

Relative Risk of Cervical Neoplasms Among Copper and Levonorgestrel-Releasing Intrauterine System Users

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OBJECTIVE: To evaluate the relative risk of cervical neoplasms among copper intrauterine device (Cu IUD) and levonorgestrel-releasing intrauterine system (LNG-IUS) users.

METHODS: We performed a retrospective cohort analysis of 10,674 patients who received IUDs at Columbia University Medical Center. Our data were transformed to a common data model and are part of the Observational Health Data Sciences and Informatics network. The cohort patients and outcomes were identified by a combination of procedure codes, condition codes, and medication exposures in billing and claims data. We adjusted for confounding with propensity score stratification and propensity score 1:1 matching.

RESULTS: Before propensity score adjustment, the Cu IUD cohort included 8,274 patients and the LNG-IUS cohort included 2,400 patients. The median age for both cohorts was 29 years at IUD placement. More than 95% of

the LNG-IUS cohort used a device with 52 mg LNG. Before propensity score adjustment, we identified 114 cervical neoplasm outcomes. Seventy-seven (0.9%) cervical neoplasms were in the Cu IUD cohort and 37 (1.5%) were in the LNG-IUS cohort. The propensity score matching analysis identified 7,114 Cu IUD and 2,174 LNG-IUS users, with covariate balance achieved over 16,827 covariates. The diagnosis of high-grade cervical neoplasia was 0.7% in the Cu IUD cohort and 1.8% in the LNG-IUS cohort (2.4 [95% CI 1.5–4.0] cases/1,000 person-years and 5.2 [95% CI 3.7–7.1] cases/1,000 person-years, respectively). The relative risk of high-grade cervical neoplasms among Cu IUD users was 0.38 (95% CI 0.16–0.78, $P<.02$) compared with LNG-IUS users. By inspection, the Kaplan-Meier curves for each cohort diverged over time.

CONCLUSION: Copper IUD users have a lower risk of high-grade cervical neoplasms compared with LNG-IUS users. The relative risk of cervical neoplasms of LNG-IUS users compared with the general population is unknown.

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Dr. Westhoff is on the Data and Safety Monitoring Board (DSMB) for Bayer and Merck Pharmaceuticals. She also is on the Abbvie advisory board, which does not produce intrauterine devices. She participates in research with the National Institutes of Health (NIH), Contraceptive, Sebela and Medicines 360. Dr. Ryan is employee of Janssen Research and Development, but this work was done under his capacity as adjunct professor at Columbia University and is unrelated to his employment. The other authors did not report any conflicts of interest.

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As early as the 1980s, studies suggested a reduced risk of cervical cancer among women who had used an intrauterine contraceptive. A 2017 systematic review of 17 case-control studies found that intrauterine devices (IUDs) were protective against cervical cancer. The summary odds ratio was 0.64 (95% CI 0.53, 0.77). Those authors suggested that the traumatic manipulation of the cervical canal may clear human papillomavirus (HPV) infection from a combination of acute and chronic inflammatory effects.¹

The studies harmonized for that meta-analysis did not report on IUD type. However, most of those studies collected data in countries and at times when the levonorgestrel-releasing intrauterine system (LNG-IUS) was not yet available. A progesterone-containing IUD, the Progestasert, was registered in

the United States from 1976 to 2001. The Mirena (LNG-IUS) was first registered in Finland in 1990 and in the United States in 2000. Consequently, the studies in the meta-analysis mainly included either copper IUDs (Cu IUDs) or inert IUDs.

The copper ions in Cu IUDs may increase the clearance rate of HPV.² In contrast, intrauterine levonorgestrel exposure may predispose the cervix to HPV infection, which is a precursor of cervical malignancy. Specifically, a decrease in prostaglandin production may suppress local immunity and render the uterus more susceptible to viral infection.² The angiogenesis and increase in matrix metalloproteinase activity reported approximately 6 months after LNG-IUS placement may accelerate the growth of dysplasia.^{3,4} This analysis evaluates the association between LNG-IUS use compared with Cu IUD use and high-grade cervical neoplasms.

