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Recent Intrauterine device use and the risk of precancerous cervical lesions and cervical cancer

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Abstract

Objective—Understanding the effect of contraceptives on the development of precancerous lesions of the cervix and cervical cancer may provide information that is valuable to women in contraceptive decision-making. The purpose of this study was to evaluate the association between recent intrauterine device (IUD) use (by type) and cervical intraepithelial neoplasia 2, 3, adenocarcinoma in situ or cancer (CIN2+ or CIN3+).

Study Design—Case-control study of 17,559 women age 18–49 with incident CIN2+ cases and 5:1 age-matched, incidence-density selected controls (N=87,378) who were members of Kaiser Permanente Northern California Healthcare System from 1996–2014. Recent IUD use, within 18 months prior to index, was the exposure of interest.

Results—We identified 1,657 IUD users among the cases and 7,925 IUD users among controls. After adjusting for sexually transmitted infection testing, smoking, HPV vaccination, hormonal contraceptive use, parity, race and number of outpatient healthcare system visits, IUD use was associated with an increased rate of CIN2+ [rate ratio (RR) 1.12, 95% confidence interval (1.05–1.18), p<0.001] but not CIN3+ [RR 1.02 (0.93–1.11), p=0.71]. Levonorgestrel-IUD use was associated with an increased rate of CIN2+ [RR 1.18 (1.08–1.30), p<0.001] but not CIN3+ [RR 1.05 (0.91–1.21), p=0.48]. Copper-IUD use was not associated with CIN2+ [RR 0.88 (0.75–1.04), p=0.13] or CIN3+ [RR 0.81 (0.64–1.02), p=0.07].

Conclusion—Recent IUD use had variable weak associations with CIN2+ but was not associated with increased risk of CIN3+.

Introduction

Infections with high-risk human papillomavirus (HPV) types, especially persistent infections, are necessary for the development of high-grade precancerous cervical lesions. These lesions are known as cervical intraepithelial neoplasia (CIN) grades 2 and 3, and adenocarcinoma *in situ* (AIS). If undetected and untreated, precancerous lesions can progress to cervical cancer [1].

Intrauterine devices (IUDs) are associated with inflammation in the genital tract [2–4] and they may alter the natural history of HPV infections, including development of cervical cancer. Two large meta-analyses found a decreased risk of cervical cancer associated with IUD use [5–6] while other studies have shown no association between IUD use and cervical cancer [7–11]. These studies were limited by use of an ever/never classification of IUD exposure and therefore little is known about more proximal relationships between IUD use and development of precancerous cervical lesions and cervical cancer. Only one of these studies reported the types of IUDs used, and given the time frame, they likely primarily included inert and copper-containing devices. The effect of IUD by type, particularly IUDs that release the hormone levonorgestrel (LNG), on development of cervical cancer is not well understood. There is some evidence to suggest a possible association between hormonal contraceptive exposure and increased risk of cervical cancer, particularly with long durations of combined hormonal contraceptive use (10 years) or injectable contraceptive use (5 years) [12–13]. This perceived association could be due to selection bias since hormonal contraception implies sexual activity and HPV is a sexually transmitted infection.

Women of reproductive age choose between a number of contraceptives during a time in life when HPV infections are very common. Understanding the effect of contraceptives on the natural history of HPV infection, and subsequent development of precancerous lesions of the cervix and cervical cancer, may provide information that is valuable to women in contraceptive decision-making. The question remains whether IUDs are associated with decreased risk of cervical cancer, and if so, the effects of IUDs on the chain of events from HPV infection to cervical cancer. The goal of this study was to evaluate the association between recent IUD use (by type) and high-grade precancerous cervical lesions (CIN2, CIN3 and AIS) and cervical cancer (collectively known as CIN2+ or CIN3+).

