Dysplasia: *Review*

Intrauterine Device Use and Cervical Cancer Risk

A Systematic Review and Meta-analysis

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OBJECTIVE: To estimate the association between use of an intrauterine device (IUD) and risk of cervical cancer by subjecting existing data to critical review, quantitative synthesis, and interpretation.

DATA SOURCES: We searched PubMed, Web of Science, ClinicalTrials.gov, and catalogs of scientific meetings and abstracts, theses, and dissertations queried from inception through July 2016.

METHODS OF STUDY SELECTION: Examination of abstracts from 225 reports identified 34 studies with individual-level measures of use of an IUD and incident cervical cancer. By critically assessing the full text of these reports, independent reviewers identified 17 studies conducted without recognized sources of systematic error, of which 16 could be harmonized for meta-analysis.

TABULATION, INTEGRATION, AND RESULTS: Point and interval estimates of the association between use of an IUD and incident cervical cancer were extracted from original reports into a structured database along with key features of study design and implementation. A random-effects meta-analysis was implemented to quantitatively synthesize extracted estimates and assess likely influence of publication bias, residual confounding, heterogeneity of true effect size, and human papillomavirus prevalence and cervical cancer incidence in source populations. Women who used an IUD experienced less cervical cancer (summary odds ratio 0.64, 95% CI 0.53–0.77). Neither confounding by recognized risk factors nor publication bias seems a plausible explanation for the apparent protective effect, which may be stronger in populations with higher cervical cancer incidence.

CONCLUSION: Invasive cervical cancer may be approximately one third less frequent in women who have used an IUD. This possible noncontraceptive benefit could be most beneficial in populations with severely limited access to screening and concomitantly high cervical cancer incidence.

(Obstet Gynecol 2017;130:1226–36)
DOI: 10.1097/AOG.0000000000002307

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Faculty effort for this research was supported in part by the Department of Obstetrics and Gynecology, Keck School of Medicine of USC. Additional author effort supported in part by National Cancer Institute grant number T32CA009492.

Presented in part at the annual meeting of the North American Forum on Family Planning, November 5–7, 2016, Denver, Colorado.

Each author has indicated that he or she has met the journal's requirements for authorship.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/17

Cervical cancer is the third most common malignancy among women worldwide, and according to the International Agency for Research on Cancer estimates, 710,000 incident cases and 383,000 cervical cancer deaths are predicted annually by 2030.[1] Control relies primarily on screening followed by removal of premalignant cervical lesions. Preferential availability of these services to affluent women created enormous disparities,[2] and poor women now experience far greater cervical cancer burden both internationally[1] and in the United States.[3,4] As of 2014, less than 2% of eligible females in low-resource countries had received one or more doses of human papillomavirus (HPV) vaccine.[5] Therefore, for decades to come, cervical cancer control will rely primarily on measures

that prevent cervical cancer after women have been exposed to HPV. Use of an intrauterine device (IUD) may prove to be such a measure.

Intrauterine devices are the most commonly used reversible contraceptive method worldwide.[6] Modern devices are safe, highly effective for contraception, and have accepted noncontraceptive benefits. Heavy menstrual bleeding and associated anemia can be controlled by levonorgestrel-containing IUDs,[7] and women who have used nonhormonal IUDs experience lower endometrial cancer incidence.[8,9] After publication of a series of studies sponsored by the International Agency for Research on Cancer,[10] the body of epidemiologic data relating IUD use to occurrence of cervical cancer also warrants quantitative summary.

In work reported here, we systematically searched for reports relating IUD use to incident cervical cancer, critically reviewed identified studies, and quantitatively summarized data addressing the association between IUD use and incident cervical cancer.

SOURCES

We interrogated PubMed from inception to July 2016 using both MeSH and keyword searches, using the latter to identify relevant papers to which the MeSH terms had not been assigned. For the MeSH search, we specified the terms "intrauterine devices (Mesh) AND uterine cervical neoplasms (Mesh)"; these terms were expanded in the search builder to "intrauterine devices" OR "intrauterine devices, medicated" OR "intrauterine devices, copper" and "cervical cancer" OR "uterine cervical neoplasms," respectively. Terms in the keyword search were "cervical cancer" AND "intrauterine device." To find relevant papers not identified by the PubMed searches, we also conducted a Web of Science citation search of all papers selected for critical review according to criteria described subsequently. This procedure resulted in citation chaining in which each paper identified in a citation search was subjected to a subsequent citation search. Finally, we searched entries on ClinicalTrials.gov for studies of IUDs or cervical cancer and sought additional reports by informal inquiry among investigators specializing in cervical cancer and contraception and by querying abstracts of presentations to scientific conferences, unrestricted queries of trials registered at ClinicalTrials.gov using each of the search terms enumerated previously, and catalogued theses and dissertations. Reports identified by each search were captured in a library created in Endnote X7.7.1, and those identified by multiple searches were reduced to unique entries.

STUDY SELECTION

The title and abstract of each unique report were reviewed independently by two investigators to identify studies meeting inclusion criteria; such studies had collected 1) individual-level data, 2) history of IUD use, and 3) history of cervical cancer. We specifically excluded studies not reported in English, studies without human participants, and case reports.

