or LSIL risk. Ever barrier method use, a young age (≤16 years) at first bar-

TABLE 2. CONTRACEPTIVE USE BY TYPE AND CERVICAL SIL RISK: ADJUSTED ODDS RATIO AND 95% CI FOR CHARACTERISTICS OF USE

Regular contraceptive use[a]	*HSIL (n = 60)*	*LSIL (n = 316)*	*Controls (n = 427)*	*Adjusted odds ratio (95% CI)*	
				HSIL vs. controls	*LSIL vs. controls*
Ever barrier user[b]	29	184	203	0.9 (0.5, 1.6)	1.3 (1.0, 1.8)
Never	31	132	224	1.0 Ref[c]	1.0 Ref
Duration of barrier method use (years)[b]	5.0 ± 3.8	4.9 ± 4.3	6.1 ± 5.0	0.97 (0.90, 1.05)	0.99 (0.96, 1.03)
<5 years	16	104	90	0.9 (0.4, 1.9)	1.2 (0.8, 1.7)
5–9.5 years	9	57	65	0.8 (0.3–1.8)	1.0 (0.6, 1.6)
≥10 years	4	23	48	0.7 (0.2, 2.3)	0.7 (0.4, 1.3)
Age at first barrier method use (years)[b]	16.1 ± 2.1	17.5 ± 3.6	19.0 ± 4.7	0.98 (0.95, 1.01)	1.01 (0.99, 1.03)
≤16 years	17	85	64	1.4 (0.7, 3.0)	1.7 (1.1, 2.5)
17–18 years	8	58	64	0.7 (0.3, 1.8)	1.3 (0.8, 2.0)
>18 years	4	41	75	0.4 (0.1, 1.2)	1.0 (0.6, 1.5)
Recency of barrier method use[b]					
Current user	19	135	130	0.8 (0.4, 1.60)	1.4 (1.0, 2.0)
Past user (>1 year since last use)	10	49	73	1.1 (0.5, 2.5)	1.1 (0.7, 1.7)
Ever oral contraceptive user[d]	47	270	364	0.9 (0.4, 1.9)	1.3 (0.8, 2.0)
Never user[e]	13	46	63	1.0 Ref	1.0 Ref
Duration of OC use (years)[d]	5.7 ± 4.9	5.8 ± 4.1	7.7 ± 5.4	0.96 (0.88, 1.04)	0.97 (0.93, 1.01)
<5 years	24	118	132	1.1 (0.5, 2.6)	1.2 (0.7, 2.0)
5–9.5 years	12	105	108	0.7 (0.3–1.9)	1.6 (0.9, 2.6)
≥10 years	11	46	124	0.8 (0.3, 2.8)	0.7 (0.4, 1.3)
Age at first OC use[d]	17.3 ± 2.6	17.3 ± 2.8	17.8 ± 2.9	0.99 (0.95, 1.04)	1.01 (0.99, 1.04)
≤16 years	22	114	125	0.9 (0.4, 2.1)	1.3 (0.8, 2.2)
17–18 years	14	92	128	0.9 (0.3, 2.2)	1.3 (0.8, 2.2)
>19 years	11	64	111	0.8 (0.3, 2.1)	1.2 (0.7, 2.0)
Recency of OC use					
Current user	34	172	212	0.9 (04, 2.0)	1.3 (0.8, 2.0)
Past user (>1 years since last use)	13	98	152	0.7 (0.3, 1.9)	1.3 (0.8, 2.1)
Ever used injectables[d]	16	58	92	1.1 (0.6, 2.3)	0.7 (0.5, 1.1)
Never user	44	258	335	1.00 Ref	1.00 Ref
Duration of injectable use (years)[d]	1.6 ± 1.0	2.0 ± 3.0	1.7 ± 1.1	1.14 (0.80, 1.61)	1.03 (0.95, 1.11)
Ever used Norplant[d]	2	30	32	0.5 (0.1, 2.2)	1.3 (0.7, 2.2)
Never user	58	286	395	1.0	Ref
Duration of Norplant use (years)[d]	4.5 ± 0.7	2.5 ± 1.3	3.0 ± 1.4	0.95 (0.90, 141)	1.00 (0.84, 1.20)

[a]Regular use defined as consistent use for at least 6 months.
[b]Adjusted for hormonal contraceptive use, age, age at first sexual intercourse, and high-risk HPV.
[c]Referent group.
[d]Adjusted for barrier contraceptive use, age, age at first sexual intercourse, and high-risk HPV.
[e]Referent group is never contraptive use by type.

rier method use, and current barrier method use (a*RR* = 1.4; 95% CI 1.0, 2.0) were associated with LSIL risk. However, increasing duration of barrier method use (in years) was not associated with LSIL risk (aOR = 0.99; 95% CI 0.96,1.03).