Materials and Methods

We conducted a case-control study of women in the Kaiser Permanente Northern California (KPNC) health system from 1996 – 2014. This is a secondary analysis of data from a study of the effect of immunosuppression on cervical cancer risk described elsewhere in detail [14]. For this analysis, cases were defined as women aged 18–49 years with biopsy-proven

CIN2, CIN3, AIS or cervical cancer. Cases had a first diagnosis of CIN2+ between 7/1/1996 and 6/30/2014, had at least 18 months of continuous enrollment in the health system prior to first CIN2+ diagnosis and had a cytology test within 12 months prior to the CIN2+ diagnosis. Only the first CIN2+ diagnosis was considered. Controls were women aged 18–49 years selected from the KPNC database with cytology screening and without a diagnosis of CIN2+ as of December 31st of the year of CIN2+ diagnosis of the matched case (index date). Incidence density sampling was used to select controls. Five controls were matched to every case (1:5) on age, cytology test in the system less than or equal to 12 months prior to case's CIN2+ diagnosis, years in the health plan (+/−1 year), and date of first health plan cytology test (+/−1 year). Women who underwent a total hysterectomy (including removal of the cervix) prior to the index date were excluded. CIN2+ was defined as a pathologic diagnosis of CIN2, CIN2/3, High grade squamous intraepithelial lesion (HSIL), CIN3, AIS or cervical cancer (adenocarcinoma, squamous cell carcinoma, or other cancer of the cervix). CIN3+ was defined as a pathologic diagnosis of CIN3, AIS or cervical cancer. Only histologic diagnoses were included; cytologic diagnoses were not.

Recent IUD use (exposure) was defined as IUD use for at least one month or more in the 18-month period prior to the diagnosis of CIN2+ (for cases) or the 18-month period prior to the index date of the matched case (for controls). We chose one month of use or more to capture any recent use. Ever using an IUD was defined as IUD use at any time prior to the index date while enrolled in the KPNC healthcare system.

We stratified our analysis based on type of IUD: copper or 52 mg LNG-IUD. A 13.5 mg LNG-IUD was introduced in 2013 but was uncommonly used in our cohort. Thus, we excluded women using this IUD.

Data sources used to identify IUD use in the electronic medical record (EMR) were (1) procedure codes for insertion, removal, reinsertion and (2) diagnostic codes for insertion, removal, reinsertion, IUD check/surveillance and (3) pharmacy prescription codes from for IUDs. IUD start and stop dates were identified. If the first event identified was an IUD removal or IUD check, then the IUD start date was set to the date the woman started enrollment in the health system and the IUD stop date was set to the removal event date. All unique episodes with IUD start and stop dates were recorded.

IUD type was ascertained using prescription and procedure codes. If we were unable to ascertain IUD type used, we categorized the IUD as unknown type. Prior to 2006 IUD type was not reliably recorded by prescription codes in the EMR. It should be noted that the majority of IUDs prior to 2001 in our system were copper-IUDs since the commonly used LNG-IUD was not introduced in our system until 2001.

Potential confounders defined a priori were ascertained including being screened for a chlamydia, gonorrhea, syphilis and/or herpes simplex infection (a possible proxy for new sexual partners) in the past 18 months, smoking status (in 18 months), HPV vaccination (ever), and other contraceptive use (in 18 months)(combined oral contraceptive pills, other combined hormonal contraceptives (patch and ring), and progestin-only contraceptives (progestin-only implant, injectable Depot medroxyprogesterone acetate, and the progestin-

only pill)), Parity >=3 (lifetime), Race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other, unknown) and number of outpatient visits in the healthcare system (visits/ year in last 18mths prior to index date). Pharmacy records were used to identify hormonal contraceptive use other than IUDs. Variables categorized as "ever" occurred any time prior to the index date while enrolled in the healthcare system.

A secondary analysis was done restricted to women who used contraception or an IUD. This analysis excluded women who used no contraception because they may be at lower risk for HPV acquisition due to less sexual activity and higher condom use.

Conditional logistic regression was used to calculate odds ratios, which provide an unbiased estimate of the rate ratio when incidence density sampling is used.

This study was approved by the institutional review boards at the University of California San Francisco and KPNC prior to beginning the analysis, and included waivers of informed consent.

Results

We identified 17,559 cases, women age 18–49 with incident CIN2+ and 87,378 5:1 age-matched, incidence-density selected controls who were members of KPNC between 1996–2014.