To determine whether minimum criteria for study quality were met, two investigators (from MB, NBW, TE, JLP, JT, CZ, JZ) independently critically reviewed the full text of the report on each study, requiring that included studies 1) enrolled a defined group of women with no history of cervical cancer, 2) did not select participants according to history of cervical cancer risk factors, 3) addressed age of participants in either design or analysis, and 4) used incident cervical cancer as the outcome variable. Recognizing that incident occurrence of cervical intraepithelial neoplasia and carcinoma in situ cannot be ascertained reliably, we excluded studies that reported on only these conditions and those for which cervical intraepithelial neoplasia could not be distinguished from cervical cancer in reported data. At least two of our investigators (from MB, NBW, TE, JLP, JT, CZ, JZ) additionally confirmed that included studies were subject to no obvious source of systematic error likely to introduce appreciable bias, potentially confounding variables addressed in the study were enumerated, and that study data had been analyzed by techniques appropriate for the data structure. Any discrepancies between results of title and abstract reviews or full-text reviews were resolved by consensus. The full search was conducted in strict adherence to Preferred Reporting Items for Systematic reviews and Meta-Analyses standards.[11] The protocol and study were not registered before implementation.

Data used in the meta-analysis were systematically extracted from reports on studies found to satisfy the aforementioned criteria and managed using REDCap 6 electronic data capture tools hosted at the University of Southern California. Information abstracted for each study included study site, years of enrollment and publication, size and characteristics of the study population, and both point and 95% CI estimates of the association between ever using an IUD and incident cervical cancer. For each study, we noted which of the following covariates had been addressed by either design or analysis: age, history of Pap test, socioeconomic status, gravidity, sexual history, age at coitarche (sexual debut), and HPV status. If provided, we also extracted information on IUD type used by participants and histologic subtype of incident cervical

cancer. Study design was categorized as follows: nested case–control study if control participants were sampled from cervical cancer-free women belonging to a defined cohort from which case participants were ascertained; population-based case–control study if control participants were sampled from a defined base population from which incident cases were identified by surveillance, hospital- or clinic-based case–control study if control participants were cervical cancer-free patients ascertained at a clinical facility related to the center where participating case participants were identified; and friend- or family-base case–control study if control participants were referred to the study by participating case participants.

The meta-analysis was designed to quantitatively assess the association between incident cervical cancer and any compared with no use of an IUD. Fortunately, estimates of this association were provided for most studies. For one study in which estimates were provided only for finer strata of IUD use, we estimated the association for any compared with no use as described in Appendix 1, available online at http://links.lww.com/AOG/B2. We requested an estimate for this association from the authors of a study in which the lowest reported level of exposure was less than 2 years of IUD use, but learned that study data were no longer available[12]; we report results of this study only in narrative form.

We estimated the summary odds ratio (OR) association between any (compared with no) use of an IUD and incident cervical cancer using both fixed-effect and random-effects models; finding results from both models comparable, we report in detail those from the random-effects model. As input data, we used reported results of multivariate analyses

Table 1. Studies Included in Meta-analysis

1st Author	Location	Data Collection	Control Source	Case Participants	Control Participants
Celentano[35]	United States	1982–1984	Mixed	153	153
Brinton[32]	Multisite[§]	1986–1987	Mixed	568	1,071
Lassise[36]	United States	1982–1984	Population	479	789
Parazzini[37]	Italy	1990	Clinic or hospital	720	820
Williams[33]	Kenya	1981–1988	Clinical or hospital	112	749
Li[38]	China	1989–1991	Population	272	893
Shields[34]	United States	1982–1984	Population	235	486
Hammouda[16]	Algeria	1997–1999	Clinic or hospital	198	202
Castellsagué[10]	Morocco	1991–1993	Clinic or hospital	202	214
Castellsagué[10]	Philippines	1991–1993	Clinic or hospital	383	387
Castellsagué[10]	Thailand	1990–1993	Clinic or hospital	348	385
Castellsagué[10]	Peru	1996–1998	Clinic or hospital	137	140
Castellsagué[10]	India	1998–1999	Clinic or hospital	76	60
Castellsagué[10]	Spain	1985–1987	Population	480	472
Castellsagué[10]	Colombia	1985–1988	Population	448	452
Roura[15]	Multisite[‖]	1992–2006	Cohort	134	264

SES, socioeconomic status; HPV, human papillomavirus; AAICC, age-adjusted incidence of cervical cancer; BMI, body mass index; OCU, oral contraceptive use.
* Method of accounting for age: M, matched; S, statistically controlled.
† Method of Pap test measurement: G, gap in Pap tests; N, number of previous Pap tests; T, time since last Pap test.
‡ Method of socioeconomic status measurement: E, education; I, household income.
§ Panama, Costa Rica, Colombia, and Mexico.
‖ Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, and United Kingdom.

extracted from original reports; this carried forward into the meta-analysis estimates of the OR, addressing confounders deemed important by the original investigators. By this approach, natural log of each adjusted OR estimate was weighted by the reciprocal of the corresponding variance estimated from the 95% CI. The fixed-effects model uses this information to account for only within-study variance. The random-effects model accounts for between- and within-study variance, thereby incorporating the conservative assumption that individual studies estimate different effect sizes.[13] A priori, we expected true value of the IUD–cervical cancer association to differ between study populations, because magnitude of this parameter is influenced by the distribution of true causal or protective factors, which is likely to differ among the diverse source populations in which contributing studies were conducted. We estimated the summary OR within strata defined by study design and overall for the full set of included studies. A forest plot was created to display each study's contribution to summary estimates.

