Received: 8 January 2019 | Revised: 18 January 2020 | Accepted: 20 January 2020

DOI: 10.1111/aogs.13817

SYSTEMATIC REVIEW

Levonorgestrel-releasing intrauterine system and breast cancer risk: A systematic review and meta-analysis

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Funding information
This study received partial financial support from the Fundação de Apoio à Pesquisa do Estado de São Paulo (FAPESP; award no. 2015/20504-9). Luis Sarian received a research stipend from the Brazilian National Council for Scientific and Technological Development (CNPq 308888/2017-0).

Abstract

Introduction: Epidemiological studies have shown that some hormonal contraceptive methods are associated with increased breast cancer risk, especially if used over long periods. Our objective was to conduct a systematic review and meta-analysis of the literature on the risk of breast cancer development in women using the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS).

Material and methods: We performed a thorough review of peer-reviewed publications from 10 January 1999, through 31 July 2019, using combinations of search terms for breast cancer risk and LNG-IUS in the Medline, EMBASE, LILACS (Latin American and Caribbean Health Sciences Literature), and Scielo databases. This review was registered in PROSPERO (CRD42017059076). Studies reporting breast cancer risk estimates among healthy users of LNG-IUS were included according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) criteria. Two authors performed data extraction, and a third author resolved disagreements. The quality of evidence was evaluated using the Downs and Black instrument. A funnel plot was generated, and a linear regression test of funnel plot asymmetry was used to assess publication bias. Finally, we performed a random-effects model (owing to high study heterogeneity) meta-analysis of seven suitable studies, stratified by the age distribution of patients (<50 years, ≥50 years, and mixed).

Results: We identified 96 studies and manually cross-referenced and excluded duplicate articles. Seventy articles were excluded on the basis of the inclusion and exclusion criteria, resulting in the assessment of 26 full-text articles. Eight articles were considered adequate for inclusion in this systematic review, and seven studies were included in the meta-analysis. Three publications were case-control studies and five were cohort studies. According to the Downs and Black instrument, 5 studies were rated as "good" and three studies were deemed "fair". Our meta-analysis results indicated increased breast cancer risk in LNG-IUS users: for all women, odds ratio (OR) = 1.16 (95% CI 1.06-1.28, I^2 = 78%, P < .01); for women aged <50 years, OR = 1.12 (95% CI 1.02-1.22, I^2 = 66%, P = .02); and for women aged ≥50 years, OR = 1.52 (95% CI 1.34-1.72, I^2 = 0%, P = .84).

Abbreviations: BMI, body mass index; CI, confidence interval; Cu-IUD, copper intrauterine device; HT, hormonal therapy; IUS, intrauterine system; LNG, levonorgestrel; LNG-IUS, levonorgestrel-releasing intrauterine system; MeSH, medical subject headings; OC, oral contraceptive; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio.

Conclusions: Current evidence suggests that LNG-IUS users have an increased breast cancer risk regardless of age and indication. The effect of LNG-IUS on breast cancer risk seems to be larger in older users. However, our systematic review detected methodological issues across the available studies, and confounding factors may be responsible for at least a fraction of the risk effects associated with LNG-IUS use. Nevertheless, users of LNG-IUS should be aware of these trends. We believe that caution is needed, and risks should be balanced against proven health benefits (eg effective treatment of heavy menstrual bleeding and avoidance of surgical interventions), when prescribing LNG-IUS for long periods of use, especially in women with other known breast cancer risk factors such as old age, obesity, and familial predisposition.

KEYWORDS

breast cancer, contraception, dysmenorrhea, levonorgestrel, levonorgestrel-releasing intrauterine system, menopause

1 | INTRODUCTION

Large epidemiological studies have shown that some hormonal contraceptive methods are associated with an increased risk for breast cancer, mainly if used over long periods.[1-4] The 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) is a highly effective contraceptive, approved for up to 5 years of use. LNG-IUS delivers levonorgestrel (LNG) to the endometrium, thereby reducing systemic exposure to LNG.[1-4] In addition, the device has been successfully used for the treatment of heavy menstrual bleeding and for endometrial protection during continuous estrogen therapy in postmenopausal women. The device is used by women seeking long-term, reversible contraception, which means that exposure to LNG could continue for many years, albeit in small concentrations. Data have shown that the LNG concentration inside the uterus is 1000 times higher than that in the plasma.[5]

The requirement for progesterone in normal mammary gland development is well established;[6] however, the role of this hormone in breast carcinogenesis remains poorly defined.[7] Studies examining the effects of progestins in human breast cancer cell lines have shown a biphasic cellular response to progesterone: initial exposure to the steroid hormone resulted in a proliferative burst, whereas sustained exposure resulted in growth inhibition.[8] These findings are in agreement with those published by other authors, who suggested that progestogens can act both as a proliferative and an antiproliferative agent in breast tissue.[9] Therefore, there is a growing body of evidence suggesting that the key to understanding the inconsistent data about the cellular effects of progestogens lies in the duration and patterns of progestogen exposure.[10]

The association between the use of LNG-IUS and breast cancer risk is a theoretical possibility that is currently debated in the medical literature. Our objective was to systematically review the evidence on the subject. Further, in order to derive a consistent effect measure of the potential association of 52-mg LNG-IUS use and breast cancer risk, we performed a meta-analysis of key studies that used appropriate methods of investigating the subject.

Key Message

Current data suggest that use of the 52-mg levonorgestrel-releasing intrauterine system may be associated with increased risk of developing breast cancer, and this risk is higher in older users.