There were several notable baseline differences of >5% between groups: cases were more likely to be white (51% vs 44%), to smoke cigarettes recently (19% vs 13%), or ever (28% vs 21%). (Table 1).

Among the cases, there were 3,080 diagnoses of CIN2, 4,706 diagnoses of CIN2/3 and HSIL, and 8,914 diagnoses of CIN3. There were 859 cancers. There were 1,657 IUD users among the cases and 7,900 IUD users among controls. (Table 2).

After adjusting for sexually transmitted infection testing, smoking, HPV vaccination, other hormonal contraceptive use, parity, race and number of outpatient healthcare system visits, IUD users had an increased rate of CIN2+ [rate ratio (RR) 1.12, 95% confidence interval (CI) (1.05–1.18), p<0.001] but not CIN3+ [RR 1.02 (0.93–1.11), p=0.71] compared to non-IUD users. LNG-IUD use was associated with an increased rate of CIN2+ [RR 1.18 (1.08–1.30), p<0.001] but not CIN3+ [RR 1.05 (0.91–1.21), p=0.48]. Copper-IUD use was not associated with CIN2+ [RR 0.88 (0.75–1.04), p=0.13] or CIN3+ [RR 0.81 (0.64–1.02), p=0.07] (Table 3).

IUD use was associated with an increased rate of CIN2 [RR 1.22 (1.06–1.40), p=0.006] but not CIN3 [RR 1.03 (0.94–1.13), p=0.53]. LNG-IUD use was associated with an elevated risk of CIN2 [RR 1.44 (1.19–1.74), p<0.001] but not CIN3 [RR 1.06 (0.94–1.20), p=0.10]. Copper-IUD use was not associated with CIN2 [RR 1.09 (0.76–1.56), p=0.65] or CIN3 [RR 0.82 (0.64–1.04), p=0.08].

Ever using an IUD was associated with an increased rate of CIN2+ [RR 1.09 (1.03–1.16), p=0.002] but not CIN3+ [RR 0.98 (0.90–1.07), p=0.64]. Compared to using contraceptives

other than IUDs, IUD use was not associated with risk of CIN2+ [RR 0.98 (0.88–1.09), p=0.70] or CIN3+ [RR 0.94 (0.80–1.10), p=0.42].

Discussion

We found variable associations between IUD use and cervical pre-cancer and cancer. When stratified by IUD type, LNG-IUD use was associated with CIN2+ but not CIN3+. Copper-IUD use was not associated with pre-cancer or cancer.

It is unclear whether the observed association between IUD use and CIN2+ is causal or whether residual unmeasured confounders account for the observed association (i.e., differential sexual activity, and therefore differential risk for HPV, between IUD users compared and non-users). Confounding often accounts for weak associations in observational studies [15]. We adjusted for STI testing as a marker of new sexual partners and HPV exposure, but this is a not a validated marker of exposure. KPNC members represent a well-screened population overall so it is unlikely that there are significant differences in screening, treatment or diagnosis for women with and without IUD use [16]. When only non-IUD contraceptive users were compared to IUD users, excluding non-contraceptive users, the association between CIN2+ and IUD use was no longer seen which supports the possibility of residual confounding.

The association we found between hormone-containing LNG-IUDs and CIN2+ continue to raise the question of whether there may be a small deleterious effect of contraceptive hormones on development of cervical pre-cancer. There has been an association observed between hormonal contraceptives and both CIN3 and cervical cancer [12,13,17] but whether these observations are causal has been questioned [18]. Whether contraceptive hormones, either ethinyl estradiol or progestins, affect progression to CIN among women with persistent HPV infection is unknown and has been highlighted as a priority area for research [19].

The effect of progestin-only contraceptives, and the differences between local and systemic delivery of progestin hormones, on risk of cervical cancer is poorly understood. While the direct effect of LNG on cervical cancer has not been well studied, a small association has been seen between cervical cancer and injectable contraceptive use (5 years or more), although this conclusion is based on limited published data [12,13]. In addition, a retrospective cohort study of new IUD users who had HPV infections found that copper IUD users were more likely to clear HPV infections than LNG-IUD users [(70% versus 42% (p=0.04)]. The authors suggested that the anti-inflammatory properties of LNG may inhibit HPV clearance [20]. Some progestins have effects on immune parameters that alter susceptibility to viral infections including effects on innate anti-viral factors such as human B-defensins, and on pro-inflammatory chemokines and cytokines [21]. Since HPV clearance depends on cellular immunity, it is possible that progestin exposure could increase or decrease HPV clearance.