We used two approaches to examine the influence of individual studies and study weights on the overall summary estimate. We calculated summary OR estimates in which contributions of each study were excluded one by one. We also conducted a cumulative meta-analysis in which contributions of each study were added to the summary OR estimate of studies' relative weights. Heterogeneity was characterized using appropriate P value and I^2 statistics,[14] and publication bias was addressed by creating a funnel plot and conducting a second cumulative meta-analysis ordered by the year each report was published.

Covariate									Values for Metaregression	
Age*	Pap Test†	SES‡	Sexual Partners	HPV	Coitarche Age	Gravidity	Smoking Status	Other	HPV Prevalence	AAICC
Yes (M)	Yes (G)	No	No	No	Yes	No	Yes	Race, residence, gynecologic visits	6	8
Yes (M)	Yes (T)	Yes (E)	Yes	Yes	Yes	No	No	Parity	—	30
Yes (M)	No	Yes (I)	Yes	No	Yes	Yes	No		6	15.3
Yes (S)	Yes (N, T)	Yes (E)	Yes	No	Yes	Yes	Yes	Race, history of genital infection, OCU	15	7.9
Yes (S)	No	No	No	No	No	No	No		—	45
Yes (M)	Yes (N)	Yes (E)	No	No	No	No	Yes	Age first married, intercourse during menstruation, use of unsanitary materials, parity	7	2.78
Yes (M)	No	No	No	No	No	No	No		—	15.3
Yes (M)	No	Yes (E)	Yes	Yes	Yes	No	No	Residence, urban or rural environment	10.5	10.9
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		20.5	11
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		9.2	25
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		15.7	18.5
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		17.7	40
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		27.7	30
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		15.6	6
Yes (S)	Yes (N)	Yes (E)	No	Yes	Yes	No	No		15.6	48.2
Yes (M)	Yes (N)	Yes (E)	No	Yes	No	Yes	Yes	Chlamydia, herpes, BMI, marital status, physical activity, menopausal status	40.7	10.7

The contributing studies addressed different sets of covariates by either matching in the design or adjusting in multivariate analysis. We explored sensitivity of the summary estimate to control in contributing studies of specific covariates by conducting stratified meta-analyses. For each, studies were assigned to a group that did or did not address a specific cervical cancer risk or protective factor. Variables used to define these strata were history of a Pap test, socioeconomic status, gravidity, lifetime number of sexual partners, age at coitarche, HPV status, and history of smoking. The limited number of contributing studies precluded joint stratification on multiple variables.

Human papillomavirus status and history of cervical cancer screening are particularly important determinants of cervical cancer risk that were not addressed in some studies and unlikely to have been perfectly controlled in others. We explored the possible influence of these factors using population-level metaregression. To implement this analysis, we regressed the natural logarithm of the OR estimated in each study on available estimates of HPV prevalence and age-adjusted incidence rate of cervical cancer in the source population for each study. Because incidence is widely measured and determined largely by frequency of screening, the age-adjusted incidence rate of cervical cancer in each study's source population during the first year of study enrollment was used as an indicator of screening. Estimates of HPV prevalence were taken from study reports[15,16] and other sources,[17–25] and estimates of incidence were obtained from one study report,[16] other reports,[19–24,26–28] and population-based cancer registries.[29–31] We excluded from the metaregression analysis studies from three source populations[32–34] for which estimates of HPV prevalence were not available. All statistical analyses were implemented using Stata 14, and Figures 2–4 were created using R 3.4.0.

RESULTS

Using the three search strategies, we identified 225 unique reports. Of these, we eliminated 25 describing only case participants, 97 that did not provide information on both IUD use and cervical cancer, 47 not written in English, eight letters and 25 reviews that did not report on original data, two that did not use individual-level data, and one book. Of the remaining 21 reports warranting critical review, 16 had been identified in PubMed searches and five by citation chaining. By critical review, we determined that 17 were reports of high-quality studies that satisfied inclusion criteria. Data from 16 of these studies[10,15,16,32–38] (Table 1) reporting on 4,945 incident cases of cervical cancer and 7,537 women who remained free from this malignancy could be harmonized for inclusion in the meta-analysis. Movement of data through the systematic search, critical review, and meta-analysis is illustrated in Figure 1, characteristics of studies used in the meta-analysis are enumerated in Table 1, and critically reviewed studies that did not satisfy inclusion criteria are enumerated in the Appendix 2, available online at http://links.lww.com/AOG/B2.