METHODS

Observational Health Data Sciences and Informatics is an international, open-science collaborative of more than 220 health care organizations with a mission to improve health through the use of large-scale observational research. Observational Health Data Sciences and Informatics maintains the Observational Medical Outcome Partnership Common Data Model, which is a deep informational model that specifies how to encode and store clinical data in a standard format, enabling standardized analysis methods on data within the Observational Health Data Sciences and Informatics network. The model's schema represents structured data such as patient demographics, visits, conditions, procedures, laboratory results, vitals, and medications. Observational Health Data Sciences and Informatics maintains more than 100 vocabularies and the mappings between them to encode all clinical data. Previous studies have evaluated various clinical data models and have determined Observational Medical Outcome Partnership the "best of breed" for comparative effectiveness research.⁵ The Columbia University Irving Medical Center participates in Observational Health Data Sciences and Informatics and provided an Observational Medical Outcome Partnership database for this analysis. We leveraged the open-source tools provided by Observational Health Data Sciences and Informatics to perform a comparative effectiveness analysis of Cu IUDs to LNG-IUSs with respect to cervical neoplasm incidence.^{6–10}

Columbia University Irving Medical Center's anonymized Observational Medical Outcome Partnership database comprises a mixture of inpatient and outpatient visits, spans a time period of four dec-

ades (1980s–present), and represents a population of 6 million patients. The data in the Observational Medical Outcome Partnership database were extracted from Columbia University Irving Medical Center and New York-Presbyterian Hospital's electronic health record systems. The Columbia University Irving Medical Center Observational Medical Outcome Partnership database used in this analysis was version 5.2 of the Observational Medical Outcome Partnership Common Data Model. The Columbia University Irving Medical Center has institutional approval for use of the Observational Health Data Sciences and Informatics tools (IRB#AAAO7805), however additional IRB approval is not necessary to access anonymized data.

We implemented a retrospective, observational, cohort study that compared a target cohort of Cu IUD to LNG-IUS users. We used the date of a first IUD placement as the index date for the study. All patients had continuous observation in our database for at least 365 days before IUD insertion. We restricted our cohorts to female patients who were 45 years or younger at the time of IUD placement. We excluded women with a history of endometrial or cervical neoplasms or who had a prior IUD placement. By default, women were in the Cu IUD cohort unless documentation of an LNG-IUS appeared in the database. We used a collection of procedure codes, such as SNOMED 65200003 ("Insertion of intrauterine contraceptive device") or CPT 58300 ("Insertion of intrauterine device [IUD]") to identify IUD placement. Whether the IUD placed was a Cu IUD or an LNG-IUS was determined by whether an LNG-IUS was identified by RxNorm codes, such as RxNorm 807283 ("Levonorgestrel 0.000833 MG/HR Intrauterine System").

The outcome was a high-grade cervical neoplasm diagnosis. We chose primary cervical neoplasms that were malignant or had a high association with malignancy, such as cervical intraepithelial neoplasia grade II or III. The outcome of a high-grade cervical neoplasm diagnosis was identified by a condition code, such as SNOMED code 372024009 ("Primary malignant neoplasm of uterine cervix"). We excluded cervical polyps, cervical intraepithelial neoplasia grade I, and metastatic spread of a neoplasm to the cervix. As part of our data-validation process, we correlated the condition code with a biopsy diagnosis.

We used a collection of procedure codes such as SNOMED 171149006 ("Screening for malignant neoplasm of cervix") to identify subsequent cervical screening and HCPCS Q0091 ("Screening Papanicolaou smear; obtaining, preparing and conveyance of

cervical or vaginal smear to laboratory") to identify preventive screening visits.

The time at risk was from 30 days to 15 years after IUD placement. The study window was restricted to all IUD placements that occurred on or after January 1, 2003, to account for a lag between U.S. Food and Drug Administration approval of the LNG-IUS in 2000 and its regular use in our clinical practice. We used an any-use design with no censoring events. Follow-up time was defined by continued observation of the patient in the Columbia University Irving Medical Center database. Observation ended either when a patient developed the outcome or had no further observation data in the Columbia University Irving Medical Center database, which contains observations through December 2018. We excluded any woman who had both a Cu IUD and an LNG-IUS placed during the study period. We also performed a subgroup analysis including only those cervical neoplasm diagnoses that occurred at least 1 year after IUD placement.

To reduce potential confounding due to imbalance between the Cu IUD and LNG-IUS cohorts in baseline covariates, we used propensity score models with a regularized logistic regression. This algorithm determined which among more than 10,000 baseline covariates should be included in the propensity score model. The covariates represented demographic characteristics, prior conditions, drug dispensing, procedures, and visit counts. We stratified or matched patients by propensity score and used a Cox proportional hazards model to determine the relative risk for cervical neoplasms between the Cu IUD and LNG-IUS cohorts. Our methods for reducing confounding are similar to what has been described recently by our research community.¹¹

We executed diagnostics to determine whether the analysis could be appropriately conducted. The diagnostics included propensity score distribution, covariate balance before and after propensity score matching, and estimation for negative controls to assess residual error. Additionally, negative control diagnoses that were unrelated to the exposures were used to evaluate the potential effect of residual systematic error in the study design, and to facilitate empirical calibration of the *P*-value and CI for the exposures and outcome of interest.