2 | MATERIAL AND METHODS

We conducted a systematic review and a meta-analysis to evaluate the association between LNG-IUS use and the risk of breast cancer development. We thoroughly reviewed the peer-reviewed literature on the subject published from 10 January 1999 through 31 July 2019. We used a combination of Medical Subject Headings (MeSH) terms for LNG-IUS and breast cancer risk (breast neoplasms, breast cancer, breast tumor, breast carcinoma, levonorgestrel system, Mirena, intrauterine device, progestin device, progestin intrauterine device). The primary and secondary outcomes were the occurrences of invasive and in situ breast cancer, respectively.

2.1 | Inclusion criteria

We included studies on the association of breast cancer risk and use of 52-mg LNG-IUS. We stratified the studies or the reported risk ratios according to the patients' age strata (<50 years, ≥50 years, and mixed).

2.2 | Exclusion criteria

Duplicate papers, duplicated data, and manuscripts without original data (eg, comments, reviews, case reports, and technical descriptions) were considered ineligible. In the review and analyses, we avoided including data from patients known to be at a high risk for breast cancer (eg, with familial risk, with known mutations) and those with a previous history of breast cancer.

2.3 | Search strategy

This review was performed in accordance with the guidelines described in Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA); International prospective register of Systematic Reviews (PROSPERO) registration code: CRD42017059076. We performed searches in the electronic databases of Medline (via PubMed), EMBASE (via OVID), LILACS (Latin American and Caribbean Health Sciences Literature; via BVS—Biblioteca Virtual en Salud), and Scielo, using combinations of the following terms: levonorgestrel, levonorgestrel-releasing intrauterine system, breast neoplasm, breast cancer, breast neoplasm risk, and Mirena.

2.4 | Study selection

Records that potentially met the inclusion criteria of this review were selected for the analysis of their full texts. In case of any disagreement among the reviewers, a third reviewer was summoned. After the full-text reading, studies for inclusion in the review were selected. Of the 8 studies included in the systematic review, we selected 7 that followed appropriate methods for inclusion in the meta-analysis. One study[11] was excluded from the meta-analysis because we were unable to obtain effect measures for the entire cohort of patients.

2.5 | Data extraction

Data were extracted independently by 2 reviewers. The following data were retrieved from the studies: author names, date of publication, number of participants, indication for LNG-IUS use, study design, case and control definitions, outcomes, and risk factors for breast cancer. In addition, we logged the reported adjusted risk estimates for breast cancer among LNG-IUS users according to the proposed age strata. All data were obtained from the published results and are summarized in Table 1.

2.6 | Assessment of risk of bias of the included studies

Two independent reviewers assessed the methodological quality of the studies using the Downs and Black instrument. This quality assessment checklist comprises 27 questions, with a maximum possible score of 28 points for randomized studies and 25 points for non-randomized studies. The reviewers assessed the methodological quality of each study and the risk of bias for the following domains: reporting bias (10 items), external validity bias (3 items), internal validity bias (7 items), confounding bias (6 items), and power of studies (1 item). We gave scores of 0 or 1 for each risk of bias domain and the associated specific questions, except for one item in reporting the subscale for the analysis of the distribution of confounders, which was scored 0, 1, or 2. Finally, the overall quality of evidence for each study was rated depending on the final score: excellent (26-28), good (20-25), fair (15-19), or poor (<14).

2.7 | Statistical analyses

The meta-analysis was performed using the "metagen" library for the R suite. We derived the effect size of LNG-IUS use on breast cancer risk directly from the reported effect measures (odds ratio [OR], relative risk [RR], and standardized incidence ratio [SIR]). We considered the ratios reported in each individual study and derived their standard errors from the reported 95% CI. All ratios (OR, RR, SIR) and their respective 95% CI were obtained from the published tables for each individual study. As mentioned above, studies were stratified according to the age of the target population (<50 years, ≥50 years, or mixed). The study by Heikkinen et al[12] separately reported on patients of both strata and so appears twice in the meta-analysis forest plot. We obtained the random-effects estimate of the RR for breast cancer development after LNG-IUS insertion owing to high study heterogeneity (I^2 = 78%). Funnel plot analysis revealed no publication bias (funnel plot asymmetry), with P = .635 in Egger's test.[13]

3 | RESULTS

We identified 96 studies and manually cross-referenced and excluded duplicate articles. Seventy articles were excluded after the application of the inclusion and exclusion criteria, resulting in the assessment of 26 full-text articles. Eight studies were deemed suitable for inclusion in this review (Figure 1).

Three of the selected papers were case-control studies,[12,14,15] whereas 5 were cohort studies.[11,16-19] Four of them were conducted in Finland,[11,12,14,16] 1 in Germany,[15] 1 in Denmark,[19] 1 in Norway,[17] and 1 in Israel[18] (Table 1).

3.1 | Systematic review of studies addressing LNG-IUS use and breast cancer risk

Four of the 8 studies in this review reported an increased breast cancer risk in women using LNG-IUS.[12,14,16,19] Taking non-users of LNG-IUS in the general Finnish female population as the reference for standard