For the 16 high-quality studies included in the meta-analysis, we estimated the summary OR association between any (compared with no) use of an IUD and incident cervical cancer to be 0.64 (95% CI 0.53–0.77; see forest plot, Fig. 2). Stratum-specific summary OR estimates did not differ appreciably between subsets of studies of like design, results from studies of the common design did not strongly aggregate in the funnel plot (Fig. 3), and summary OR estimates did not materially change by omitting data from any of the 16 studies (Fig. 4). These findings reveal a robust inverse association that is unlikely to have arisen spuriously from either random error or participation bias.

The single high-quality study that could not be harmonized for inclusion[12] provided estimates for 2–9 years of use (OR 0.6, 95% CI 0.3–1.2, 23 case participants, 33 control participants) and 10 or more years of use (OR 0.9, 95% CI 0.1–1.3, five case participants, five control participants) compared with less than 2 years of use of an IUD (172 case participants, 162 control participants). Because the reference group could include an undetermined number of women who ever used an IUD, we expected study estimates to be closer to the null value, 1.0, than the summary OR estimated from 16 studies in which no use was the reference level. We therefore consider results of this study to be compatible with results of the meta-analysis.

Results of the cumulative meta-analyses contradict patterns that typically create publication bias: small studies reporting extreme results in early years followed by larger studies reporting null estimates. Instead, cumulative meta-analyses of these data show that results would have been substantively identical if data from the smallest 10 or 12 studies had not been included (Appendix 3, available online at http://links.lww.com/AOG/B2). Moreover, an inverse association is apparent from the summary of data available throughout the history of published reports, and the summary estimates achieved statistical significance on publication of only the second report in 1990 (Appendix 4, available online at http://links.lww.com/AOG/B2). Accordingly, results of individual studies do not aggregate in the lower left portion of the funnel plot (Fig. 3), betraying no indication that there are numerous small unpublished studies

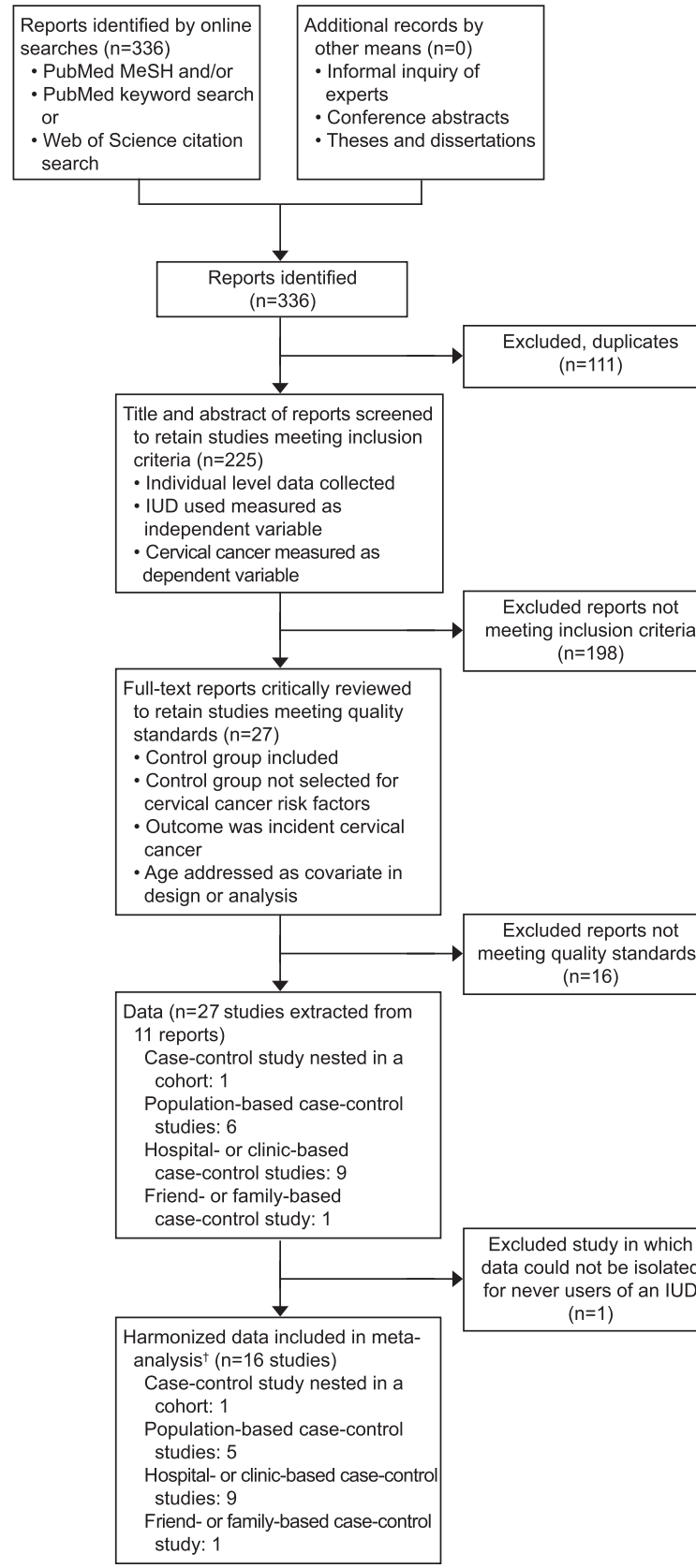

Fig. 1. Flow of information through the systematic review and meta-analysis. *See Appendix 2, available online at http://links.lww.com/AOG/B2. †See Table 1. MeSH, medical subject headings; IUD, intrauterine device.