We found that the risk of CIN2 was elevated among recent LNG-IUD users but the risk of CIN3 was not. As CIN2 is in the low grade spectrum, this suggests a perturbation on the

HPV infection/regression end of the spectrum, not on the carcinogenic end of the spectrum, which is further reassurance that IUDs are safe for women with HPV-related disease. While power may be limited when looking at associations between IUD use and CIN2 or CIN3 alone, the magnitude of the measure of association is still meaningful and the reasonably narrow confidence intervals would suggest a moderate degree of precision.

Two large meta-analyses demonstrated a statistically significant decrease in cervical cancer associated with IUD use; women who reported ever using an IUD had a decreased likelihood of being diagnosed with cervical cancer compared with never users in both analyses [5,6]. Many studies included adjusted for self-reported number of lifetime cytology (Pap) tests. Given the timing and location of the studies included, the IUDs used were most likely almost exclusively copper-IUDs. We also adjusted for cervical cancer screening thereby decreasing potential screening bias. Unlike these meta-analyses, our data do not provide clear support for the hypothesis that copper-IUD use decreases the risk of cervical dysplasia or cancer. There was a trend towards decreased risk of CIN2+ among copper-IUD users in our study. Therefore, it is possible that there is a modest protective effect of copper-IUDs and this is an area for future research.

A prospective multi-center European cohort study showed no association between ever using an IUD and CIN3+, but there was a trend towards a protective effect of IUD use [OR 0.70, (0.4–1.1)]. In a nested case-control study of HPV sero-positive women, IUD use was associated with a statistically significant decrease in the risk of CIN3+ [OR 0.70 (0.5–0.96)] [10]. We were unable to assess the effects of IUD use on CIN2+ restricted to HPV positive women. Protection against precancerous lesions of the cervix in HPV-infected women is a potential non-contraceptive benefit of the IUD that warrants further research.

Two studies have evaluated the association between IUD (by duration of use) and cervical cancer. One found that 5 years of IUD use was protective against cervical cancer [OR 0.3 (0.2–0.8)] while < 5 years was not [OR 0.6 (0.3–1.1)] [22] while the other found no association between cancer and 5 years IUD use [OR 1.29 (0.83–2.03)] [23]. We were unable to assess the influence of duration of IUD on CIN2+.

The strengths of our study are the large sample size, utilization of a population that is well screened for cervical cancer, and the comprehensive EMR used by the health system. In addition, we identified women with IUD use proximal to the development of CIN2+, whereas most previous studies were limited by use of an ever/never classification of IUD exposure.

Our study has several limitations. We were unable to ascertain IUD type used in 46% of IUD users, limiting our power to assess effect by IUD type. Another limitation of our study is that we are unable assess the association between IUD use and CIN2+ by duration of IUD use. Some evidence suggests a protective effect only when the IUD was used for 5 years or more [22]. Our study included women who may have had a short time of IUD exposure and thus may not have had time for a conferred benefit to manifest. We chose to include women who had any recent IUD use because one proposed mechanism for the protective effect of IUDs on cervical cancer is the hypothesis that the transformation zone is manipulated during IUD

placement eliciting an immune response that promotes clearance of HPV and pre-cancerous lesions [24]. In addition, we were unable to ascertain, and therefore adjust for, some non-hormonal contraceptive use (such as condoms) when women buy products over the counter. Finally, we were unable to ascertain the effect IUDs on CIN2+ restricted to women who tested positive for HPV limiting our ability to isolate the effect of IUDs on progression of HPV to CIN2+.