TABLE 1 Summary of the studies included

Author	Design	Objective	Methods	Population	Population ref (comparative)	Adjustment variables	Results
Dinger, 2010[a]	Case-control (retrospective)	To assess breast cancer risk of LNG-IUS compared to copper-IUD users in women below the age of 50 years old.	Retrospective study used a non-inferiority design and the null hypothesis to be tested was OR ≥1.5.	Cases: women diagnosed with breast cancer (in situ or invasive) younger than 50 years old. Controls: nation populations registry in Finland, and in Germany, neighborhood selected by a controlled random route method.	Women using copper-IUD younger than 50 years of age.	BMI, family history of breast cancer, age at first birth, age at menarche, and physical activity.	OR for the breast cancer among women who had ever used LNG-IUS vs Copper-IUD (adjusted OR 0.99, 95% CI 0.88-1.12). Among current users of LNG-IUS vs users of copper-IUD (OR) LNG-IUS = 0.85 (95% CI 0.52-1.39).
Soini, 2015[b]	Cohort (retrospective)	To test the hypothesis that risk for lobular breast cancer is elevated among LNG-IUS users.	Standardized incidence ratio-SIR (observed-to-expected ratio) was calculated by dividing the number of observed cancer cases by the number of expected cancers.	All Finnish women who received reimbursement for the LNG-IUS purchase prescribed for treatment or prevention of HMB at the age of 30-49 years old in 1994-2007.	Breast cancer incidence rate among general female population of similar age during the same time period.	No adjustment of their analyses for factors related to breast cancer risk.	SIR invasive ductal carcinoma (IDC) = 1.20 (95% CI 1.14-1.25) and for lobular carcinoma was SIR (ILC) = 1.33 (95% CI 1.20-1.46). For more than 5 years had increased invasive lobular breast cancer risk SIR (ILC) = 1.40 (95% CI 1.20-1.62), which increased to SIR for ductal carcinoma SIR (IDC) = 1.25 (95% CI 1.16-1.34). The risk of IDC was significantly higher only in women using LNG-IUS for more than 10 years SIR (IDC) = 1.26 (95% CI 1.14-1.38).
Lyytinen, 2009[c]	Case-control (retrospective)	To evaluate the association between postmenopausal hormone therapy (HT) and the risk for breast cancer in recently postmenopausal Finnish women.	A multivariate conditional logistic regression model was used to estimate by means of the OR the relative risk for breast cancer associated with each category of HT.	Cases: All Finnish women diagnosed with their first invasive breast cancer between 50 and 62 years between 1 January 1995 and 31 December 2007, were identified from the Finnish Cancer Registry. Controls: For each cancer case, 3 control women born at the same time and alive and free of breast cancer at the date of breast cancer diagnosis of the case.	Women from the Finnish Population Register without systemic HT (only vaginal estrogens were allowed).	Age at the first birth and the parity.	Comparing the 329 women users of LNG-IUS with the 708 controls of the same age, there was an increased risk for breast cancer in the cases, with OR = 1.53; 95% CI 1.33-1.75 (P = .001).

(Continues)

TABLE 1 (Continued)

Author	Design	Objective	Methods	Population	Population ref (comparative)	Adjustment variables	Results
Backman, 2005[d]	Cohort (retrospective)	To evaluate breast cancer incidence in users of the LNG-IUS.	Epidemiologic study based on a questionnaire sent to women in Finland who had had a LNG-IUS inserted. The study was based on a reanalysis of the data obtained in an earlier post marketing study and the data on breast cancer diagnoses from Finnish Cancer Registry from the year 1998.	LNG-IUS users, between January 1990 and December 1993, of Finnish female population (30-54 years of age).	Incidence data derived from the national Finnish Cancer Registry from the year 1998.	No adjustment of their analyses for factors related to breast cancer risk.	For women aged 30-34 years incidence per 100 000 is 27.2 in LNG-IUS and 25.5 in general population (95% CI $P = .84$), 35-39 years 74.0 in LRIS vs 49.2 (95% CI $P = .056$), 40-44 years 120.3 vs 122.4 (95% CI $P > .99$), 45-49 years 203.6 vs 232.5 (95% CI $P = .41$) and finally for 50-54 years, the incidence per 100 000 woman-years in LNG-IUS is 258.5 vs 272.6 (95% CI $P = .85$) in general population.
Mørch, 2018[e]	Cohort (prospective)	To evaluate breast cancer incidence in users of the LNG-IUS.	Nationwide prospective cohort study involving all women in Denmark between 15 and 49 years of age. Nationwide registries provided individually updated information about the use of hormonal contraception.	All women living in Denmark who were between 15 and 49 years (a total of 1 837 297 women) who had not had cancer or venous thromboembolism and who had not received treatment for infertility current and recent users of hormonal contraception.	Women who had never used hormonal contraception.	Age, education, previous OC use, endometriosis, parity, and family history of premenopausal breast or ovarian cancer.	Among women who used the LNG-IUS intrauterine system, the relative risk of breast cancer was 1.21 (95% CI 1.11-1.33), compared with never users. This risk did not differ significantly from the risk associated with products containing oral levonorgestrel alone.
Siegelmann-Danieli, 2017[6]	Cohort (retrospective)	To evaluate the incidence of breast cancer in perimenopausal women using LNG-IUS.	A cohort of all Maccabi Healthcare Services female members aged 40-50 years between 1/2003 and 12/2013 was used to identify LNG-IUS users as "cases," and 2 age-matched non-users as "controls'."	LNG-IUS users and age-matched "controls" were selected from 338 184 women who were 40-50 years old between January 2003 and December 2013. Cases included all perimenopausal users of LNG-IUS in this timeframe. The controls (2 per case) were selected sequentially to be aged-matched ±2 years.	Women who were not exposed to other hormone therapies in the 5 years preceding inclusion and during study period till last follow up.	Age at the start of follow up, female hormones in the form of oral contraceptives (OC), fertility drugs, or HT or prophylactic use of tamoxifen.	After 5 years of study, 16 DCIS and 120 invasive tumors were reported in LNG-IUS users and in the controls, these included 42 DCIS and 241 invasive tumors. Five-year Kaplan-Meyer estimates for overall BC risk in LNG-IUS users and controls were 1.2% (SE 0.1%) and 1.1% (SE 0.06%), respectively ($P = .23$). For DCIS risk, the respective values were 0.14% (SE 0.03%) and 0.16% (SE 0.03%) ($P = .22$).