Negative control diagnoses were unrelated to IUD exposure and were assumed to be equally distributed between the cohorts. The distribution of effect estimates across all negative controls was used to fit an empirical null distribution, which modeled the observed residual systematic error. The empirical

null distribution was applied to the Cu IUD and LNG-IUS exposure and cervical neoplasm outcome to calibrate the *P*-value. We selected 123 negative control outcomes. We fit a systematic error model and performed CI calibration.¹²

We compared the Cu IUD cohort to the LNG-IUS cohort for the hazards of cervical neoplasm during the time-at-risk by applying a Cox proportional hazards model. Patients were matched on the propensity score by two methods: stratification and 1:1 matching.^{13,14} Propensity score distributions and Kaplan-Meier estimates were plotted.

To validate our findings, we did a manual chart review of a sample of an identified patient database. In accordance with Columbia University IRB approval (Protocol# AAAS5403), we selected 115 patients who had high-grade cervical neoplasms in the Cu IUD and LNG-IUS cohorts in our institution to validate that we had identified Cu IUD users, LNG-IUS users, and high-grade cervical neoplasms accurately. Eighty cases were in the Cu IUD cohort and 35 cases were in the LNG-IUS cohort.

RESULTS

The Columbia University Irving Medical Center database contains a total of 13,362 Cu IUD users and 3,440 LNG-users. We restricted our analysis to patients with at least 365 days of prior observation in this hospital system, which resulted in 9,510 patients in the Cu IUD cohort and 2,418 patients in the LNG-IUS cohort. Among the LNG-IUS users, 97% had received an LNG 52 mg device; conversely, only 3% had received an IUS with a lower LNG dose.

Since 2003, there were a total of 10,674 patients in our study population. Of those, 8,274 patients were in the Cu IUD cohort and 2,400 patients were in the LNG-IUS cohort. Of the 2,400 LNG-IUS users, 2,332 (97.2%) received an LNG 52 mg device. We show a representative group of variables that could be measured and adjusted for those cohorts in Table 1. Among the patients who had an IUD placed during the study period, the total baseline observations (ie, before IUD observation) for the Cu IUD and LNG-IUS cohorts were 72,398.0 and 23,074.4 person-years with mean observation periods of 8.8 and 9.6 person-years per patient, respectively. The median follow-up observation period was 2.8 (0.5–6.5) person-years for the Cu IUD cohort and 2.6 (0.6–5.0) person-years for the LNG-IUS cohort. During follow up, the Cu IUD cohort contributed 32,664.8 person-years and a mean of 3.9 observation years per patient. The LNG-IUS contributed 7,846.9 person-years and a mean of 3.3 observation years per patient. The median age for the

Table 1. Representative Descriptive Baseline Characteristics of the Copper Intrauterine Device and Levonorgestrel Intrauterine System Cohort Patients in the Propensity Score Model

Variable	Before Propensity Score Matching			After Propensity Score Matching		
	Cu IUD Cohort (n=8,274)	LNG-IUS Cohort (n=2,400)	Standardized Difference	Cu IUD Cohort (n=2,039)	LNG-IUS Cohort (n=2,039)	Standardized Difference
Age (y)						
10–19	565 (6.8)	304 (12.7)	−0.2	262 (12.8)	234 (11.5)	0.02
20–29	3,821 (46.2)	1,023 (42.6)	0.08	836 (41.0)	895 (43.9)	−0.07
30–39	3,130 (37.8)	872 (36.3)	0.04	736 (36.1)	727 (35.7)	0.01
40–45	757 (9.1)	200 (8.3)	0.03	205 (10.1)	182 (8.9)	0.04
Black	513 (6.2)	209 (8.7)	−0.10	165 (8.1)	177 (8.7)	−0.02
White	2,097 (25.3)	761 (31.7)	−0.14	622 (30.5)	630 (30.9)	−0.01
Asian	119 (1.4)	51 (2.1)	−0.05	43 (2.1)	44 (2.2)	0.00
Hispanic or Latina	2,648 (32.0)	767 (32.0)	0.47	607 (29.8)	649 (31.8)	−0.04
Not Hispanic or Latina	1,745 (21.1)	723 (30.1)	−0.03	613 (30.1)	601 (29.5)	−0.02
Prior HPV vaccine within 1 y before IUD placement	43 (0.5)	27 (1.1)	−0.07	18 (0.9)	23 (1.1)	−0.02
Prior nonintrauterine hormonal preparations within 1 y before IUD placement	1,272 (15.4)	426 (17.8)	−0.06	385 (18.9)	355 (17.4)	−0.04
Tobacco smoking behavior within 1 y before IUD placement	3,261 (39.4)	1,290 (53.8)	0.49	1,077 (52.8)	1,060 (52.0)	0.02
Positive HPV test result within 1 y before IUD placement	210 (2.5)	59 (2.5)	0.03	38 (1.9)	55 (2.7)	−0.06