If the observed association between the LNG-IUD and CIN2+ is causal, the true attributable risk is likely small. Furthermore, LNG-IUD use was associated with CIN2, a transient infection, but not CIN3, a high grade pre-cancer. The lack of association between LNG-IUDs and CIN3+ suggests that there may not be a clinically meaningful harmful effect. The lack of association between IUD use and CIN2 when compared to other contraceptive use only suggests residual confounding or bias related to sexual behavior may be present in our primary analysis. Given the clear benefits of highly effective long-acting contraception, these findings should not be used to limit the use of all types of IUDs among women with cervical dysplasia or at risk for cervical dysplasia. The association between LNG-IUDs and CIN2+ warrants further investigation. It may have clinical importance for contraceptive counseling if this finding is shown to be consistent across other studies and other populations.

Acknowledgments

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Implications

Recent Levonorgestrel-IUD use may be associated with CIN2, a lesion with a high rate of regression, but not CIN3, which is considered a true pre-cancerous lesion. The observed association between levonorgestrel-IUDs and CIN2+ was modest but warrants further investigation. It may have clinical importance for contraceptive counseling if this finding is shown to be consistent across other studies and other populations.

Table 1

Baseline characteristics, cases with cervical intraepithelial neoplasia grade 2 or worse cases and matched controls, Kaiser Permanente, 1996–2014

Characteristic	Cases N=17,559	Controls[2] n=87,378
Mean age1 (SD), years	32.4 (8.0)	32.4 (7.9)
Mean years prior membership[1] (SD)	6.1 (4.2)	6.3 (4.3)
Index year[1], %		
1996–2000	18.8	18.8
2001–2005	24.0	23.9
2006–2010	34.5	34.5
2011–2014	22.8	22.8
Mean outpatient visits per year (SD)	7.5 (6.0)	6.9 (5.4)
Race/ethnicity, %		
White	51.3	44.2
Black/African-American	8.3	8.9
Hispanic	20.1	21.2
Other	17.0	19.7
Unknown	3.4	6.1
Smoking		
Recent[3], %	19.2	12.5
Ever, %	27.6	20.7
Sexually transmitted infection[5]		
Recent3, %	4.1	2.5
Ever, %	12.4	8.2
Tested for Sexually transmitted infection[4]		
Recent[3], %	50.8	48.7
Ever, %	78.3	77.1
3 or more live births, %	9.4	9.3
Any prior HPV vaccination (all patients),%	2.5	2.8
Any prior HPV vaccination (eligible[5] patients), %	9.9	11.1

HPV, human papillomavirus; SD, standard deviation

[1]Matching variable.

[2]P<0·05 for all variables comparing cases and controls based on univariate conditional logistic regression models. Not computed for matching variables.

[3]Within 18 months prior to index

[4]Herpes, gonorrhea, syphilis, chlamydia

[5]Index 2006 and age 26 years as of 1/1/2006

Table 2

Frequencies of Contraception Use

	Cases N=17,559 (%)	Controls N=87,378 (%)
Within the past 18 months		
No IUD or hormonal contraception	7140 (40.7)	41.707 (47.7)
Any IUD	1657 (9.4)	7900 (9.0)
Copper	184 (1.1)	1111 (1.3)
Unknown	758 (4.3)	3641 (4.2)
LNG	715 (4.1)	3148 (3.6)
Any hormonal contraception[1]	8762 (49.9)	37,771 (43.2)
Combined oral contraceptives	7063 (40.2)	29,856 (34.7)
Progestin-only pills	1080 (6.15)	5341 (6.1)
Patch and ring	276 (1.6)	1127 (1.3)
Injectable	302 (1.7)	1198 (1.4)
Implant	3 (<1)	25 (<1)
Cervical cap and diaphragm	36 (<1)	217 (<1)
Ever		
No IUD or hormonal contraception	4340 (24.7)	25,364 (29.0)
Any IUD	1901 (10.8)	9074 (10.4)
Copper	215 (1.2)	1256 (1.4)
Unknown	912 (5.2)	4418 (5.1)
LNG	774 (4.4)	3400 (3.9)
Any hormonal contraception	11,318 (64.5)	52,940 (60.6)
Combined oral contraceptives	8813 (50.2)	40,508 (46.4)
Progestin-only pills	1562 (8.9)	8292 (9.5)
Patch and ring	329 (1.9)	1446 (1.7)
Injectable	543 (3.1)	2231 (2.6)
Implant	14 (<1)	81 (<1)
Cervical cap and diaphragm	53 (<1)	373 (<1)