(Continues)

TABLE 1 (Continued)

Author	Design	Objective	Methods	Population	Population ref (comparative)	Adjustment variables	Results
Heikkinen, 2015[f]	Case-control (retrospective)	To estimate the association between use of exogenous hormones and breast cancer risk.	Breast cancer cases from Finland in 2009 matched population controls. Conditional logistic regression was used to estimate odds ratios and their 95% CI. For validation, exposure prevalences were compared with population data from Statistics Finland and two large population-based surveys.	Cases: women diagnosed with breast cancer (in situ or invasive) at 22-60 years of age between 1 January 2000 and 31 December 2007 from the Finnish Cancer Registry. Controls: were retrieved from the central population register by a third party under a delivery agreement.	Never users of any hormonal contraceptive (exclusively copper intrauterine device).	Birth year, previous hormone contraceptive use and HT, age at menarche, parity, family history of breast cancer, BMI, years of schooling, smoking, and alcohol use.	A statistically significant increase in breast cancer risk was observed for postmenopausal women with exclusive use of LNG-IUS (use before breast cancer diagnosis) an odds ratio of 1.48 (95% CI 1.10-1.99) was observed in postmenopausal women.
Jareid, 2017[g]	Cohort (prospective)	To investigate the association between hormone use and hormone-dependent female cancers.	104 318 women from the Norwegian Women and Cancer Study. Exposure information was taken from self-administered questionnaires, and cancer cases were identified through linkage to the Cancer Registry of Norway.	Women from the Norwegian Women and Cancer Study, 9144 of whom were ever users of LNG-IUD and 95 174 of whom were never users of LNG-IUS.	Never users of LNG-IUS.	Age at the start of follow up, BMI, physical activity level at enrolment, maternal history of breast cancer, age at menarche, ever use of OCs, parity and menopausal status at the start of follow up.	Median age at inclusion was 52 years and mean follow-up time was 12.5 (standard deviation 3.7) years, for a total of 1 305 435 person-years. Among ever users of LNG-IUS there were 297 cases of breast cancer. Whenever users were compared to never users of LNG-IUS, the multivariable RR of breast cancer was 1.03 (0.91, 1.17).

[a]Dinger J, Bardenheuer K, Minh TD, Soini T, Hurskainen R, Grénman S, et al. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. *Contraception* 2010.

[b]Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Joensuu H, et al. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: a nationwide cohort study. *Acta Oncol* 2016.

[c]Lyytinen HK, Dyba T, Ylikorkala O, Pukkala EI. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. *Int J Cancer* 2010.

[d]Backman T, Rauramo I, Jaakkola K et al. Use of the levonorgestrel-releasing intrauterine system and breast cancer. *Obstet Gynecol* 2005.

[e]Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med* 2017.

[f]Heikkinen S, Koskenvuo M, Malila N, Sarkeala T, Pukkala E, Pitkäniemi J. Use of exogenous hormones and the risk of breast cancer: results from self-reported survey data with validity assessment. *Cancer Causes Control*. 2016.

[g]Jareid M, Thalabard JC, Aarflot M, Bøvelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer without increased risk of breast cancer. Results from the NOWAC study. *Gynecologic Oncol*. 2018.

[h]Siegelmann-Danieli N, Katzir I, Landes JV, Segal Y, Bachar R, Rabinovich HR, et al. Does levonorgestrel-releasing intrauterine system increase breast cancer risk in peri-menopausal women? An HMO perspective. *Breast Cancer Res Treat* 2018.

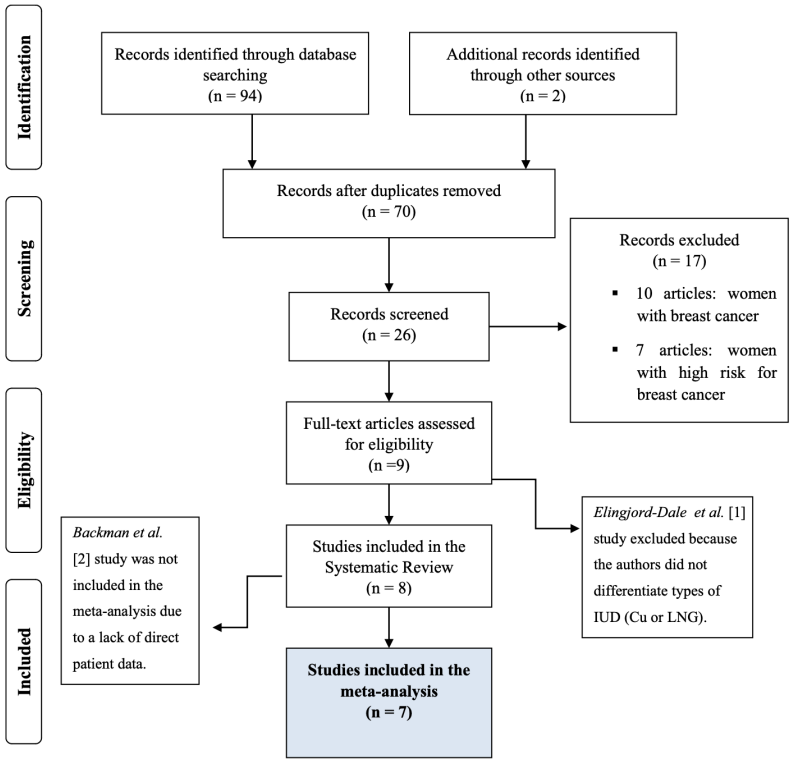

FIGURE 1 PRISMA flowchart

breast cancer risk (for comparison against LNG-IUS users), Soini et al[16] described 2015 new breast cancer cases in women aged 30-49 years using LNG-IUS for heavy menstrual bleeding (1598 invasive ductal carcinoma, 376 lobular carcinoma, and 41 carcinoma of other histological types) during a mean follow up of 11 years (maximum 19 years). The SIR for invasive ductal carcinoma was 1.20 (95% CI 1.14-1.25, $P < .001$), whereas that for invasive lobular carcinoma was 1.33 (95% CI 1.20-1.46, $P < .001$). However, the authors of that study found that only women who used LNG-IUS for >5 years had an increased risk for invasive lobular breast cancer (SIR = 1.40, 95% CI 1.20-1.62, $P < .001$).