Cu IUD, copper intrauterine device; LNG-IUS, levonorgestrel intrauterine system; HPV, human papillomavirus.

Data are n (%) unless otherwise specified. The study period was from 2003 to 2019 in the Columbia University Irving Medical Center database. Covariates that were not in both cohorts were not included.

Cu IUD cohort was 29 (24–35) years and for the LNG-IUS cohort was 28 (23–34) years.

During follow-up, 1,820 (22.0%) Cu IUD users and 797 (33.2%) of LNG-IUS users had a documented IUD removal procedure. A smaller percentage of the Cu IUD cohort had subsequent screening (30.9%) or preventive health visits (22.9%) compared with the LNG-IUS cohort (34.8% and 29.0%, respectively). In both cohorts, more than 50% of the patients had unknown race and more than 35% had unknown ethnicity. Consequently, the accuracy of adjusting for confounding by race or ethnicity was limited.

Without adjusting for this or other confounding variables, a total of 114 patients in our study population had a cervical neoplasm diagnosis. Of those, 77 of 8,247 women in the Cu IUD cohort (0.9%) and 37 out of 2,400 women in the LNG-IUS cohort (1.5%) developed a high-grade cervical neoplasm. Seventy-one (0.9%) of 8,247 women in the Cu IUD cohort and 37 (1.5%) of 2,410 women in the LNG-IUS cohort had diagnoses of cervical intraepithelial neoplasia grades II or III. There were two (0.0%) cases of primary invasive cervical cancer in the Cu IUD cohort, but none in the LNG-IUS cohort. In our subgroup analysis of patients who developed

high-grade cervical neoplasms at least 365 days after IUD placement, 66 (0.8%) patients in the Cu IUD cohort and 33 (1.4%) patients in the LNG-IUS cohort had a high-grade cervical neoplasm.

To balance the cohorts for known and unknown possible confounding variables, we used a propensity score model. The model calculated that 7,118 patients in the Cu IUD cohort and 2,175 patients in the LNG-IUS cohort, which is 76% of the study population, were in equipoise. The overlapping propensity scores in our study population are represented in purple (Fig. 1). Only six of the 123 negative controls were outside of the null distribution (Figs. 2 and 3). After propensity score adjustment, an algorithm filtered four Cu IUD users and one LNG-IUS user from the analysis because of insufficient data.

For the propensity score stratification analysis, the algorithm balanced 7,114 Cu IUD users and 2,174 LNG-IUS users over 20,086 baseline covariates, to minimize residual confounding. No covariate differed by more than an absolute SD of the mean greater than 0.11 (Fig. 3A). In the analysis limited to the individuals who were balanced by propensity score stratification, 75 of 7,114 Cu IUD users (1.1%) and 37 of 2,174 LNG-IUS users (1.7%) developed

