



# Relative Risk of Cervical Neoplasms Among Copper and Levonorgestrel Releasing Intrauterine Device Users: Preliminary Results from a Network Analysis of Claims Databases

Matthew E. Spotnitz, M.D., M.P.H.<sup>1,4</sup>, Carolyn L. Westhoff, M.D. M.Sc.<sup>1</sup>, Rupa Makadia, Ph.D.<sup>2,4</sup>, Kristin Kostka, M.P.H.<sup>3,4</sup>, Henry Morgan Stewart, Ph.D.<sup>3,4</sup>, Patrick B. Ryan, Ph.D.<sup>2,4</sup>, Karthik Natarajan, Ph.D.<sup>1,4</sup>. <sup>1</sup>Columbia University Medical Center, New York, NY, <sup>2</sup>Janssen Pharmaceuticals, Titusville, NJ, <sup>3</sup>IQVIA, Durham, NC, <sup>4</sup>Observational Health Data Sciences & Informatics, New York, NY.

## Abstract

The OHDSI community has presented evidence from a single database to suggest that Copper IUD (Cu IUD) exposure may decrease the risk of high grade cervical neoplasms relative to levonorgestrel-releasing intrauterine system (LNG-IUS) exposure [1]. We replicated the analysis on multiple claims databases of the OHDSI network.

## Background

- Research suggests that women who had ever used an intrauterine device (IUD) had a lower risk of cervical cancer but studies comparing IUD types have not been studied widely.
- A prior study from Columbia University Irving Medical Center (CUIMC) found a lower relative risk of cervical neoplasms for Cu IUD relative to LNG-IUS users.
- The incidences of cervical neoplasms for Cu-IUD compared with LNG-IUS was 0.38 (95% CI 0.16-0.78, uncalibrated P <0.02). These results were similar to the reported incidences in a premarket randomized control trial conducted by Berlex Laboratories which was 0.4% absolute difference.
- This work aims to expand the analysis by conducting the analysis in various databases in the OHDSI network.

## Methods

- We implemented a retrospective, observational, cohort study. Using ATLAS, we made cohorts for Cu IUD and LNG-IUS users that were optimized on data from claims databases.
- For the new Cu IUD cohort, the index event was either placement or exposure to an intrauterine copper contraceptive as indicated by HCPCS code J7300 (“Intrauterine Copper Contraceptive”).
- For the new LNG-IUS cohort, the index event was either placement or exposure to an LNG-IUS as indicated by codes such as RxNorm 1366343 (“Levonorgestrel 0.00354 MG/HR Drug Implant”).
- All patients had continuous observation for at least 365 days prior to the index event, were 45 years or younger and female. We excluded women with a history of cancer.
- The study data came from the IBM MarketScan Commercial Claims & Encounters (CCAE), MarketScan Medicaid Multi-state (MDCD) and IQVIA Open Claims databases.

## Results

Variables N(%)	Cu IUD Cohort Before (n=612,078)	LNG-IUS Cohort Before (n=2,555,704)	Standardized Difference Before	Cu IUD Cohort After (n=561,572)	LNG-IUS Cohort After (n=561,572)
Age Group:10-19	32,067 (5.24)	195,375 (7.64)	-0.06	30,048 (5.35)	29,324 (5.22)
Age Group:20-29	286,751 (46.85)	1,137,172 (44.50)	0.028	261,675 (46.60)	265,019 (47.19)
Age Group:30-39	236,475 (38.63)	926,000 (36.23)	0.030	217,757 (38.78)	2,15,184 (38.32)
Age Group:40-45	54,992 (8.98)	293,806 (11.50)	-0.059	51,673 (9.20)	51,563 (9.18)
HPV Vaccine Within 1 Year Prior	2,828 (0.46)	16,528 (0.65)	0.006	2,566 (0.46)	2,628 (0.47)
Tobacco User Within 1 Year Prior	1,695 (0.28)	10,934 (0.43)	-0.025	1,543 (0.27)	1,687 (0.30)
Positive HPV Test Within 1 Year Prior	3,323 (0.54)	16,127 (0.63)	-0.011	2,661 (0.47)	2,641 (0.47)
Prior nonintrauterine hormonal preparations within 1 y before IUD placement	106,387 (17.38)	519,039 (20.31)	-0.074	1,00,394 (17.88)	99,874 (17.78)

Table 1: Descriptive Statistics of the Target and Comparator Cohorts Before and After 1:1 Propensity Score Matching From 2003 to 2019 in the IQVIA Open Claims Database. Cu IUD, copper intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; HPV = Human Papillomavirus; IUD = Intrauterine Device.

- The equipoise between target and comparator cohorts ranged from 79.7% to 86.5%. Covariate balance was achieved in all 1:1 propensity score matched analyses.
- No covariate differed by a standard deviation of the mean by greater than 0.06.
- The inferential statistics are shown in Table 2 and a representative Kaplan-Meier plot of high-grade cervical neoplasm-free survival is shown in Figure 1.