To evaluate whether study results differed by the interview mode (phone versus face-to-face interview), we calculated adjusted odds ratios (OR) for the association between SIL (HSIL and LSIL combined) and duration of contraceptive use. The OR for SIL risk and duration of OC use, adjusted for age, HR-HPV, age at first sexual intercourse, and barrier method use, among those interviewed by phone was 0.97 (95% CI 0.93, 1.02) and among those completing face to face interview was also 0.97 (95% CI 0.91, 1.04). Similarly the aOR for SIL risk and duration of barrier method use among those completing phone interviews was 1.01 (96% CI 0.97, 1.09) and was 0.98 (95% CI 0.91, 1.05) for those completing face-to-face interviews.

Because HR-HPV positivity may modify the association between contraceptive use and SIL risk, we stratified analyses by HR-HPV-positive and HR-HPV-negative cases and controls (Table 3). Because of limited study power to detect meaningful differences in SIL risk by grade and by HR-HPV positivity, we combined HSIL and LSIL for this subanalysis. Ever barrier method use was associated with an increased risk of SIL among HR-HPV-negative cases and controls (aOR = 1.5; 95% CI 1.0, 2.1), yet increasing duration of barrier method use was not associated with SIL risk among HR-HPV-negative women. Increasing duration of barrier method use was associated with a reduced SIL risk among HR-HPV-positive cases and controls (aOR = 0.89; 95% CI 0.81, 0.98) and this was specifically true for longer-term use (≥10 years). Early (<age 16) and recent barrier method use was associated with a slight increase in SIL risk among HR-HPV-negative women. Neither OC, injectables, nor Norplant use was associated with SIL risk among HR-HPV-positive or HR-HPV-negative women.

We additionally explored whether protection afforded by longer duration barrier method use among HR-HPV-positive women differed for those having one or two lifetime sex partners compared with women having three or more sex partners. Women having one or two lifetime sex partners were less likely to use barrier methods for 5 or more years ($p = 0.04$). Among those HR-

Table 3. Contraceptive Use Patterns and Cervical SIL Risk by HR-HPV Positivity

	Adjusted odds ratio (95% CI)	
Contraceptive use by type	*HR-HPV positive (181 SIL cases/79 controls)*	*HR-HPV negative (195 SIL cses/348 controls)*
Ever contraceptive use		
Barrier methods[a]	0.8 (0.5, 1.4)	1.5 (1.0, 2.1)
Oral contraceptives[b]	1.4 (0.6, 3.0)	1.1 (0.7, 1.8)
Duration of contraceptive use (years)		
Barrier methods (continuous)[a]	0.89 (0.81, 0.98)	0.97 (0.92, 1.02)
<5	0.8 (0.4, 1.6)	1.4 (0.9–2.3)
5–9.5	0.5 (0.2, 1.1)	1.4 (0.8, 2.3)
≥10	0.3 (0.1, 0.9)	1.0 (0.5, 1.9)
Oral contraceptives (continuous)[b]	0.91 (0.81, 1.01)	0.95 (0.91, 1.00)
<5	1.5 (0.6, 3.6)	1.0 (0.6, 1.8)
5–9.5	1.0 (0.4, 2.6)	1.6 (0.9, 2.8)
≥10	0.6 (0.2, 2.2)	0.7 (0.3, 1.3)
Age at fist OC use (years)		
≤16	1.8 (0.7, 4.8)	1.5 (0.8, 3.0)
17–18	2.2 (0.8, 6.4)	1.6 (0.8, 3.0)
19+	2.0 (0.7, 5.9)	1.3 (0.7, 2.5)
Age at first barrier method use (years)		
≤16	1.8 (0.7, 4.7)	2.3 (1.2, 4.2)
17–18	2.0 (0.8, 5.3)	1.6 (0.9, 2.9)
19+	0.9 (0.3, 2.3)	1.4 (0.8, 2.5)

[a]Adjusted for hormonal contraceptive use, age, and age at first sex.
[b]Adjusted for barrier contraceptive use, age, and age at first use.

HPV-positive women having one or two sex partners and adjusting for age, age at first sex, and duration of OC use, the aOR for SIL risk and duration of barrier methods was 0.79 (95% CI 0.55, 1.14), whereas the aOR among those with three or more sex partners was 0.91 (95% CI 0.84, 0.98). The p value for the Breslow-Day test for homogeneity of the OR across strata of number of sex partner of 0.41 did not indicate that aOR differed significantly by number of lifetime sex partners.

