

# Letters

## RESEARCH LETTER

### Breast Cancer in Users of Levonorgestrel-Releasing Intrauterine Systems

Use of levonorgestrel-releasing intrauterine systems (LNG-IUSs) has been increasing. LNG-IUS use constitutes the preferred hormonal contraception among Danish premenopausal women older than 30 years. However, whether use of an LNG-IUS is associated with breast cancer risk remains unclear.<sup>1-5</sup>

#### **+** Supplemental content

Increased breast cancer risk was found in users of LNG-IUSs,<sup>1</sup> but that study was not designed to address duration of continuous use. Also, previous studies have not adequately accounted for other hormonal contraceptive use.<sup>1-5</sup> This study assessed breast cancer risk with continuous use of an LNG-IUS, accounting for other hormonal exposures.

**Methods** | Using nationwide Danish registers (eTable 1 in Supplement 1), all first-time initiators of any LNG-IUS (doses of 52 mg, 19.5 mg, and 13.5 mg) aged 15 to 49 years in 2000 to 2019 were identified and birth year-matched (1:1) to nonusers of hormonal contraceptives on the date of initiation (index date). Exclusion criteria were use of other hormonal contraceptives within 5 years before the index date, previous use of postmenopausal hormone therapy, previous cancer, and pregnancy at index date. This register study complies with Danish General Data Protection Regulation; ethical approval and patient consent were not required.

Participants were followed up from the index date until breast cancer diagnosis, other cancer diagnosis, pregnancy, postmenopausal hormone therapy initiation, emigration, death, or December 31, 2022, whichever occurred first (eTable 1 in Supplement 1). Participants were censored at exposure deviation: nonusers at hormonal contraception initiation and LNG-IUS users at other hormonal contraceptive initiation or at the end of the maximum period for continuous LNG-IUS use (ie, maximum recommended use plus 1 year accounting for use beyond recommendation and short pauses with no additional redeemed prescriptions). Codes for LNG-IUS removal were not valid and therefore not used.

Continuous LNG-IUS use was time-varying, defined from the date of a filled prescription until the maximum period for continuous LNG-IUS use, which was 6 years for 95% of devices initiated in the present study. A new prescription within the maximum duration period added another maximum period from that date.

Cox proportional hazard models were used to analyze the association between continuous LNG-IUS use and breast cancer adjusted for age, calendar period, previous hormonal contraception duration, fertility drugs, parity, age at first delivery, polycystic ovarian syndrome, endometriosis, and educational level at index date (Table).

Table. Characteristics of Females Initiating Levonorgestrel-Releasing Intrauterine Systems (LNG-IUSs) and Nonusers of Hormonal Contraception

Characteristics	No. (%)	
	LNG-IUS users <sup>a</sup>	Nonusers <sup>a</sup>
<b>Females, No.</b>	<b>78 595</b>	78 595
Person-years, No.	462 271	601 066
Person-years, mean (SD)	5.9 (3.1)	7.7 (5.4)
Age, mean (SD), y	38.3 (7.7)	38.3 (7.7)
Breast cancer, No.	720	897
Parity		
0	8779 (11)	21 148 (27)
1	9637 (12)	11 571 (15)
2	40 009 (51)	29 338 (37)
3	16 442 (21)	12 678 (16)
≥4	3728 (4.7)	3860 (4.9)
Age at first delivery, (SD), y	26.4 (4.2)	26.0 (4.6)
Duration of previous hormonal contraception use, (SD), y <sup>b</sup>	6.5 (4.6)	5.9 (4.6)
Polycystic ovary syndrome	430 (0.5)	469 (0.6)
Endometriosis	1131 (1.4)	972 (1.2)
Fertility drugs	4652 (5.9)	4714 (6.0)
Education		
Primary and lower secondary	12 570 (16)	18 093 (23)
Upper secondary	32 101 (41)	30 751 (39)
Short cycle tertiary	3872 (4.9)	3078 (3.9)
Bachelor's or equivalent	21 523 (27)	17 454 (22)
Master's or higher	8269 (11)	6870 (8.7)
Unknown	260 (0.3)	2349 (3.0)

<sup>a</sup> Initiators of LNG-IUS were birth year matched 1:1 at initiation to nonusers of hormonal contraception (index date).

<sup>b</sup> Females who used hormonal contraception within 5 years up to index date were excluded from this study. Duration of previous hormonal contraception use (all products) was assessed more than 5 years before index date. Percent of females who used hormonal contraception more than 5 years before index date: LNG-IUS users, 68%; nonusers, 57%.