Lyytinen et al[14] evaluated the risk of breast cancer in postmenopausal women aged 50-62 years using LNG-IUS for endometrial protection. These women were compared against women who had never used hormonal therapy (HT) or had not used HT for at least the last 6 months. In this study, several drug regimens for HT were analyzed, including oral agents, injectable drugs, and LNG-IUS; however, only 14% of the women used LNG-IUS exclusively for endometrial protection. Comparing LNG-IUS users with controls matched for age, the authors observed an increased risk of breast cancer in LNG-IUS users, with an OR of 1.53 (95% CI 1.33-1.75, $P = .001$).

A similar case-control study by Heikkinen et al[12] reported data from the Finnish Cancer Registry. A total of 13 265 breast cancer cases were identified. The median age for both cases and controls was 57.5 years. In that study, the breast cancer risk among LNG-IUS users was compared with the overall breast cancer risk for the general female Finnish population (premenopausal or postmenopausal). The authors detected a positive association between breast cancer risk and use of LNG-IUS in postmenopausal women (OR = 1.48, 95% CI 1.10-1.99). There was no increased breast cancer risk in premenopausal women using LNG-IUS in that study (OR = 0.77, 95% CI 0.52-1.13).

Mørch et al[19] published a study based on data from 1.8 million Danish women who were followed up for an average of 10.9 years. Women who used LNG-IUS at the time of data collection (current users) or who reported recent use of contraception had a higher risk of breast cancer than women who had never used hormonal contraceptives. Data from 503 441 women-years using LNG-IUS showed an RR of 1.21 (95% CI 1.11-1.33). Mørch et al[19] reported 571 cases of breast cancer among LNG-IUS users.

Backman et al[11] performed a re-analysis of the data obtained in an earlier postmarketing study about the adverse effects of a commercial LNG-IUS for contraception. The incidence of breast cancer in LNG-IUS users by age group per 100 000 women-years was contrasted with the breast cancer incidence data derived from the National Finnish Cancer Registry. For three age groups (40-44, 45-49, and 50-54 years), the point estimates for breast cancer incidence were higher in the average population than in LNG-IUS

users. In two age groups (30-34 and 35-39 years), the point estimate in LNG-IUS users was higher than that in the average Finnish female population. However, these trends were not significant considering 95% CI.

With respect to case-control studies, Dinger et al[15] evaluated the risk for breast cancer in users of LNG-IUS vs that in users of a copper intrauterine device (Cu-IUD), using population-based data from Germany and Finland. Devices, either LNG-IUS or Cu-IUD, were used for contraception by women up to age 50 years. Data were retrieved from Finnish and German cancer registries. Data from 5133 breast cancer cases and 20 452 non-breast cancer cases were included. The point estimate of the crude and adjusted ORs for the risk of breast cancer among women who had ever used LNG-IUS compared with those who had ever used Cu-IUD was OR LNG-IUS = 1.04 (95% CI 0.93-1.17). The adjusted OR was 0.88 (95% CI 0.49-1.59) among current LNG-IUS users (women who were using an IUD at the time of breast cancer diagnosis).

Siegelmann-Danieli et al[18] performed a retrospective cohort study in perimenopausal women aged 40-50 years from Israel,[18] in which the breast cancer risk was compared between 13 354 LNG-IUS users and 27 324 age-matched non-users of LNG-IUS. Patients receiving hormone replacement therapy or oral contraceptive (OCs) were excluded from the analysis. No significant differences in the 5-year Kaplan-Meier estimates for overall breast cancer were observed; however, there was a trend towards a higher risk for breast cancer in LNG-IUS users than in non-users (5-year Kaplan-Meier estimate: 1.06% vs 0.93%, $P = .051$). This difference was primarily observed in younger women (40-45 years; 0.88% vs 0.69%, $P = .014$), whereas it was non-significant (1.44% vs 1.21%, $P = .26$) in older women (46-50 years).

A Norwegian-based prospective cohort study (NOWAC—Norwegian Women and Cancer study)[17] logged data from 9144 LNG-IUS users and 95 174 non-users. After 12.5 years, 297 breast cancer cases were reported. The RR of breast cancer in LNG-IUS users was 1.03 (95% CI 0.91-1.17) and body mass index (BMI), physical activity level, maternal history of breast cancer, and menopausal status were considered in the analyses.

3.2 | Meta-analysis

Seven of the 8 studies reviewed had complete data on the number of users and non-users of LNG-IUS and the risk of breast cancer after LNG-IUS insertion. Three[12,14,15] were case-control studies and 4 were cohort studies[16-19] (Figure 2). The study by Backman et al[11] was not included in the meta-analysis owing to a lack of direct patient data, as the effects of LNG-IUS use were reported for 5-year age strata of women. We failed to reach the authors to obtain usable effect measures.

A funnel plot (Figure 3) was generated, and a linear regression test of funnel plot asymmetry was performed to assess publication bias. Funnel plot symmetry and a negative result from the funnel plot asymmetry test (Egger's test, $P = .635$)[13] led us to conclude that there is no detectable publication bias.

