GYNECOLOGY

Association of levonorgestrel-releasing intrauterine device with gynecologic and breast cancers: a national cohort study in Sweden

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BACKGROUND: The levonorgestrel-releasing intrauterine device (LNG-IUD) is widely used for the treatment of menorrhagia, dysmenorrhea, and for contraception. However, the association between the use of LNG-IUD and the risk of site-specific gynecologic and breast cancers remains inconclusive.

OBJECTIVE: We aim to address this knowledge gap by investigating whether the use of LNG-IUD is associated with a significant risk of site-specific gynecologic and breast cancers. This will be achieved by accessing the nationwide Swedish Registers, with consideration given to the influence and potential interaction of family history of cancer.

STUDY DESIGN: A total of 514,719 women aged 18 to 50 years who have used LNG-IUD between July 2005 and December 2018 were identified from the Swedish Prescribed Drug Register and randomly matched with 1,544,157 comparisons who did not use LNG-IUD at a ratio of 1:3. The propensity score was calculated and matched among women who used LNG-IUD and the matched comparisons. The follow-up period started from the date of the first prescription of LNG-IUD for users as well as for their matched comparisons and ended at the date of diagnosis of gynecologic and breast cancers, date of death from any cause, and the end of the study period, whichever came first. The Cox proportional hazard model with a competing risk analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Additive interaction was calculated as the relative excess risk for interaction, while multiplicative interaction was calculated by including a product term in the regression model.

RESULTS: The use of LNG-IUD was associated with a 13% higher risk of breast cancer (adjusted HR, 1.13; 95% CI, 1.10—1.17), a 33% lower risk of endometrial cancer (adjusted HR, 0.67; 95% CI, 0.56—0.80), a 14% lower risk of ovarian cancer (adjusted HR, 0.86; 95% CI, 0.75—0.99), and a 9% reduced risk of cervical cancer (adjusted HR, 0.91; 95% CI, 0.84—0.99) compared to women who did not use LNG-IUD. A significant additive interaction between LNG-IUD use and family history of cancer was observed in breast cancer, indicating a relative 19% excess risk for interaction ($P<.002$), and 1.63 additional cases per 10,000 person-years.

CONCLUSION: The risk of gynecologic and breast cancers exhibits a site-specific effect among LNG-IUD users. It is important to note that the observed effect is small for breast cancer and the results are limited by the observational study design. Clinical recommendations regarding the use of LNG-IUD should carefully weigh its potential benefits and risks. Close monitoring is advisable for the potential development of breast cancer, particularly among women with a family history of breast cancer.

Key words: breast cancer, family history, gynecologic cancer, levonorgestrel-releasing intrauterine device

Introduction

The levonorgestrel-releasing intrauterine device (LNG-IUD) is primarily used for the treatment of endometriosis and menorrhagia,[1,2] but it is increasingly chosen by young women for contraception because of its ability to suppress menstruation and reduce discomfort.[3,4] LNG-IUD is a well-proven form of long-acting highly reversible contraception associated with superior effectiveness and high satisfaction compared to oral contraceptives.[5,6] Based on the strong evidence for contraception, the updated National Guidelines for contraceptive counseling have recommended LNG-IUDs use in young and nulliparous women and even as a first-line choice for women starting contraceptive use in 2014.[7] However, it is still controversial whether progesterone, which can act on progesterone receptors distributed throughout the body, causes lesions or cancer in the corresponding target organs.