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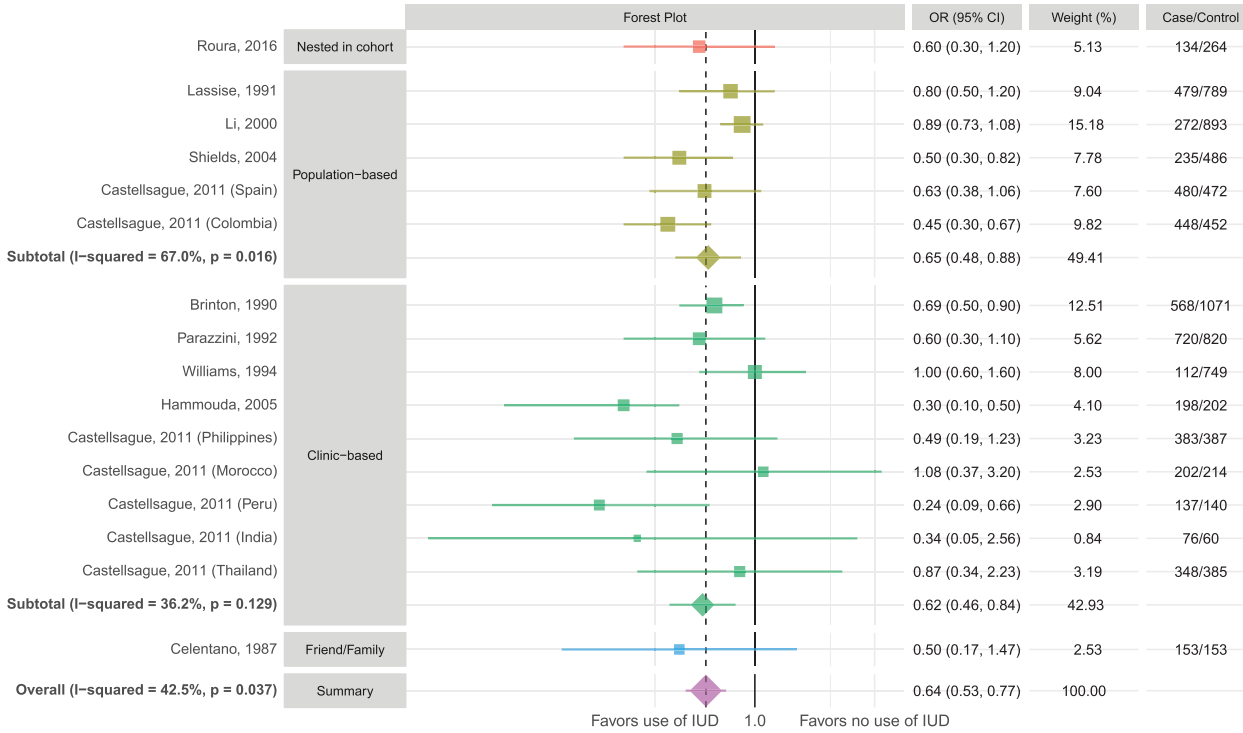

Fig. 2. Forest plot from random effects meta-analysis of 16 studies stratified by study design and ordered within stratum by year of publication and relative weight (%) of study. *Centers of squares and horizontal bars* through each indicate point and 95% CI estimates of individual study odds ratio (sOR). *Area of squares* indicate relative weights of individual studies. *Vertical apices of diamonds* and *horizontal bars* through each indicate interval sOR estimates. *Dashed black line* indicates combined sOR. OR, odds ratio; IUD, intrauterine device.

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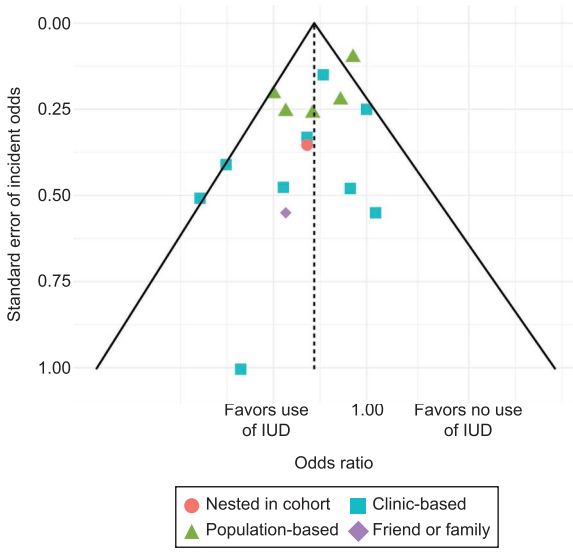

Fig. 3. Funnel plot from random effects meta-analysis of 16 studies. *Dotted black line* indicates summary odds ratio. *Solid black lines* indicate pseudo 95% CIs. IUD, intrauterine device.

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with null results, the classic missing studies that create publication bias. Thus, all relevant results indicate that the observed association between IUD use and cervical cancer is unlikely to have arisen from publication bias.