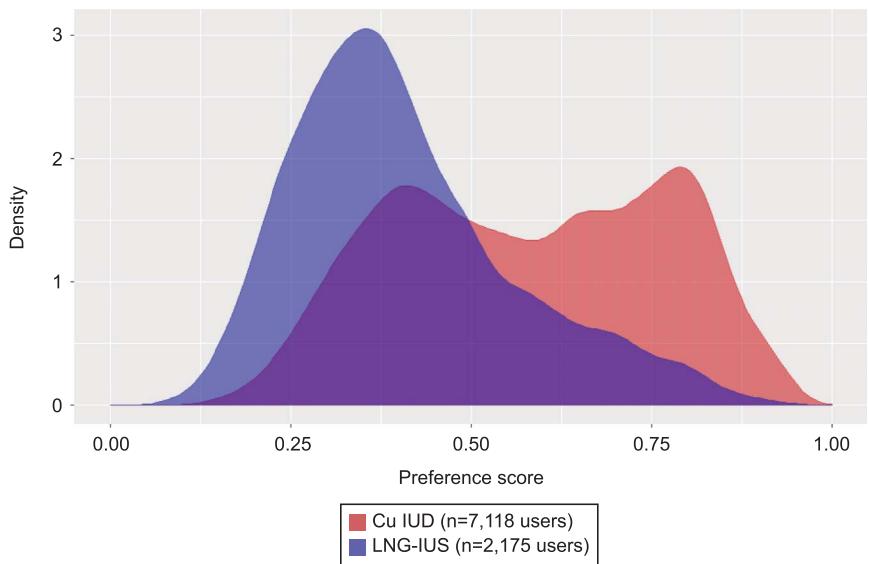


Fig. 1. Propensity score distribution of copper intrauterine device (Cu IUD) and levonorgestrel intrauterine system (LNG-IUS) users. Area under the curve: 0.76; 75.5% is in equipoise.

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a cervical neoplasm. The incidence rates for the Cu IUD and LNG-IUS cohorts were 2.4 (95% CI 1.9–2.9) cases per 1,000 person-years and 4.9 (95% CI 3.5–6.8) cases per 1,000 person-years, respectively (Table 2). The relative risk for high-grade cervical neoplasms for Cu IUD compared with LNG-IUS was 0.49 (95% CI 0.32–0.76 [calibrated $P < .01$ and uncalibrated $P < .01$: the consistency between uncalibrated and calibrated P -values suggests that the magnitude of residual confounding in our analysis is small]).

To further reduce possible confounding, we evaluated a propensity score 1:1 matching analysis; using this approach, the algorithm balanced 2,039 Cu IUD users and 2,039 LNG-IUS users over 16,827

baseline covariates, to minimize residual confounding. Some of the patients were different in the matching analysis, as well as the covariates necessary to minimize confounding among them. We show a representative group of baseline covariates for these patients before and after propensity score matching in Table 1, such as age, race, and ethnicity. We also present data on medication exposures such as HPV vaccine and nonintrauterine hormonal contraception (Table 1). No covariate differed by more than an absolute SD of the mean greater than 0.10 (Fig. 3B). Fifteen of 2,039 Cu IUD users (0.7%) and 37 of 2,039 LNG-IUS users (1.8%) developed a high-grade cervical neoplasm. The incidence rates for the Cu