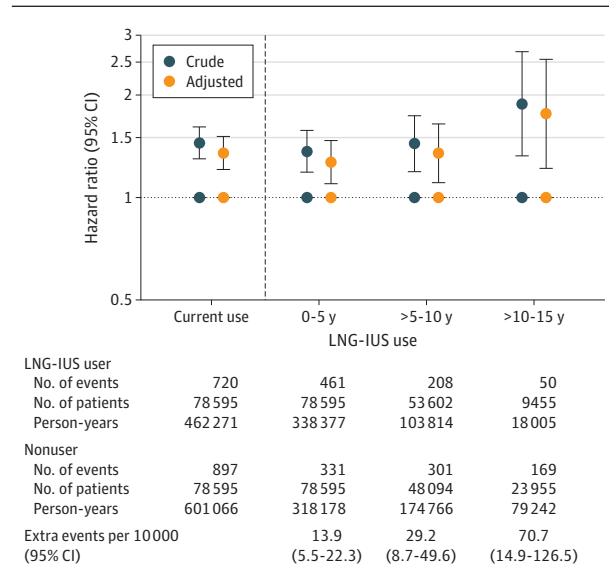
Further, the analysis was stratified in 5-year intervals: 0 to 5 years, more than 5 years to 10 years, and more than 10 years to 15 years. A trend test was performed to examine differences in duration of use.

Excess breast cancers were estimated as the difference between the adjusted cumulative incidence functions for continuous use vs nonuse.<sup>6</sup>

Statistical significance was defined as a  $P < .05$  (2-sided). SAS version 9.4 (SAS Institute) was used for all statistical analyses.

**Results** | A total of 78 595 new LNG-IUS users and 78 595 nonusers of hormonal contraceptives were identified. During a mean follow-up of 6.8 years, 1617 participants were diagnosed with breast cancer: 720 LNG-IUS users and 897 nonusers. The mean (SD) age of participants was 38 (7.7) years. Participant characteristics are shown in the Table.

**Figure. Adjusted Hazard Ratios and Excess Breast Cancers per 10 000 Continuous Users of Levonorgestrel-Releasing Intrauterine System (LNG-IUS)**



Adjusted by age, calendar period, duration of previous hormonal contraception use, fertility drugs, parity, age at first birth, polycystic ovarian syndrome, endometriosis, and highest achieved educational level. Current use: hazard ratio (HR) for breast cancer in LNG-IUS users vs nonusers of hormonal contraceptives. HR for breast cancer in LNG-IUS users vs nonusers of hormonal contraceptives stratified in 5-year intervals (0-5, >5-10, and >10-15 years). The numbers of participants (LNG-IUS users and nonusers) and cases of breast cancer in the stratified analyses do not add up to the numbers for the "current use" estimate because of the restriction on follow-up to 15 years.

The hazard ratio (HR) for breast cancer was 1.4 (95% CI, 1.2-1.5) with LNG-IUS use compared with nonuse of hormonal contraceptives. For 0 to 5, more than 5 to 10, and more than 10 to 15 years of use, the HRs were 1.3 (95% CI, 1.1-1.5), 1.4 (95% CI, 1.1-1.7), and 1.8 (95% CI, 1.2-2.6), respectively, compared with corresponding durations of nonuse, resulting in an excess of 14 (95% CI, 6-23), 29 (95% CI, 9-50), and 71 (95% CI, 15-127) breast cancer diagnoses per 10 000 users, respectively (Figure). The test for trend was not statistically significant ( $P = .15$ ).

**Discussion |** This Danish nationwide study found an association between LNG-IUS use and increased breast cancer risk in females aged 15 to 49 years, compared with nonuse. Although the absolute breast cancer risk is low in young women, this study found an excess risk of 14 per 10 000 females. The risk did not increase with duration of use.

Given the increase in LNG-IUS use among females at an age with some risk for breast cancer, and its likely long-term use, information about breast cancer risk should accompany discussions about benefits and risks. The HR with short-term LNG-IUS use was similar to that of contraceptive pills<sup>1</sup> (1.2 [95% CI, 1.1-1.3]).

Limitations of this study include that some women may have had the LNG-IUS removed before the end of recom-

mended use, leading to an underestimation of breast cancer risk. Lack of dose-response could indicate low statistical precision or no causal association. Also, unmeasured confounding cannot be excluded.

Lina Steinrud Mørch, MSc, PhD  
 Amani Meaidi, MD, PhD  
 Giulia Corn, MSc, PhD  
 Marie Hargreave, MSc, PhD  
 Charlotte Wessel Skovlund, MSc, PhD

**Author Affiliations:** Cancer and Medicine, The Danish Cancer Institute, Copenhagen, Denmark (Mørch, Meaidi, Wessel Skovlund); Statistics and Data Analysis, The Danish Cancer Institute, Copenhagen, Denmark (Corn); Virus, Lifestyle and Genes, The Danish Cancer Institute, Copenhagen, Denmark (Hargreave).

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**Corresponding Author:** Lina Steinrud Mørch, MSc, PhD, Cancer and Medicine, The Danish Cancer Institute, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark (morch@cancer.dk).

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**Concept and design:** Mørch, Corn, Skovlund.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Mørch.

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