Heterogeneity among all studies (I^2 42.5%) is not explained by differences in study design, because stratum-specific summary OR estimates did not differ appreciably between subsets of studies of like design, and heterogeneity was apparent even within these subsets (Fig. 2). Accordingly, results were slightly overdispersed with point estimates from four studies situated slightly outside pseudo 95% confidence limits (Fig. 3). We considered two possible sources for the observed heterogeneity: differing degrees of residual confounding and true differences in effect size.

We explored potential influences of residual confounding by stratified meta-analysis of subsets of studies that did or did not address each of seven specific risk or protective factors as potential confounding variables. Notably, inverse associations were observed in both strata defined by each of these factors, and results for all but one of the smallest strata (three studies that did not address socioeconomic

Fig. 4. Results of influence analyses comparing summary odds ratio (sOR) from all 16 studies (*middle of red square* and *horizontal red line* through it, further denoted by *dashed bar* and *two solid vertical bars* through entire figure, indicate point estimate and 95% CI) to sOR estimate from each of 16 sets of 15 studies in which data from indicated study were excluded (*middle of each blue square* indicates point estimates; *blue bars through each blue square* indicate 95% CI estimates).

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status) achieved statistical significance. Confounding by any of these factors is therefore unlikely to explain the inverse association in the overall data (Table 2).

True effect size is expected to differ between populations with unequal prevalence of cervical cancer causes and protective factors.[39] Stronger associations predicted in populations with higher prevalence of HPV and lower frequency of screening were borne out in results of metaregression. The natural logarithm of the OR values from individual studies were inversely correlated with both HPV prevalence and our proxy for lower access to screening, age-adjusted incidence rate of cervical cancer (Table 3), although only the age-adjusted incidence rate coefficient achieved statistical significance (P=.005). These results accord with the possibility that protective effects of IUDs may be somewhat greater in populations that experience higher cervical cancer risk.

DISCUSSION

The meta-analysis revealed a robust inverse association between any use of an IUD and incident cervical cancer with overall incidence approximately 30% lower in women who reported ever using a device. Because contributing studies were completed before an HPV vaccine was available, the magnitude of the association may be most relevant to populations in which women 30 years of age and older remain largely unvaccinated. The analysis identified between-study heterogeneity, an indication that distribution of results of individual studies was not the result of random error alone. Potential influences include different levels of screening and HPV infection between contributing studies, which were conducted over a range of years and sociodemographic circumstances. The inverse correlation between cervical cancer incidence in a study's source population and effect size accords with the possibility that difference in incidence between users and nonusers could be greatest in populations subject to higher risk.

Table 2. Results of Meta-analyses Stratified on Whether Studies Did or Did Not Address Each of Six Demonstrated Cervical Cancer Risk and Protective Factors

	Addressed*			Not Addressed		
Variable	n†	Summary OR	95% CI	n†	Summary OR	95% CI
SES	13	0.63	0.51–0.77	3	0.67	0.40–1.12
Smoking history	4	0.81	0.66–0.99	12	0.61	0.49–0.75
Coitarche age	11	0.62	0.52–0.73	5	0.66	0.46–0.96
No. of lifetime partners	4	0.65	0.45–0.96	12	0.62	0.49–0.79
HPV status	10	0.56	0.45–0.70	6	0.78	0.63–0.96
No. of Pap tests	12	0.66	0.54–0.81	4	0.58	0.36–0.93
Gravidity	3	0.64	0.53–0.77	13	0.62	0.49–0.78

OR, odds ratio; SES, socioeconomic status; HPV, human papillomavirus.
* By matching on variable in study design or adjusting for it in multivariate analysis.
† Number of studies in stratum.

Table 3. Results of Analyses in Which the Natural Logarithm of the Odds Ratio Was Regressed on Levels of Two Risk Factors in Source Populations of Contributing Studies*

Variable	$R^{\dagger}$	95% CI	*P*
Prevalence HPV in source population†	−0.010	−0.029 to 0.010	.319
AAIR cervical cancer in source population‡	−0.014	−0.024 to –0.004	.005

HPV, human papillomavirus; AAIR, age-adjusted incidence rate.
* Excluding data from Brinton,[32] Williams,[33] and Shields.[34]
† Coefficient estimated in weighted multivariate linear regression analysis.
‡ Based on world standard population.

Results of influence, sensitivity, and cumulative meta-analyses indicate that the observed association is unlikely to be explained by study design, residual confounding by recognized cervical cancer risk and protective factors, or publication bias. The association is also unlikely to represent artifact of lesion detection during IUD placement, because cervical lesions are visualized by use of indicators (eg, acetowhite) that are not applied for purposes of IUD placement. These considerations leave us encouraged that the observed association may plausibly reflect a true difference in cervical cancer risk between IUD users and other women.