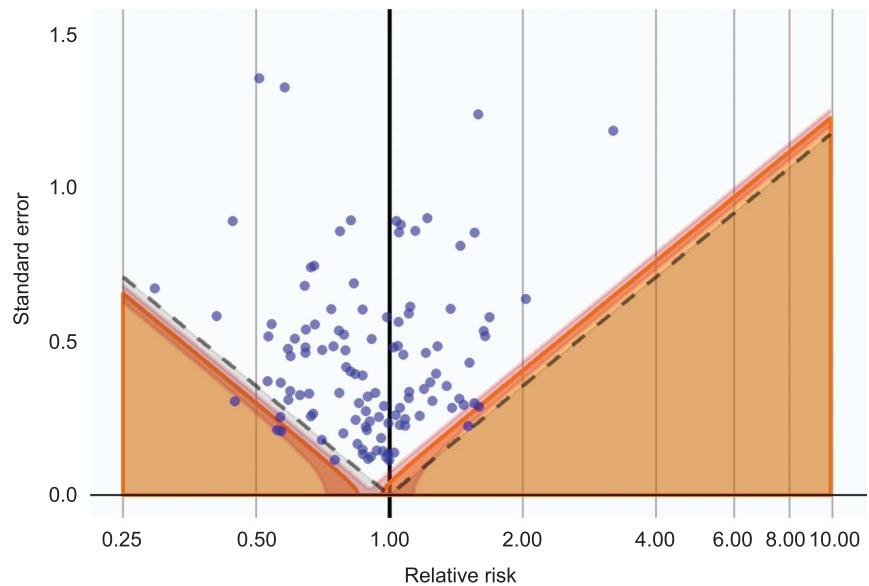
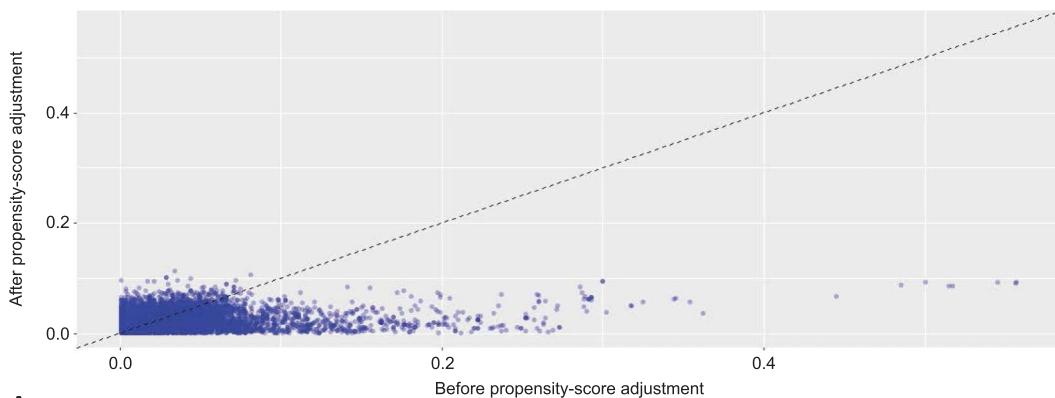
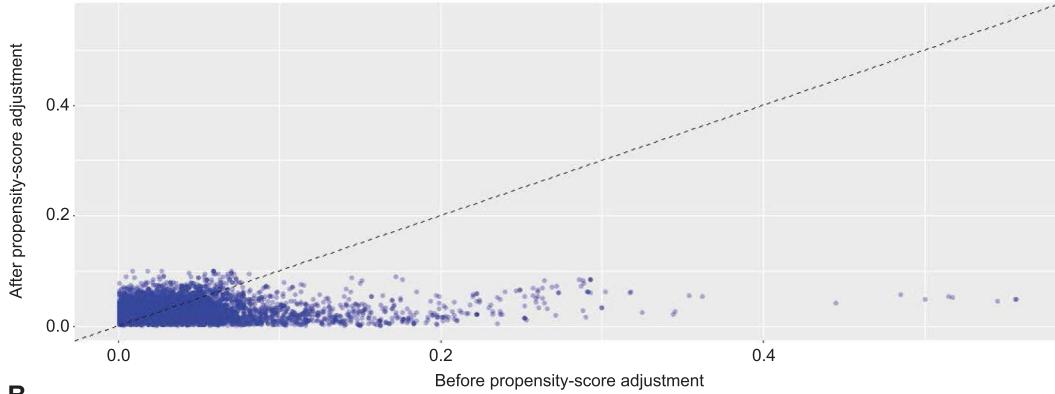


Fig. 2. A plot of traditional and calibrated significance testing for the propensity score stratification analysis. Estimates below the dashed line (gray area) have a $P < .05$ using traditional P -value calculation. Estimates in the orange areas have a $P < .05$ using the calibrated P -value calculation. Blue dots indicate negative controls.

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A



B

Fig. 3. Covariate balance showing the absolute standardized difference of a mean before and after propensity score stratification (**A**) and propensity score 1:1 matching (**B**). Each blue dot represents a covariate. **A.** Number of covariates: 20,086; after propensity score adjustment maximum (absolute): 0.11. **B.** Number of covariates: 16,827; after propensity score adjustment maximum (absolute): 0.10.

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IUD and LNG-IUS cohorts were 2.4 (95% CI 1.5–4.0) cases per 1,000 person-years and 5.2 (95% CI 3.7–7.1) cases per 1,000 person-years, respectively (Table 3). The relative risk for cervical neoplasms for Cu IUD compared with LNG-IUS was 0.38 (95% CI 0.16–0.78, uncalibrated $P < .02$). These results are consistent

with the results from the propensity score stratification analysis. We have chosen to report the relative risk from this analysis with less residual confounding.

We show a Kaplan-Meier plot of the propensity score 1:1 matching analysis (Fig. 4). By inspection, the magnitude of the slope of the LNG-IUS Kaplan-Meier

Table 2. Inferential Statistics of the Target and Comparator Cohorts After Propensity Score Stratification From 2003 to 2019 in the Columbia University Irving Medical Center Database