DISCUSSION

Our finding that barrier method use may reduce the risk of SIL development among HR-HPV-positive women is consistent with the literature[12] and is important, as it suggests that increased duration of barrier method use may be particularly useful in preventing SIL development even when women are HR-HPV positive. We found that first barrier method use earlier in one's life (<age 16) was associated with an increased risk of LSIL, whereas a later age at first barrier method use was associated with a reduced risk, particularly for HSIL, even when adjusting for the age at first sexual intercourse. Women beginning sexual activity earlier may be less likely to use effective methods first (barrier methods). Early intercourse may be so strongly correlated with early barrier method use that we cannot remove the residual confounding effect of age at first intercourse. However, we observe that when controlling for duration of OC use and age at first sex, longer duration of barrier method use is associated with a reduced SIL risk among HR-HPV-positive women. Consistent protection of the cervix by a barrier method (primarily condoms in these data) may confer protection even when the woman is already HR-HPV positive because the cervix is not repeatedly exposed to an HR-HPV-positive partner. This finding is important as it suggests that consistent condom use may protect a woman from developing cervical neoplasia perhaps by decreasing the chances of additional HR-HPV exposure. Undoubtedly, our method of barrier method use is misclassified. We cannot establish that partners of women used condoms consistently (during each sex act) and that condoms did not break. We have a general measure of barrier method use by age at first and last use as well as duration of use. We hypothesize, however, that longer-duration condom users may be more consistent users, thus, longer-duration barrier method use may be associated with a reduced risk of SIL, particularly among HR-HPV-positive women.

We did not find that OC use was consistently associated with SIL risk. This finding is consistent with several past studies addressing SIL,[13,14,16–18,24] yet differs from several others.[9,15,20–22,25] In a large case-control study of cervical intraepithelial neoplasia (CIN) among young women (<40 years of age), Cuzick et al.[20] found that shorter duration of OC use was associated with SIL risk. Although the majority of case-control or cohort studies did not conduct analyses by HR-HPV strata, Kjaer et al.[12] were able to conduct such a stratified analysis and found that early age at first use of OC (≤16 years of age) was associated with an increased risk of SIL only among HPV-negative women. Longer duration of OC use was not associated with SIL risk by HR-HPV strata. Many of the studies finding an association between longer-duration OC use and cervical neoplasia specifically addressed HSIL or invasive cancer.[3,21–22,25] We had few women with higher-grade SIL lesions.

Our finding that injectable contraception was not associated with an increased risk of HSIL or LSIL is consistent with the existing literature. As reviewed by LaVecchia,[44] injectable contraceptives have not been consistently linked to CIS or ICC,[45–47] yet few studies have addressed injectable contraception and SIL risk. Like Mascarenhas et al.,[48] we did not find that Norplant use was associated with SIL risk, yet caution must be applied in evaluating our findings for Norplant use as so few women (6%) used Norplant beyond 2 years. Larger studies with longer follow-up periods are needed to address this question adequately.

In these data, we do not find racial differences in risk of HSIL or SIL. This may be a function of our including only low-income women. If racial differences in risk of SIL exist, the reasons for the differences are likely to be a function of differences in risk of exposure or likelihood of being detected as having disease—not in biological differences between races.

This study has several limitations. Our study power is limited because of the anticipated large proportion of women using OC (80%) and the smaller proportions using injectables (20%) or Norplant (8%) and for the HSIL subanalysis. However, we do have >80% power to detect a 2-fold difference in LSIL risk for OC use, barrier

method use, and injectable contraceptive use. We did not ask women about the specific dose of OC and, therefore, cannot assess its association with SIL risk. When we began this study, Digene's Hybrid Capture II was not available. Hybrid Capture I is less sensitive and specific than Hybrid Capture II and certainly less sensitive than PCR-based methods of HPV detection. The misclassification introduced by our using this less sensitive and specific measure of HR-HPV positivity is likely to affect HPV infection with low viral load (those not strongly positive). With additional funding, we plan to reanalyze the HR-HPV results using Hybrid Capture II.

This study has important methodological strengths also deserving mention. Cases and controls were sampled from the same population, low-income women seeking family planning services. Thus, the potential for selection bias in this case-control study is reduced. We collected cervical samples and can control for the potentially confounding or modifying effect of HR-HPV positivity on SIL risk. We assessed the association between SIL risk and the range of contraceptive methods currently available and controlled for the potentially confounding effect of other method use (specifically barrier method use when assessing hormonal methods) in logistic regression models. Finally, we add to the existing literature by providing one of the first studies to explore Norplant use and SIL risk using a case-control design and controlling for HR-HPV positivity. Based on these data, we do not find that any of the range of contraceptive methods assessed was associated with an increased SIL risk.

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