Mechanisms whereby placement of an IUD might mediate malignant potential focus on proximity of the cervical canal to the transformation zone, where preneoplastic lesions arise. The transformation zone is both targeted by HPV and a major effector and inductive site for cell-mediated immune responses.[40] Tissue underlying the transformation zone is manipulated during IUD placement, and the possibility that this procedure may elicit an immune response appears to have first been articulated by Petry, who proposed that "tissue trauma associated with…insertion induces a cellular immune response that might finally clear persistent HPV infections and preinvasive lesions."[41] This suggestion followed research indicating that cellular immune response may influence the course of premalignant cervical lesions. Key findings were greater lesion progression in immunocompromised patients,[42,43] and better outcomes when tissue resected to remove cervical lesions demonstrated $CD4^{+}$ T-cells and CD11c+ dendritic cells, indicating immune infiltration.[44] Mechanisms involving more chronic response to the presence of an IUD have also been suggested. Castellsague et al[10] hypothesized that IUDs may affect HPV persistence through "changes in local mucosal immune status" caused by chronic, low-grade inflammation in the endocervix and cervix or by induction of "local small foci of chronic inflammation" resulting from IUD insertion or removal and subsequent long-lasting immune reaction. These investigators also noted that preinvasive cervical lesions might be removed mechanically during IUD insertion or removal.

A limitation of the meta-analysis is that data could be harmonized to estimate only associations between any use and nonuse. We were unable to examine further influences of IUD type (eg, hormonal compared with copper), duration of use, or age at placement. Such findings could potentially provide insight useful for comparing postulated mechanisms such as acute compared with chronic effects and inform specific guidelines. A further limitation is that between-study heterogeneity may reflect inconsistently or inadequately addressed differences in risk or protective factors, including access to preventive care and other consequences of socioeconomic status.

Despite slow accrual of high-quality epidemiologic data, a credible inverse association between IUD use and cervical cancer has emerged. Accelerated exploration of potential efficacy of IUD use for cervical cancer prevention now seems warranted by the robust summary results reported here together with plausible biological mechanisms defined in earlier research. If such efforts substantiate a preventive influence of the IUD, future contraceptive counseling may routinely incorporate this potential noncontraceptive benefit of the IUD. Translational potential of this avenue of research is underscored by the great and growing need for approaches to cervical cancer prevention that can be widely used by HPV-exposed women in low-resource settings, frequent need for contraception among these women, and credible documentation of other noncontraceptive benefits of IUDs.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.
2. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. Lancet 2004; 364:249–56.
3. Beavis AL, Gravitt PE, Rositch AF. Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. Cancer 2017;123:1044–50.