[1] Combined oral contraceptive pills, other combined hormonal contraceptives (patch and ring), and progestin-only contraceptives (progestin-only implant, injectable Depot medroxyprogesterone acetate, and the progestin-only pill)

[2] Combined oral contraceptive pills and other combined hormonal contraceptives (patch and ring)

Table 3

Rate ratios of CIN 2+, CIN 3+ and cervical cancer for recent IUD use within the past 18 months, by type

	Unadjusted[1]		Adjusted[1]	
	RR (95% CI)	P	RR (95% CI)	P
CIN2+				
IUD use				
any	1.05 (0.99–1.11)	0.09	1.12 (1.05–1.18)	<0.001
no IUD use (reference)	1.0		1.0	
IUD type				
copper	0.83 (0.71–0.98)	0.02	0.88 (0.75–1.04)	0.13
unknown	1.04 (0.96–1.13)	0.33	1.12 (1.03–1.21)	0.009
LNG	1.15 (1.05–1.25)	0.002	1.18 (1.08–1.30)	<0.001
no IUD use (reference)	1.0		1.0	
CIN3+				
IUD use				
any	0.97 (0.89–1.05)	0.41	1.02 (0.93–1.11)	0.71
none (reference)	1.0		1.0	
IUD type				
copper	0.77 (0.61–0.97)	0.03	0.81 (0.64–1.02)	0.07
unknown	0.98 (0.87–1.10)	0.71	1.05 (0.94–1.18)	0.38
LNG	1.03 (0.90–1.18)	0.70	1.05 (0.91–1.21)	0.48
no IUD use (reference)	1.0		1.0	
Cancer				
IUD use				
any	1.30 (0.84–2.00)	0.23	1.28 (0.82–1.99)	0.28
none (reference)	1.0		1.0	
IUD type				
copper	1.40 (0.46–4.30)	0.55	1.27 (0.40–3.96)	0.69
unknown	1.16 (0.65–2.07)	0.62	1.18 (0.65–2.12)	0.59
LNG	1.54 (0.75–3.20)	0.24	1.47 (0.71–3.06)	0.30
no IUD use (reference)	1.0		1.0	

[1] Rate ratios obtained from conditional logistic regression models. Adjusted models include terms for smoking, hormonal contraceptive use, race/ethnicity, tested for sexually transmitted infections, parity >=3, prior outpatient visits

Table 4

Rate ratios of CIN 2+, CIN 3+ and cervical cancer for IUD use

	Unadjusted[1]		Adjusted	
	RR (95% CI)	**P**	**RR (95% CI)**	**P**
CIN2+				
IUD use, ever				
any	1.05 (0.96–1.11)	0.07	1.09 (1.03–1.16)[1]	0.002
no IUD use (reference)	1.0		1.0	
CIN3+				
IUD use, ever				
any	0.95 (0.87–1.03)	0.17	0.98 (0.90–1.07)[1]	0.64
no IUD use (reference)	1.0		1.0	
CIN2+				
IUD use				
any recent use	0.86 (0.80–0.92)	<0.001	0.98 (0.88–1.09)[3]	0.70
other hormonal contraception[2] (reference)	1.0		1.0	
CIN3+				
IUD use				
any recent use	0.78 (0.71–0.86)	<0.001	0.94 (0.80–1.10)[3]	0.42
other hormonal contraception[2] (reference)	1.0		1.0	

[1] Rate ratios obtained from conditional logistic regression models. Adjusted models include terms for smoking, hormonal contraceptive use, race/ethnicity, tested for sexually transmitted infections, parity >=3, prior outpatient visits

[2] Combined oral contraceptive pills, other combined hormonal contraceptives (patch and ring), and progestin-only contraceptives (progestin-only implant, injectable Depot medroxyprogesterone acetate, and the progestin-only pill)

[3] Rate ratios obtained from conditional logistic regression models. Adjusted models include terms for smoking, race/ethnicity, tested for sexually transmitted infections, parity >=3, prior outpatient visits