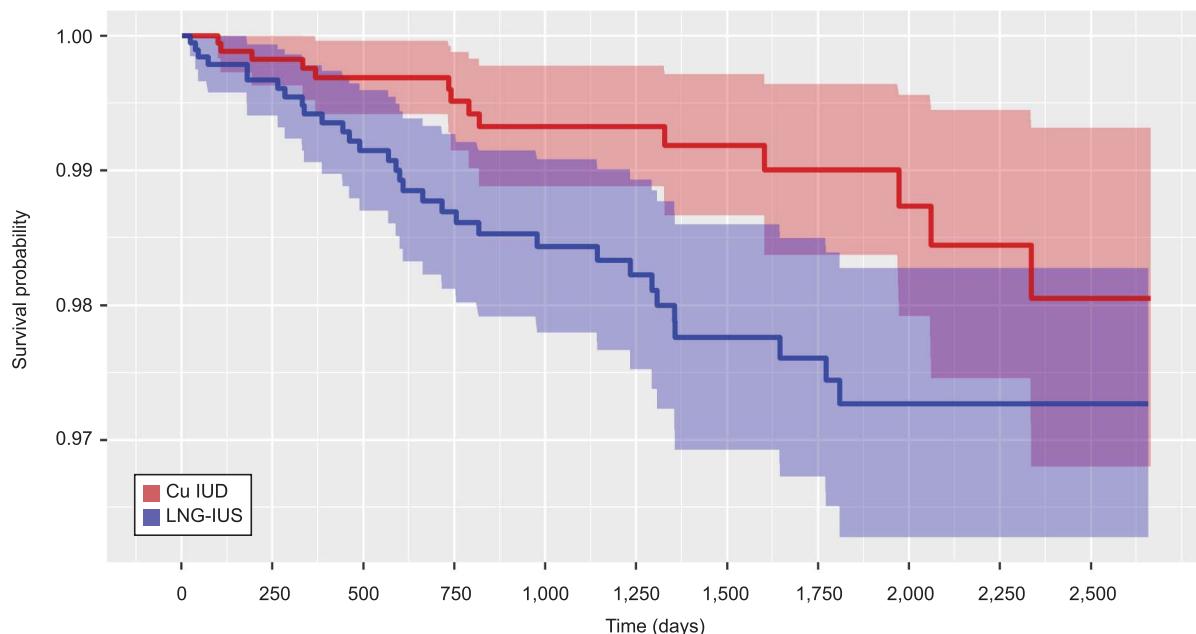
Variable	Cu IUD Cohort (n=7,114)	LNG-IUS Cohort (n=2,174)
Person-years at risk	31,787.7	7,559.3
No. of events	75	37
Cases/1,000 persons	10.5	17.0
Cases/1,000 person-years (95% CI)	2.4 (1.9–2.9)	4.9 (3.5–6.8)

Cu IUD, copper intrauterine device; LNG-IUS, levonorgestrel intrauterine system.

Table 3. Inferential Statistics of the Target and Comparator Cohorts After 1:1 Propensity Score Matching From 2003 to 2019 in the Columbia University Irving Medical Center Database

Variable	Cu IUD Cohort (n=2,039)	LNG-IUS Cohort (n=2,039)
Person-years at risk	6,186.8	7,167.7
No. of events	15	37
Cases/1,000 persons	7.4	18.2
Cases/1,000 person-years (95% CI)	2.4 (1.5–4.0)	5.2 (3.7–7.1)

Cu IUD, copper intrauterine device; LNG-IUS, levonorgestrel intrauterine system.



	At risk (n)											
	Cu IUD	2,039	1,579	1,327	1,115	937	759	601	464	359	277	203
	LNG-IUS	2,039	1,639	1,413	1,213	1,057	895	730	599	457	373	299

Fig. 4. Kaplan-Meier plot of high-grade cervical neoplasm-free survival compared with time (days) by intrauterine device (IUD) type as calculated by propensity score 1:1 matching. The Kaplan-Meier curves are shown with CI shading. The time at risk was from 30–2,530 days. Day 0 corresponds with 30 days after the index events. The number of patients at risk in each cohort as a function of time is shown below and parallel to the x-axis. Cu IUD, copper IUD cohort; LNG-IUS, levonorgestrel-releasing intrauterine system cohort.

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plot increases between 6 months and 1 year after IUD placement and continues to diverge from the Cu IUD curve over time. A subgroup analysis of propensity score 1:1 matching that restricted the start of the follow-up period to 365 days after the index event resulted in a relative risk of 0.64 (0.27–1.47, $P=.31$).

For the validation chart review, we sampled 80 women who developed a high-grade cervical neoplasm in the Cu IUD cohort and 35 who developed a high-grade cervical neoplasm in the LNG-IUS cohort. Ninety percent of the patients in each cohort had a retrievable biopsy confirmation of a high-grade cervical neoplasm. Of 80 Cu IUD patients, we found that 10% of them had an LNG-IUS placed and of the 35 LNG-IUS, we validated that 100% of them had an LNG-IUS placed.