4. Haile RW, John EM, Levine AJ, Cortessis VK, Unger JB, Gonzales M, et al. A review of cancer in U.S. Hispanic populations. Cancer Prev Res 2012;5:150–63.
5. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health 2016;4:e453–63.
6. United Nations, Department of Economic and Social Affairs, Population Division. Trends in contraceptive use worldwide 2015. Report No. ST/ESA/SER.A/349. New York (NY): United Nations; 2015.
7. Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update 2015;21: 640–51.
8. Beining RM, Dennis LK, Smith EM, Dokras A. Meta-analysis of intrauterine device use and risk of endometrial cancer. Ann Epidemiol 2008;18:492–9.
9. Felix AS, Gaudet MM, La Vecchia C, Nagle CM, Shu XO, Weiderpass E, et al. Intrauterine devices and endometrial cancer risk: a pooled analysis of the epidemiology of endometrial cancer consortium. Int J Cancer 2015;136: E410–22.
10. Castellsagué X, Díaz M, Vaccarella S, de Sanjosé S, Muñoz N, Herrero R, et al. Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: a pooled analysis of 26 epidemiological studies. Lancet Oncol 2011;12: 1023–31.
11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med2009;6: e1000097.
12. Peters RK, Thomas D, Hagan DG, Mack TM, Henderson BE. Risk factors for invasive cervical cancer among Latinas and non-Latinas in Los Angeles County. J Natl Cancer Inst 1986; 77:1063–77.
13. Sutton AJ, Abrams KR, Jones DR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Chichester (United Kingdom): John Wiley & Sons; 2000.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
15. Roura E, Travier N, Waterboer T, de Sanjosé S, Bosch FX, Pawlita M, et al. The influence of hormonal factors on the risk of developing cervical cancer and pre-cancer: results from the EPIC cohort. PLoS One 2016;11:e0147029.
16. Hammouda D, Muñoz N, Herrero R, Arslan A, Bouhadef A, Oublil M, et al. Cervical carcinoma in Algiers, Algeria: human papillomavirus and lifestyle risk factors. Int J Cancer 2005;113: 483–9.
17. Liu SS, Chan KY, Leung RC, Chan KK, Tam KF, Luk MH, et al. Prevalence and risk factors of human papillomavirus (HPV) infection in southern Chinese women–a population-based study. PLoS One 2011;6:e19244.
18. Bruni L, Barrionuevo-Rosas L, Albero G, Serrano B, Mena M, Gómez D, et al. Human papillomavirus and related diseases in Italy. Barcelona (Spain): ICO Information Centre on HPV and Cancer; 2016.
19. Chaouki N, Bosch FX, Muñoz N, Meijer CJ, El Gueddari B, El Ghazi A, et al. The viral origin of cervical cancer in Rabat, Morocco. Int J Cancer 1998;75:546–54.
20. Bosch FX, Muñoz N, de Sanjosé S, Navarro C, Moreo P, Ascunce N, et al. Human papillomavirus and cervical intraepithelial neoplasia grade III/carcinoma in situ: a case-control study in Spain and Colombia. Cancer Epidemiol Biomarkers Prev 1993;2:415–22.
21. Franceschi S, Rajkumar T, Vaccarella S, Gajalakshmi V, Sharmila A, Snijders PJ, et al. Human papillomavirus and risk factors for cervical cancer in Chennai, India: a case-control study. Int J Cancer 2003;107:127–33.
22. Chichareon S, Herrero R, Muñoz N, Bosch FX, Jacobs MV, Deacon J, et al. Risk factors for cervical cancer in Thailand: a case-control study. J Natl Cancer Inst 1998; 90:50–7.
23. Ngelangel C, Muñoz N, Bosch FX, Limson GM, Festin MR, Deacon J, et al. Causes of cervical cancer in the Philippines: a case-control study. J Natl Cancer Inst 1998;90:43–9.
24. Santos C, Muñoz N, Klug S, Almonte M, Guerrero I, Alvarez M, et al. HPV types and cofactors causing cervical cancer in Peru. Br J Cancer 2001;85:966–71.
25. Centers for Disease Control and Prevention. Tracking the hidden epidemics: trends in STDs in the United States. Atlanta (GA): Centers for Disease Control and Prevention; 2000.
26. Arbyn M, Raifu AO, Autier P, Ferlay J. Burden of cervical cancer in Europe: estimates for 2004. Ann Oncol 2007;18: 1708–15.
27. Gichangi P, De Vuyst H, Estambale B, Rogo K, Bwayo J, Temmerman M. HIV and cervical cancer in Kenya. Int J Gynaecol Obstet 2002;76:55–63.
28. Lei T, Mao WM, Lei TH, Dai LQ, Fang L, Chen WQ, et al. Incidence and mortality trend of cervical cancer in 11 cancer registries of China. Chin J Cancer Res 2011;23:10–4.
29. Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents. Available at: http://ci5.iarc.fr. Retrieved May 11, 2016.
30. Surveillance Epidemiology and End Results Program. SEER*Stat database: incidence–SEER 9 Regs research data (1973–2014)–linked to county attributes–total U.S. Available at: www.seer.cancer.gov. Retrieved May 11, 2016.
31. Maryland Department of Health and Mental Hygiene. Baseline cancer report. Available at: http://phpa.dhmh.maryland.gov/cancer/pages/mcr_regs.aspx. Retrieved May 11, 2016.
32. Brinton LA, Reeves WC, Brenes MM, Herrero R, de Britton RC, Gaitan E, et al. Oral contraceptive use and risk of invasive cervical cancer. Int J Epidemiol 1990;19:4–11.
33. Williams MA, Kenya PR, Mati JK, Thomas DB. Risk factors for invasive cervical cancer in Kenyan women. Int J Epidemiol 1994;23:906–12.
34. Shields TS, Brinton LA, Burk RD, Wang SS, Weinstein SJ, Ziegler RG, et al. A case-control study of risk factors for invasive cervical cancer among U.S. women exposed to oncogenic types of human papillomavirus. Cancer Epidemiol Biomarkers Prev 2004;13:1574–82.
35. Celentano DD, Klassen AC, Weisman CS, Rosenshein NB. The role of contraceptive use in cervical cancer: the Maryland Cervical Cancer Case-Control Study. Am J Epidemiol 1987; 126:592–604.
36. Lassise DL, Savitz DA, Hamman RF, Barón AE, Brinton LA, Levines RS. Invasive cervical cancer and intrauterine device use. Int J Epidemiol 1991;20:865–70.
37. Parazzini F, La Vecchia C, Negri E. Use of intrauterine device and risk of invasive cervical cancer. Int J Epidemiol 1992;21:1030–1.
38. Li HQ, Thomas DB, Jin SK, Wu F. Tubal sterilization and use of an IUD and risk of cervical cancer. J Womens Health Gend Based Med 2000;9:303–10.

39. Maldonado G, Greenland S. Estimating causal effects. Int J Epidemiol 2002;31:422–9.

40. Pudney J, Quayle AJ, Anderson DJ. Immunological microenvironments in the human vagina and cervix: mediators of cellular immunity are concentrated in the cervical transformation zone. Biol Reprod 2005;73:1253–63.

41. Petry KU. Loops in the natural history of cervical cancer. Lancet Oncol 2011;12:986.

42. Petry KU, Scheffel D, Bode U, Gabrysiak T, Köchel H, Kupsch E, et al. Cellular immunodeficiency enhances the progression of human papillomavirus-associated cervical lesions. Int J Cancer 1994;57:836–40.

43. Hinten F, Meeuwis KA, van Rossum MM, de Hullu JA. HPV-related (pre)malignancies of the female anogenital tract in renal transplant recipients. Crit Rev Oncol Hematol 2012; 84:161–80.

44. Origoni M, Parma M, Dell'Antonio G, Gelardi C, Stefani C, Salvatore S, et al. Prognostic significance of immunohistochemical phenotypes in patients treated for high-grade cervical intraepithelial neoplasia. Biomed Res Int 2013;2013:831907.

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rev 12/2017