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# The Effect of Intrauterine Devices on Acquisition and Clearance of Human Papillomavirus

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## Abstract

**Background—**Previous studies have shown a decrease in cervical cancer associated with intrauterine device use. It has been hypothesized that intrauterine device use may alter the natural history of human papillomavirus infections, preempting development of precancerous lesions of the cervix and cervical cancer, but the effect of intrauterine devices on the natural history of human papillomavirus infection and subsequent development of cervical cancer is poorly understood.

**Objective—**The purpose of this study was to evaluate the association between intrauterine device use and cervical high-risk human papillomavirus acquisition and clearance.

**Study Design—**This is a prospective cohort study conducted between October 2000 and June 2014 among 676 sexually active young women enrolled from family planning clinics in San Francisco, California. Data was analyzed using a Cox proportional hazards model, including time varying indicators of intrauterine device use, and adjusting for fixed and time-dependent predictor variables.

**Results—**A total of 85 women used an intrauterine device at some time during follow up. Among 14,513 study visits, women reported intrauterine device use at 505 visits. After adjusting for potential behavioral confounders, there was no association between intrauterine device use and

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or human papillomavirus acquisition, HR= 0.50 (95% CI 0.20–1.23) p=0.13 or clearance of human papillomavirus infection, HR=1.44 (95% CI 0.76–2.72) p=0.26.

**Conclusions—**Current intrauterine device use is not associated with acquisition or persistence of human papillomavirus infection. Intrauterine device use is safe among women with human papillomavirus infections and at risk for human papillomavirus acquisition. Intrauterine device use may play a role further downstream in the natural history of cervical cancer by inhibiting the development of precancerous lesions of the cervix in intrauterine device -infected women, or enhancing clearance of established precancerous lesions.

### Keywords

IUD; HPV; contraception; STI; cervical cancer; dysplasia

## Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the US [1]. Persistent cervical infection with a high-risk type of HPV [HR-HPV] is necessary for the development of cervical cancer. [2] Although HPV vaccination is the only known intervention to prevent HPV associated precancerous lesions, [3] it has been hypothesized that intrauterine device (IUD) use may alter the natural history of HPV infections, preempting development of precancerous lesions of the cervix and cervical cancer. In fact, a 2011 meta-analysis of 26 studies from around the world demonstrated a statistically significant decrease in cervical cancer associated with IUD use; women who reported ever using an IUD had approximately half the likelihood of being diagnosed with cervical cancer compared with never users after adjusting for lifetime number of screening pap tests. [4] The interpretation of this study is limited since it was cross-sectional and it did not correct for many possible confounders including some sexual and health behaviors. For instance, more intensive screening, diagnosis and treatment among IUD users compared with non-users or differential sexual behavior may still have resulted in differing exposure to HPV between IUD-users and non-users.

However, on a biological level, it is plausible that IUDs may protect against cervical cancer through their association with inflammation in the genital tract, [5] which may result in rapid clearance of infections and/or protection against initial HPV acquisition. Some studies have shown that cytokine levels are elevated in the setting of persistent HPV infections suggesting that recruitment of immune mediators is necessary for clearance of the virus. [6] Conversely, other studies have shown that chronic inflammation in the setting of HPV promotes development of high risk pre-malignant lesions. [7] The effect of inflammation in the genital tract on HPV is complex and there is a paucity of data on the specific effect of IUDs on cervical HPV infection.

The goal of our study was to evaluate the association between IUD use and HR-HPV acquisition and clearance in a large prospective cohort.

## Materials and Methods

This is an analysis of The San Francisco Natural History of HPV Cohort described elsewhere in detail. [8] Briefly, between October 2000 and October 2006, 676 women were enrolled from two family planning clinics in San Francisco, CA. Women ages 13–22 with less than 5 years of sexual experience were included. Women who were immunosuppressed or had a history of ablation or excision of the cervix were excluded. Women were followed until study close in June 2014. Each visit included a speculum examination with collection of cervico-vaginal lavages for HR-HPV testing, and an interviewer-administered questionnaire to obtain information on demographics and sexual behaviors. Samples were obtained yearly, or sooner if a woman was symptomatic, to test for *Chlamydia trachomatis, and Neisseria gonorrhoeae.* HPV testing was done by Linear Array (Roche Molecular Diagnostics, Alameda, CA) and a novel Luminex-based approach, PGMY-LX, which was shown to have a sensitivity and specificity comparable to Linear Array in this population and is described elsewhere in detail. [9] Sexual and substance use behavior and contraceptive use, including IUD use, were assessed by interview-administered questionnaire. IUD use was verified at the time of speculum examination but the type of IUD strings observed were not recorded.