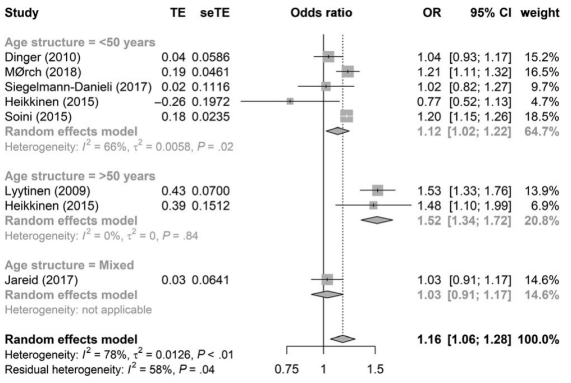

FIGURE 2 Forest Plot meta-analysis

Our meta-analysis model was constructed using data derived from the original results reported in the studies. We stratified the analyses by the age strata of the women included in each paper (<50 years, ≥50 years, and mixed). Because of study heterogeneity (I^2 = 78%), especially among studies reporting on patients aged <50 years, we used the random-effects model. By standardizing the effect sizes of all studies and combining the results from these 7 studies, the meta-analysis indicated an increased breast cancer risk in LNG-IUS users: age <50 years, OR = 1.12 (95% CI 1.02-1.22, I^2 = 66%, $P = .02$); age ≥50 years, OR = 1.52 (95% CI 1.34-1.72, I^2 = 0%, $P = .84$). For all women, the meta-analysis indicated an increased breast cancer risk in LNG-IUS users (OR = 1.16, 95% CI 1.06-1.28, I^2 = 78%, $P < .01$).

3.3 | Controlling for known breast cancer risk factors

The control of factors influencing the breast cancer incidence (education, socioeconomic status, reproductive and hormone factors, previous history of breast cancer, use of alcohol, elevated BMI)[20] varied greatly among the studies included in this meta-analysis. Backman et al[11] and Soini et al[16] did not adjust their analyses for factors related to breast cancer risk. Siegelmann-Danieli et al[18] excluded from the analysis women with exposure to female hormones in the form of OCs, fertility drugs, or HT or prophylactic use of tamoxifen in the 5 years preceding day 1 and through November 2015. Dinger et al[15] considered potential risk factors for breast cancer, including BMI, family history of breast cancer, age at first birth, age at menarche, and physical activity. Heikkinen et al[12] adjusted the results for year of birth, previous hormonal contraceptive use and HT, age at menarche, parity, family history of breast cancer, BMI, years of schooling, smoking, and alcohol use. Lyytinen et al[14] were able to control only for age at first birth and parity. Jareid et al[17] identified age at the start of follow up, BMI, physical activity level at enrolment, maternal

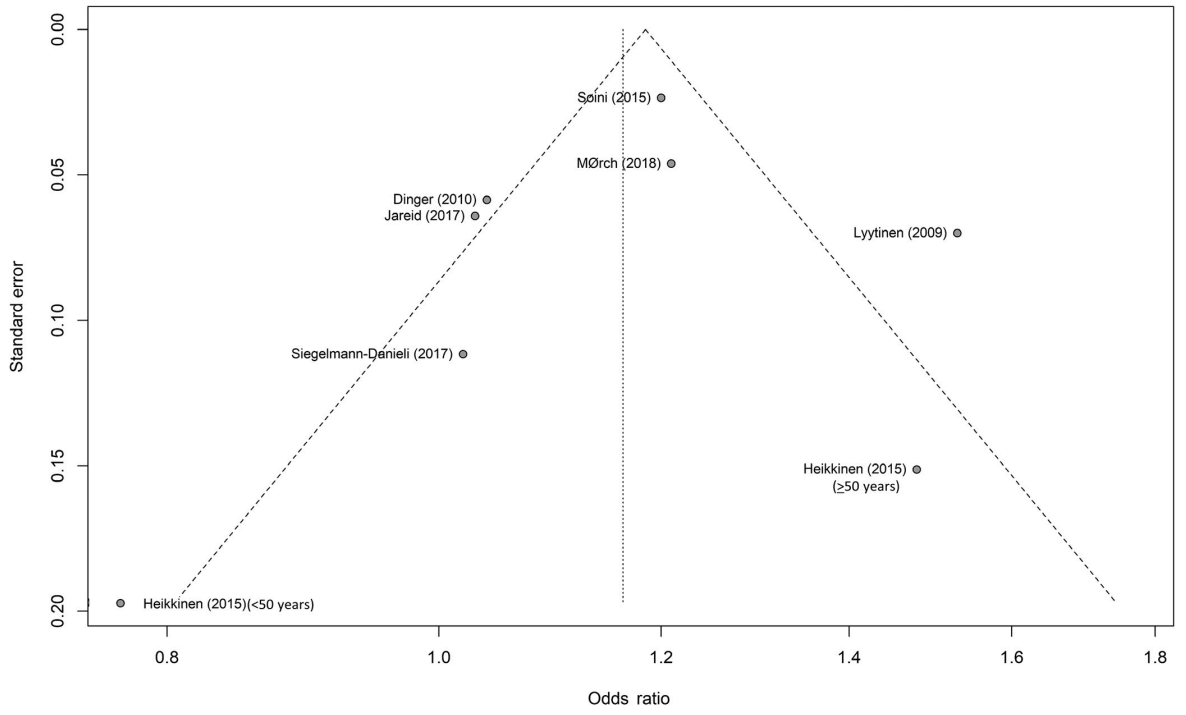

FIGURE 3 Funnel plot of the studies included

history of breast cancer, age at menarche, ever use of OCs, parity, and menopausal status at the start of follow-up. Mørch et al[19] adjusted for age, education, previous OC use, endometriosis, parity, and family history of premenopausal breast or ovarian cancer.