Database	Cu IUD cohort count	LNG-IUS cohort count	Cu IUD Cases/1K Persons	LNG-IUS Cases/1K Persons	Cu IUD P-Y (95% CI)	LNG-IUS P-Y (95% CI)	RR (95% CI)	P
IQVIA Open Claims	561572	561572	11.52	13.55	2.49 (2.43-2.55)	2.88 (2.82-2.94)	0.84 (0.81-0.87)	0.03
MDCD	14770	14770	6.78	8.53	4.11 (3.38-5.00)	4.99 (4.19-5.93)	0.84 (0.58-1.21)	0.32
CCAE	109812	109812	7.12	8.11	3.10 (2.89-3.32)	3.38 (3.17-3.61)	0.88 (0.76-1.00)	0.15

Table 2: Inferential Statistics of the Target and Comparator Cohorts After 1:1 Propensity Score Matching From 2003 to 2019 in the IQVIA Open Claims, IBM MarketScan Commercial Claims & Encounters (CCAE) and MarketScan Medicaid Multi-state (MDCD) Databases. Cu IUD, copper intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; 1K,1000; P-Y, Person- Years; 95% CI, 95% Confidence Interval; RR, Relative Risk; P, P-Value.

## Results

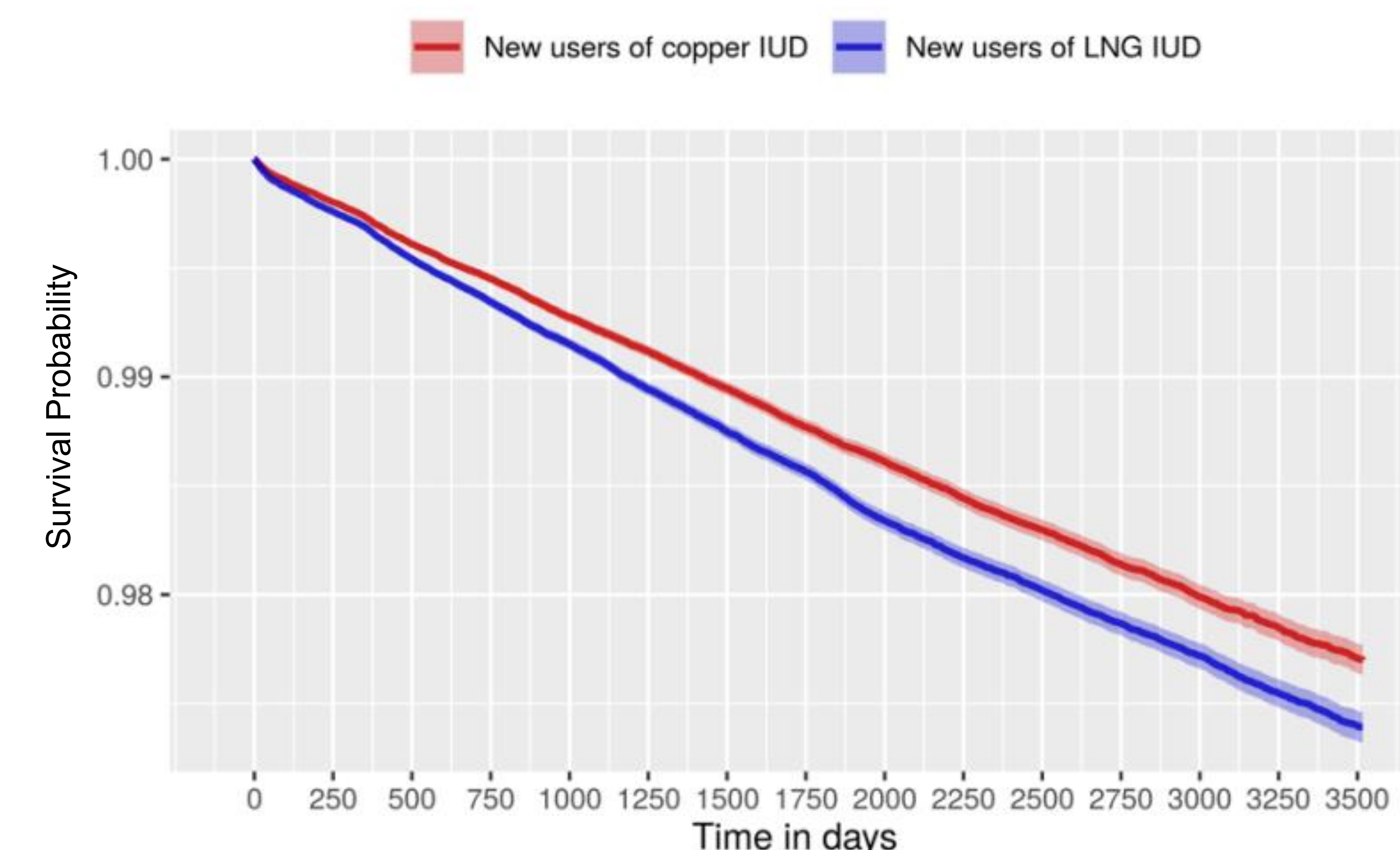


Figure 1: Kaplan-Meier plot of high-grade cervical neoplasm-free survival compared with time (days) by intrauterine device (IUD) type as calculated by propensity score 1:1 matching. The Kaplan-Meier curves are shown with CI shading. The time at risk was from 30–3,530 days. Day 0 corresponds with 30 days 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. Data Source: IQVIA Open Claims Database. LNG = Levonorgestrel.

## Conclusions

- The relative risk of cervical neoplasms for copper intrauterine device users was lower compared to levonorgestrel-releasing intrauterine device users in multiple claims databases.
- The consistency of results among several databases supports the validity of an association.
- Physiological studies may be needed to identify the mechanism of the reported relationship.

Reference:

[1] Spotnitz ME, Natarajan K, Ryan PB, Westhoff CL *Relative Risk of Cervical Neoplasms Among Copper and Levonorgestrel-Releasing Intrauterine Device Users*. *Obstet Gynecol* 135(2):319-327 (2020).