Incident HR-HPV infection was defined as the first visit where HR-HPV DNA was detected following at least two preceding visits in which HR-HPV DNA was not detected. Multiple episodes of acquisition were not allowed for this analysis. Time to HR-HPV acquisition was defined as the time from first visit with no HR-HPV DNA detection to first HR-HPV detection.

HPV clearance was defined as having two visits negative for all HR-HPV types following a visit with a positive HR HPV type. Time to HR-HPV clearance was defined as the time from first HR-HPV DNA detection to first of two negative visits. Prevalent infections detected at baseline were included in the clearance analysis but not the acquisition analysis.

Initial analyses focused on descriptive comparisons of baseline characteristics between women classified as ever users and non-users of IUDs (or women who did not use an IUD ever during study follow-up). Significance testing was based on the chi-squared/Fisher's exact test for categorical and the t-test/Wilcoxon rank sum test for continuous characteristics.

We considered two complementary approaches to analyses investigating the association between IUD use and HPV outcomes: The first was based on a "new user" design. [10] A new-user design identifies all of the participants in a population who start a course of treatment and study follow-up begins at the same time as initiation of the treatment. The goal of this approach is to mimic trial assignment. The rationale is to attempt to balance possibly time varying confounding factors between users and non-users, similar to what might be achieved in a randomized trial. Results from observational data analyzed using a new users design has been shown to be similar to data from randomized trials. [10] We matched each IUD user to 5 women who were not using IUDs based on user's age and date of IUD initiation. IUD initiation date was estimated within 3 months. IUD users contribute

data beginning at the time that they initiated their IUD (or on entry into the study if they had an IUD at baseline).

The outcomes were clearance for those who were HPV positive and acquisition for those who were HPV negative following initiation of the IUD (or start date for matched control). Between-group comparisons of cumulative outcome risks were based on Kaplan-Meier estimates and log-rank tests.

Because the new-user approach uses only a subset of available data, and does not allow explicit control for time variation in IUD use and other variables potentially related to HPV outcomes, we also analyzed data from the entire cohort using a Cox proportional hazards model, including time varying indicators of IUD use, and adjusting for fixed and time-dependent predictor variables including age at baseline, age at first intercourse, STI during study follow up, HPV vaccination status, condom use since last visit, new partner since the last visit, combined hormonal contraceptive use (pill, patch and ring), smoking since last visit and pregnancy.

Statistical analysis was performed using SAS version 9.4 (Cary, NC).

Participants gave written consent according to guidelines approved by the Committee for Human Research, University of California, San Francisco.

## Results

Table 1 describes the baseline characteristics of the entire cohort by IUD use; 591 women never used an IUD and 85 women used an IUD some time during study follow up. Among 14,513 study visits, women reported IUD use at 505 visits.

Women who had used an IUD were slightly younger at enrollment, younger at first intercourse, more likely to have ever been pregnant, more likely to identify as white or latina, and less likely to identify as black, Asian/Pacific Islander, or mixed. There were no other statistically significant differences in baseline characteristics between ever and never users of the IUD.

In the Kaplan-Meier analysis there was a trend towards IUD use being associated with lower HR-HPV acquisition but this difference was not statistically significant (p=0.10) (Figure 1). The biggest difference was seen at around 3 years when 28% of IUD users had acquired a new HR-HPV infection versus 42% of non-IUD users had acquired a new HR-HPV infection.

Similar to the Kaplan-Meier analysis, in the unadjusted cox proportional hazards model there was a trend towards IUD use being protective against HPV acquisition (Table 2). Women with an IUD had 0.48 times the rate of any HPV acquisition compared to women without an IUD (0.23–1.02; p=0.057). After adjusting for potential confounders (age at baseline, age at first intercourse, STI during study follow up, HPV vaccination status, condom use since last visit, new partner since the last visit, combined contraceptive use, smoking since last visit and pregnancy) the reduced risk of HPV acquisition in IUD users

was not statistically significant although the direction of the association remained the same; HR= 0.50 (95% CI 0.20–1.23) p=0.13.