3.4 | Use of OCs and postmenopausal HT before LNG-IUS insertion

The authors of the studies included in the meta-analysis had different approaches to data from OC and HT use before the insertion of LNG-IUS. Siegelmann-Danieli et al[18] excluded from the analysis women with exposure to female hormones in the form of OCs, fertility drugs, or HT or prophylactic use of tamoxifen in the 5 years preceding day 1 and through November 2015. Dinger et al[15] captured information about hormone exposure (contraception, HT) and controlled this information as a confounding factor; however, there was no information about the duration of previous use and when/if it was withdrawn. Heikkinen et al[12] categorized the duration of hormonal contraceptive use as none, 1 month, 1-6 months, 6 months to 2 years, 2-4 years, 4-8 years, 8-12 years, 12-16 years, 16-20 years, 20-25 years, and 25 years. They pooled these categories to form a trinomial variable, with levels of 1 month, 1-6 months, and 6 months to 2 years. Thereafter, these women were further grouped according to the duration of exposure to HT (<2 or >2 years). Use of IUD was categorized as ever use vs never use. For ever users, the type of device was also asked, with the options being Cu-IUD, hormone-releasing IUD, and other IUDs. For further analysis, a reference category with never users of any hormonal contraceptive (hormone-releasing IUD or other hormonal contraceptives) was also formed. The use of HT was classified as ever use vs never use regardless of duration. Information on current use of HT was used only as a reference factor in survey validation. Jareid et al[17] included OC use as a dichotomous variable and analyzed OC use by duration; however, they did not change the estimate of the main exposure and did not adjust for time since OC use. Mørch et al[19] categorized OC use as current use or recent use (discontinuation within the previous 6 months) or previous use (discontinuation >6 months previously). LNG-IUS was assumed to be used for 4 years, unless the woman became pregnant or another hormonal contraceptive was prescribed before the end of the 4-year period. Backman et al,[11] Lyytinen et al,[14] and Soini et al[16] did not control for previous OC use.

3.5 | Methodological quality of the studies

The methodological quality of the studies was evaluated using the Downs and Black instrument for adapted quality assessment.[21] Five studies[12,15-17,19] were considered to be "good", whereas the three remaining studies were considered "fair".[11,14,18] Table 2 lists the risk of bias of each of the selected studies.

TABLE 2 Methodological quality of the studies using the Downs and Black Instrument adapted quality assessment checklist

Studies Year of publication	Dinger 2010[a]	Soini 2015[b]	Lyytinen 2009[c]	Backman 2005[d]	Mørch 2018[e]	Siegelmann 2017[f]	Heikkinen 2015[g]	Jareid 2017[h]
Reporting								
Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1	1	1	1	1
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1	1	1	1	1
Are the characteristics of the patients included in the study clearly described?	1	1	1	1	1	1	1	1
Are the interventions of interest clearly described?	1	1	1	1	1	1	1	1
Are the distributions of principal confounders in each group of participants to be compared clearly described?	2	0	1	0	1	0	1	2
Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1	1	1	1	1
Have all important adverse events that may be a consequence of the intervention been reported?	0	0	0	0	0	0	0	0
Have the characteristics of patients lost to follow up been described?	1	1	0	1	0	0	0	0
Have actual probability values been reported for the main outcomes except where the probability value is <.001?	1	1	1	1	1	1	1	1
External validity								
Were the women asked to participate in the study representative of the entire population from which they were recruited?	0	1	0	0	1	0	0	0
Were those women who were prepared to participate representative of the entire population from which they were recruited?	1	1	1	1	1	1	1	1
Were the stay, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1	1
Internal validity—bias								
Was an attempt made to blind study participants to the intervention they have received?	0	0	0	0	0	0	0	0
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	0	0	0	0	0	0	0
If any of the results of the study were based on "data dredging", was this made clear?	1	1	1	1	1	1	1	1
In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	1	1	1	1	1	1	1	1
Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1	1	1	1	1
Was compliance with the intervention/s reliable?	1	1	1	1	1	1	1	1
Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1	1	1	1	1
Internal validity—confounding (selection bias)								
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	0	1	1	1	1	1	1	1

(Continues)

TABLE 2 (Continued)

Studies Year of publication	Dinger 2010[a]	Soini 2015[b]	Lyytinen 2009[c]	Backman 2005[d]	Mørch 2018[e]	Siegelmann 2017[f]	Heikkinen 2015[g]	Jareid 2017[h]
Were study participants in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	1	1	1	1	1	1	1
Were study participants randomized to intervention groups?	0	0	0	0	0	0	0	0
Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0	0	0	0	0	0	0	0
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	0	1	0	1	1	1	1
Were losses of patients to follow up taken into account?	1	1	0	0	1	0	1	1
Power								
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	1	1	1	1	1	1	1
Final score	21	20	19	18	21	18	20	21

[a]Dinger J, Bardenheuer K, Minh TD, Soini T, Hurskainen R, Grénman S, et al. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. *Contraception* [Internet]. 2011;83(3):211-17. Available from: http://dx.doi.org/10.1016/j.contraception.2010.11.009

[b]Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Joensuu H, et al. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. *Acta Oncol* [Internet]. 2016;55(2):188-92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26243443

[c]Lyytinen HK, Dyba T, Ylikorkala O, Pukkala EI. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: Intrauterine system carries a risk as well. *Int J Cancer* [Internet]. 2010 Jan 15 [cited 2016 Aug 29];126(2):483-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19588504

[d]Backman T, Rauramo I, Jaakkola K et al. Use of the levonorgestrel-releasing intrauterine system and breast cancer. *Obstet Gynecol* [Internet]. 2005;106:813- Available from: http://linkinghub.elsevier.com/retrieve/pii/S0015028207012009

[e]Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med* [Internet]. 2017;377(23):2228-39. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1700732

[f]Siegelmann-Danieli N, Katzir I, Landes JV, Segal Y, Bachar R, Rabinovich HR, et al. Does levonorgestrel-releasing intrauterine system increase breast cancer risk in peri-menopausal women? An HMO perspective. *Breast Cancer Res Treat* 2018;167(1):257-62.

[g]Heikkinen S, Koskenvuo M, Malila N, Sarkeala T, Pukkala E, Pitkäniemi J. Use of exogenous hormones and the risk of breast cancer: results from self-reported survey data with validity assessment. *Cancer Causes Control* 2016;27(2):249-58.

[h]Jareid M, Thalabard JC, Aarflot M, Bøvelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. *Gynecol Oncol* 2018:4-9.