DISCUSSION

We have presented data from an academic medical center to suggest that Cu IUD users are at a lower risk for high-grade cervical neoplasms relative to LNG-IUS users. The lower incidence of high-grade cervical neoplasms in the Cu IUD cohort is consistent with

findings that were reported in the LNG-IUS U.S. Food and Drug Administration application from the year 2000.¹⁵ The authors from Berlex Laboratories reported that according to 5-year results from a phase III multicenter randomized control trial that compared LNG-IUS users with Nova-T users (the Nova T is a copper-bearing IUD), the incidence of high-grade cervical dysplasia was lower for the Nova-T cohort¹⁶: 13 out of 937 Nova-T users and 33 of 1,821 LNG-IUS users developed high-grade cervical neoplasms, which was a 0.4% absolute difference, similar to the difference observed here. A simple analysis suggests that these results would correspond with an odds ratio of 0.76 (0.40–1.4) for Nova-T users relative to LNG-IUS users, which would cross the null. The authors concluded that the difference was not statistically significant; however, that study of 2,758 patients was insufficient to evaluate an effect of this size. Replication of the present analysis throughout other sites in the Observational Health Data Sciences and Informatics network may help verify our findings and improve the power of our main and subgroup analyses.

Our findings are supplemental to a recent systematic review of case-control studies that concluded that IUD use decreases the incidence of cervical cancer. Based on the date and location of the individual studies that constitute the systematic review, we believe that those patients were predominately Cu IUD users, or perhaps inert IUD users.¹ Copper IUDs release copper ions that are believed to increase prostaglandin levels in the uterine and tubal fluids. In contrast, LNG-IUSs suppress cervical and uterine immunity through decreased prostaglandin production. One retrospective analysis concluded that these differences in immunomodulation may cause LNG-IUS users to clear HPV infections at a slower rate and be more susceptible to infection than Cu IUD users.²

Whether the finding that Cu IUD exposure is associated with a relatively lower incidence of high-grade cervical neoplasms than LNG-IUS exposure is due to copper ion release or other biochemical changes is unknown. Further toxicology studies regarding the effects of Cu IUDs and LNG-IUS are warranted. Ideally, a direct comparison between LNG-IUS users and women who do not use intrauterine contraception would be relevant. However, women who do not use intrauterine contraception are dissimilar from those who do.

We chose to balance our cohorts with a propensity score model, because there are a number of risk factors that may have confounded the association between Cu IUD or LNG-IUS exposure and high-grade cervical neoplasm incidence. For example, smoking history and HPV infection are examples of variables that could confound the association if unbalanced.¹⁷ Some strengths of our methodology are that we were able to balance more than 10,000 covariates at baseline, and demonstrate minimal residual confounding over more than 100 negative controls. The fact that our crude analysis, propensity score stratification, and 1:1 matching had concordant results is reassuring that our observed effect is real. *P*-value calibration did not change the results of our adjusted analysis. We are also reassured by the fact that our results are concordant with a phase III randomized control trial that evaluated the LNG-IUS.¹⁵

Our study, however, is limited by the amount of information in our database regarding HPV vaccination and follow up time with screening. Significant portions of our population had unknown race or ethnicity. Because we restricted to female gender in our study population, some transgender men may not have been included. These data come from a single

medical center and were analyzed retrospectively. Patients may have received care at more than one health care organization, including some that do not contribute information to our database; thus, we would have missed cervical neoplasm diagnoses made in other health care settings. However, we have no reason to believe that we would have differentially missed these diagnoses in the Cu IUD users.

The results of our validation process suggest that the LNG-IUS patients were identified with a high level of specificity, however there was differential misclassification in the Cu IUD cohort. The effect of such misclassification would be to bias the cervical neoplasm incidence in the Cu IUD cohort slightly upward, and thus to bias the relative risk toward the null.

The outcome misclassification errors affected both groups equally and likely underestimated the incidences of cervical neoplasms. Uptake to screening may have been an unadjusted confounder between the cohorts. At baseline, the LNG-IUS patients were more likely to have had a previous cervical cancer screening or a preventive health visit. Confounding by screening uptake likely decreased after we adjusted for other covariates that are related to socioeconomic status.

The association between IUD usage and high-grade cervical neoplasm incidence has implications for public health on a global scale. More than 100 million women use IUDs as contraception worldwide. An approximate 1% difference in high-grade cervical neoplasm incidence between LNG-IUS and Cu IUD users, as observed in this analysis, could have large worldwide effects, especially in those areas with the highest incidence of cervical cancer.^{18–20}

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