In the Kaplan-Meier analysis there was no difference in clearance of all HR-HPV infections when comparing IUD users to non-users (p=0.15) (Figure 2). By 5 years, all IUD-users and most of the non-IUD users had cleared their HR-HPV infections. For example, at 5 years 100% of IUD users and 77% non-IUD users had cleared their HPV infection.

There was no association between IUD use and HPV clearance in the unadjusted Cox proportional hazards model HR= 0.75 (95% CI 0.48–1.18) p=0.21 or after adjusting for potential confounders (age at baseline, age at first intercourse, STI during study follow up, HPV vaccination status, condom use since last visit, new partner since the last visit, combined contraceptive use, smoking since last visit and pregnancy) HR=1.44 (95% CI 0.76–2.72) p=0.26 (Table 3). Twenty-four percent of cases included in the clearance analysis were prevalent cases. In a model excluding prevalent cases, after adjusting for the same potential behavioral confounders, there was no association between IUD use and HPV clearance HR = 1.46 (95% CI 0.77–2.75) p=0.24.

To further investigate the apparent difference in the magnitude and direction of the effect of IUD use on HPV clearance between the marginal and adjusted associations presented in Table 3, we conducted a sensitivity analysis in which adjustment covariates were added singly to a model already including IUD use. This revealed that condom use was the only adjustment variable that had an appreciable effect on the estimated hazard ratio for IUD use. However, because of the substantial overlap in the 95% confidence intervals for these two estimates, definitive conclusions about possible confounding are not possible.

## Comment

This study further supports the safety of IUD use among women with HPV infections and at risk for HPV acquisition. Current IUD use was not associated with persistence of HR-HPV infections among women in this cohort. This finding is consistent with other prospective longitudinal studies which also observed no association between IUD use and HPV persistence. [11–14] We also found that current IUD use was not associated with HPV acquisition. It is certainly possible that a larger study might lead to more precise and significant findings supporting that IUD use is protective against HPV acquisition if the direction and magnitude of our estimated effects was maintained.

The strengths of this study include the longitudinal design, which allowed for many women-years of observation, and the fact that the exposure variable (IUD use) was collected prior to determination of the outcome (HPV clearance or acquisition). Also, frequent study visits were conducted allowing for a precise determination of the time dependent exposure and outcome variables, IUD use, HPV acquisition and clearance as well as detailed sexual behavior which allowed us to identify potential confounding factors.

The main limitation of our study was the inability to differentiate between levonorgestrel (LNG) releasing IUDs and copper IUDs. Other studies have suggested that the effect of these IUDs on HPV biology may be different. [15] Our study was conducted among young

women in the US, and most of the IUD use was in the late 2000s, therefore many of our IUD users were likely using LNG-releasing IUDs. Older studies, including the meta-analysis showing that IUDs are associated with decreased risk of cervical cancer,[4] likely included mostly copper IUDs. If only copper IUDs, which evoke a significant inflammatory response,[16] are effective at preventing cervical cancer, then our findings evaluating HPV acquisition for both types of IUD together may underestimate the effectiveness of copper IUDs. In addition, women who ever used an IUD were more likely to have ever been pregnant compared to women who never used an IUD. This suggests that selection bias may limit the generalizability of the findings to nulliparous women. For this reason, previous pregnancy was included in the multivariate model. Previous history of pregnancy, however, was not independently associated with acquisition or clearance of HPV.

If IUDs are, in fact, causally associated with decreased risk of cervical cancer, the question remains as to the precise link(s) in the chain of events within the natural history from HR-HPV infection to cervical cancer that IUDs affect. There are several plausible biological mechanisms by which IUDs may exert a protective effect other than decreased acquisition or enhanced clearance of HPV infections. IUD may play a role further downstream in the natural history by inhibiting the development of precancerous lesions of the cervix in HPV-infected women, or enhancing clearance of established precancerous lesions. As we did not have enough cases of CIN 2/3 in this cohort, we were unable to examine these potential associations.

To our knowledge, this is the first study examining the role of IUD use in incident infection with HPV and viral clearance in a prospective design. Certainly, there appeared to be no harmful effects and trends suggested a possible protective effect. There is a need for future work in larger samples of IUD users to evaluate the effect of IUD use on the precise link(s) in the chain of events of HR-HPV pathogenesis leading to cervical cancer.