4 | DISCUSSION

This systematic review and meta-analysis points towards an augmented breast cancer risk among LNG-IUS users, especially for women aged 50 years or older. Importantly, there are no randomized data for women using LNG-IUS vs those using other methods. In addition, the studies in this meta-analysis included cohorts of women using LNG-IUS for different reasons, including contraception, abnormal bleeding, endometrial protection, and other medical reasons.

We obtained separate risk estimates for women according to different age strata, which allowed us to perform a stratified meta-analysis. The meta-analysis clearly demonstrated that the breast cancer risk increases in parallel with the age strata of LNG-IUS users. In fact, in the meta-analysis, only 2 of 5 studies reporting on women aged <50 years found an increased risk for breast cancer among LNG-IUS users.[16,19] The breast cancer risk in older women was examined in 2[12,14] of the 8 studies[11,12,14-19] included in this review, and both studies indicated that older (in general, postmenopausal) women using LNG-IUS for reasons other than contraception have a higher breast cancer risk.[12,14]

Nonetheless, we were particularly concerned about the reported and unreported use of LNG-IUS after a period of exposure to other forms of hormonal contraception, typically combined OCs.[19] Hence, if there is no or only a very small gap between previous hormonal contraceptive use and insertion of an IUS, then it will be difficult to discriminate the possible biological effects of LNG-IUS itself from a lingering effect of previous hormonal contraception. Most authors acknowledge that "Insufficient adjustment for this (OC/HT use) and for use of other hormonal contraceptives may have caused residual confounding in our estimates."[14,16] Notably, it is worth mentioning that some studies included in the meta-analysis had no results adjusted for OC use (yes or no, although duration was not accounted for) before LNG-IUS

insertion. The study by Mørch et al,[19] however, must be singled out as the only study to have found evidence of an increased breast cancer risk in women who had used LNG-IUS for >10 years, a group of women for whom the risk attributable to previous use of other hormonal contraception methods or HT is offset by the time elapsed since these other treatments had been terminated.

It is important to note that some risk factors for breast cancer may be relatively common in women with clinical indications for perimenopausal/postmenopausal LNG-IUS use. Abnormal bleeding and heavy menstrual bleeding are indications for the use of LNG-IUS,[22] and these conditions are more frequent in obese women who are at increased risk of breast cancer owing to long periods of anovulation or abnormal ovulation.[23] Other factors of similar association are hypoestrogenic conditions and premature ovarian failure.[23,24]

Postmenopausal HT has also been associated with breast cancer, making it difficult to discriminate the possible biological effects of IUS in protecting the uterus in postmenopausal women from the effects of concurrent use of HT.[25] Thereby, Jones et al,[23] in a cohort of 113 693 English women older than 16 years, evaluated the risks associated with HT for the development of breast cancer. These authors controlled for the aforementioned factors. The hazard ratio for invasive and in situ breast cancer, adjusted for age at menopause, was 1.95 (95% CI 1.55-2.46, P = .001) for current users of all types of HT compared with women who had never used HT. The risk increased by 3.8% per year (95% CI 0.4-7.3%, P = .027) of HT use, and HT use in excess of 15 years was associated with a hazard ratio of 2.02 (95% CI 1.12-3.66, P = .020). More recently, a large meta-analysis concluded that in women of average weight in developed countries, 5 years of HT (estrogen plus daily progestogen) starting at age 50 years could result in one case of breast cancer per 50 HT users. The HT-attributable breast cancer risk decreases to one case in every 70 users of estrogen plus intermittent progestogen, and one in every 200 users of estrogen only.[26]

It can be argued that the question of whether LNG-IUS use is safe from the oncological standpoint remains unresolved, largely owing to unsurmountable difficulties in discriminating the effects of several confounding factors in the analysis of data obtained from LNG-IUS users. From a strictly technical point of view, that affirmation is true, as there are no randomized studies on the association between LNG-IUS use and breast cancer. However, our meta-analysis of non-randomized cohorts showed a clear association between LNG-IUS use and breast cancer risk, which seems strikingly pervasive among users aged ≥50 years. This risk was observable in studies examining women with different clinical and epidemiological backgrounds.

In our opinion, the increased risk of breast cancer among LNG-IUS users needs to be weighed against the potential health benefits of LNG-IUS, such as highly effective, long-acting, and reversible contraception. LNG-IUS has many proven useful applications, being, for example, an effective contraception method, and effective to treat heavy menstrual bleeding. However, caution is needed when indicating LNG-IUS for long periods of use, especially in women with other known breast cancer risk factors such as older age, obesity, and familial predisposition.

5 | CONCLUSION

We obtained evidence suggesting a link between breast cancer risk and LNG-IUS use at any age and for any indication. However, methodological issues across the available studies may cast some doubts about this relation, and concerns about problems inherent to studying such a complex issue in different sets of women are certainly worth considering. If our analysis is valid, the attributable breast cancer risk is most likely marginal for premenopausal LNG-IUS users; however, for women older than 50 years, there may be a nearly 40% increased breast cancer risk. Given the evidence showing an association between hormonal contraception and HT with breast cancer risk, it is difficult to believe that LNG-IUS use may be devoid of any oncological risk. Users of LNG-IUS should therefore be aware of these trends, and risks associated with LNG-IUS use must be balanced against its proven health benefits, eg effective treatment of heavy menstrual bleeding and reduced need for surgical interventions.

CONFLICT OF INTEREST

Luis Bahamondes received an honorarium from Bayer to be a member of the advisory board. The other authors have no conflicts of interest to disclose.

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How to cite this article: Conz L, Mota BS, Bahamondes L, et al. Levonorgestrel-releasing intrauterine system and breast cancer risk: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2020;99:970–982. https://doi.org/10.1111/aogs.13817