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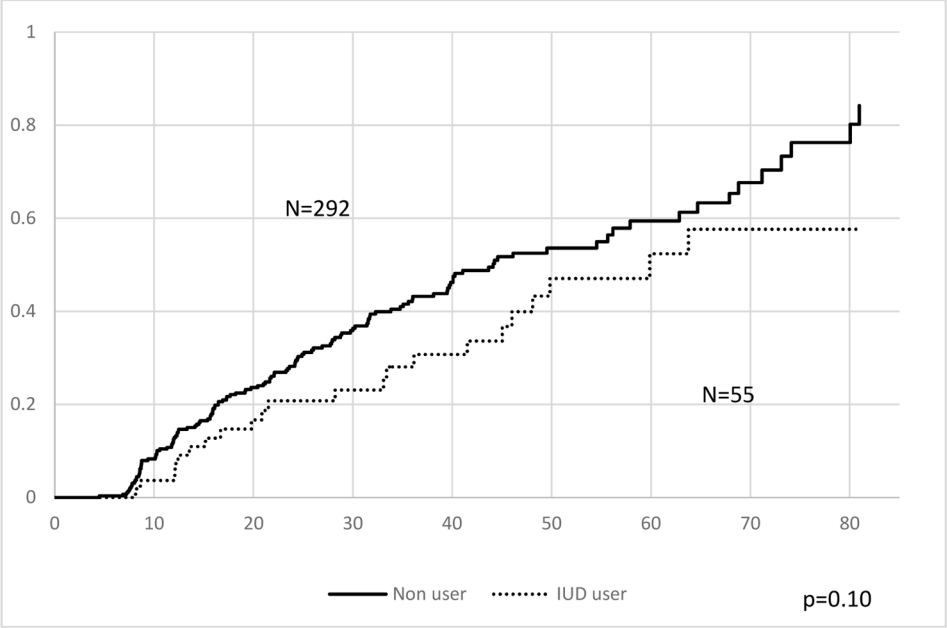


**Figure 1. Time to acquisition of High-risk human papillomavirus (HR-HPV) by Intrauterine device (IUD) use**

Time to HR-HPV acquisition among IUD users compared to non-users. Between-group comparisons of cumulative outcome risks were based on Kaplan-Meier estimates and log-rank tests.

*x-axis is time in months

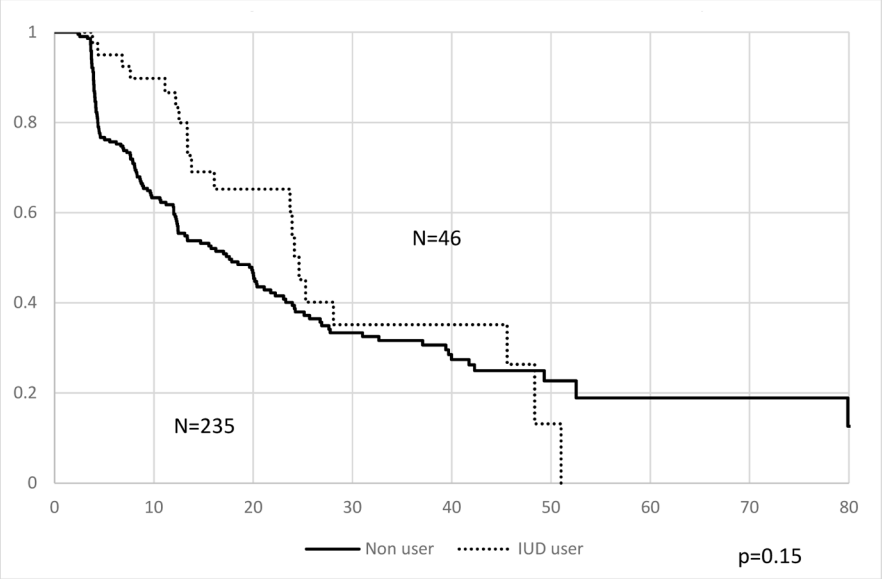


**Figure 2. Time to clearance of High-risk human papillomavirus (HR-HPV) by Intrauterine device (IUD) use**

Time to HR-HPV clearance among IUD users compared to non-users. Between-group comparisons of cumulative outcome risks were based on Kaplan-Meier estimates and log-rank tests.

*x-axis is time in months

## Table 1

Baseline characteristics of IUD using and non-using participants.

| | IUD users (ever) (N = 85) | Never users (N=591) | P-value |
|---|---|---|---|
| **Median age** yrs(IQR) | 17.8 (16.4–18.8) | 18.6 (17.3–19.9) | P<0.001 |
| **Age first intercourse** yrs(IQR) | 15.1 (14.5–15.9) | 16.3 (15.0–17.7) | p<0.001 |
| **Race** (N%) | | | p<0.001 |
| White | 36 (42) | 153 (26) | |
| Latina | 34 (40) | 152 (26) | |
| Black | 7 (8) | 89 (15) | |
| Asian/Pacific Islander | 2 (2) | 177 (30) | |
| Mixed/Other | 6 (7) | 12 (2) | |
| **Previous history of STI[a] (%)** | 22 (26) | 142 (24) | p=0.57 |
| **Ever pregnant (%)** | 32 (38) | 74 (13) | p<0.001 |
| **Lifetime number of sexual partners** (median(IQR)) | 3 (2–6) | 3 (2–6) | p=0.97 |
| **Current smoker (%)** | 21 (25) | 159 (28) | p=0.80 |
| **Condom use always (%)** | 31 (37) | 223 (38) | p= 0.42 |

[a]Neisseria gonorrhoeae or Chlamydia trachomatis

**Table 2**

Acquisition of any incident HR-HPV infection

| Univariable | HR | 95% CI | P-value | aHR | 95% CI | P-value |
|---|---|---|---|---|---|---|
| **IUD-use** | **0.48** | **0.23–1.02** | **0.057** | **0.50** | **0.20–1.23** | **0.13** |
| Age | 0.91 | 0.87–0.95 | <0.001 | 0.89 | 0.84–0.95 | <0.001 |
| Age at first intercourse | 0.98 | 0.94–1.03 | 0.44 | 1.07 | 1.00–1.15 | 0.05 |
| STI during study follow–up | 1.66 | 0.89–3.13 | 0.11 | 1.17 | 0.90–1.51 | 0.24 |
| HPV vaccination (ever) | 1.07 | 0.53–2.14 | 0.85 | 0.79 | 0.34–1.86 | 0.59 |
| Condom use since last visit | 1.02 | 0.84–1.25 | 0.82 | 0.86 | 0.69–1.08 | 0.20 |
| New partner since last visit | 2.14 | 1.66–2.45 | <0.001 | 2.08 | 1.66–2.60 | <0.001 |
| Combined hormonal contraceptive use since last visit | 1.17 | 0.95–1.43 | 0.14 | 1.18 | 0.94–1.47 | 0.16 |
| Smoking since last visit | 1.10 | 0.89–1.36 | 0.36 | 0.91 | 0.72–1.16 | 0.47 |
| History of Pregnancy (ever) | 1.02 | 0.83–1.26 | 0.82 | 1.14 | 0.89–1.44 | 0.30 |

**Table 3**

Clearance of all HR-HPV infections

| Univariable | HR | 95% CI | P-value | aHR | 95% CI | P-value |
|---|---|---|---|---|---|---|
| **IUD-use** | **0.75** | **0.48–1.18** | **0.21** | **1.44** | **0.76–2.72** | **0.26** |
| Age | 0.97 | 0.94–0.99 | 0.04 | 0.96 | 0.90–1.03 | 0.24 |
| Age at first intercourse | 1.02 | 0.97–1.07 | 0.54 | 1.06 | 0.97–1.16 | 0.21 |
| STI during study follow-up | 0.30 | 0.07–1.20 | 0.09 | 0.83 | 0.61–1.12 | 0.20 |
| HPV vaccination (ever) | 0.95 | 0.61–1.47 | 0.82 | 0.58 | 0.23–1.46 | 0.25 |
| Condom use since last visit | 1.08 | 0.88–1.32 | 0.48 | 0.92 | 0.69–1.23 | 0.58 |
| New partner since last visit | 0.92 | 0.73–1.17 | 0.51 | 0.98 | 0.82–1.17 | 0.87 |
| Combined hormonal contraceptive use since last visit | 1.03 | 0.80–1.32 | 0.83 | 0.97 | 0.71–1.33 | 0.86 |
| Smoking since last visit | 0.82 | 0.65–1.04 | 0.11 | 0.89 | 0.65–1.23 | 0.50 |
| History of Pregnancy (ever) | 0.97 | 0.79–1.20 | 0.86 | 1.28 | 0.93–1.76 | 0.13 |