Malignancies that are susceptible to hormonal factors include breast, endometrial, cervical, and ovarian cancers,[8—10] which have a strong correlation with reproductive history. Breast cancer is the most common cancer in women, with approximately 2.3 million new cases worldwide each year,[11] The role of hormonal contraception in breast cancer development has been debated for decades. A study demonstrated that combining progestins with estrogens significantly increases the risk of breast cancer.[9] However, the effect of LNG-IUD on breast cancer remains controversial. Although the amount of levonorgestrel released by LNG-IUD is the lowest of all hormone supplementation therapy modalities,[12] there is still an increased risk of breast cancer. Endometrial, cervical, and ovarian cancers are the 3 most common gynecologic malignancies.[13] Although the protective effects of combined hormonal contraception against endometrial and ovarian cancer and tubal sterilization against ovarian cancer are generally well-accepted,[14,15] little is known about the influence of LNG-IUD on the incidence of gynecologic malignancies. Therefore, large-scale population-based study is

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AJOG at a Glance

Why was this study conducted?

The association between the use of levonorgestrel-releasing intrauterine device (LNG-IUD) and the risk of site-specific gynecologic and breast cancers remains controversial. The influence and potential interaction of family history of cancer with LNG-IUD has not been explored so far. These unanswered questions could be explored by a population-based cohort study utilizing the nationwide Swedish registers.

Key findings

This nationwide cohort study in Sweden presents novel evidence indicating a 13% higher risk of breast cancer among women using LNG-IUD. Importantly, a synergistic effect was observed among women with a family history of breast cancer who also used LNG-IUD. Women who used LNG-IUD have a 33% reduced risk of endometrial cancer. LNG-IUD use is associated with a 14% lower risk of cervical cancer and a 9% lower risk of ovarian cancer.

What does this add to what is known?

LNG-IUD use shows a site-specific association with gynecologic and breast cancers. The synergistic effect between LNG-IUD use and a family history of breast cancer calls for extra attention to monitor the development of breast cancer, especially for women with a family history. The observed effect is small for breast cancer and the results are limited by the observational study design.

still needed to confirm the effect of LNG-IUD use on gynecologic and breast cancers.

Other factors, including age, diet, body mass index, and a family history of cancer, also contribute to the development of gynecologic and breast cancers.[16,17] Studies have shown that up to 24% of ovarian cancer and 5% to 10% of breast cancer are caused by genetic factors.[18,19] Lynch syndrome is reported to be associated with endometrial cancer and Peutz-Jeghers syndrome is associated with cervical cancer, suggesting the possible contribution of genetic factors.[20,21] Considering the potential interactive effect of genetic factors and LNG-IUD on the development of gynecologic and breast cancers, it is crucial to consider the family history of cancer in women planning to use LNG-IUD. Unfortunately, there have been no previous studies exploring this specific issue.

In this nationwide cohort study in Sweden, including a total of 514,719 women who have used LNG-IUD and up to 13 years of follow-up, we aimed to explore the subsequent development of gynecological and breast cancers among these LNG-IUD users. Additionally, we explored the potential interaction of family history of cancer and LNG-IUD on the development of these cancers. Such evidence could guide clinical recommendations, especially for those with a family history of cancer.

Methods

Data sources

The present nationwide cohort study was approved by the Ethics Committee at Lund University (protocol number: Dnr 2012/795 and later amendments), Sweden.

The source population comprised 4,108,251 cancer-free Swedish females registered between July 2005 and December 2018 in the Swedish Total Population Register, which provides detailed demographic data for almost 100% of Sweden's residents.[22] The Swedish Prescribed Drug Register, initiated on July 1, 2005, encompasses information on all prescribed medications, covering the entire Swedish population with a less than 0.3% estimated rate of missing individual identity data.[23] Using the Anatomical Therapeutic Chemical Classification code G02BA03, we identified 514,719 females aged 18 to 50 years who received LNG-IUD prescriptions from July 2005 to December 2018 (Figure 1). For each LNG-IUD user, 3 individuals without LNG-IUD prescriptions were randomly chosen from the source population, matched by propensity score based on age, education level, income, parity, age at the birth of the first child, history of endometriosis, history of uterine leiomyoma, history of hormonal therapy, obesity, chronic obstructive pulmonary disease (COPD), Charlson Comorbidity Index (CCI), and family history of cancer.

Assessment of outcome

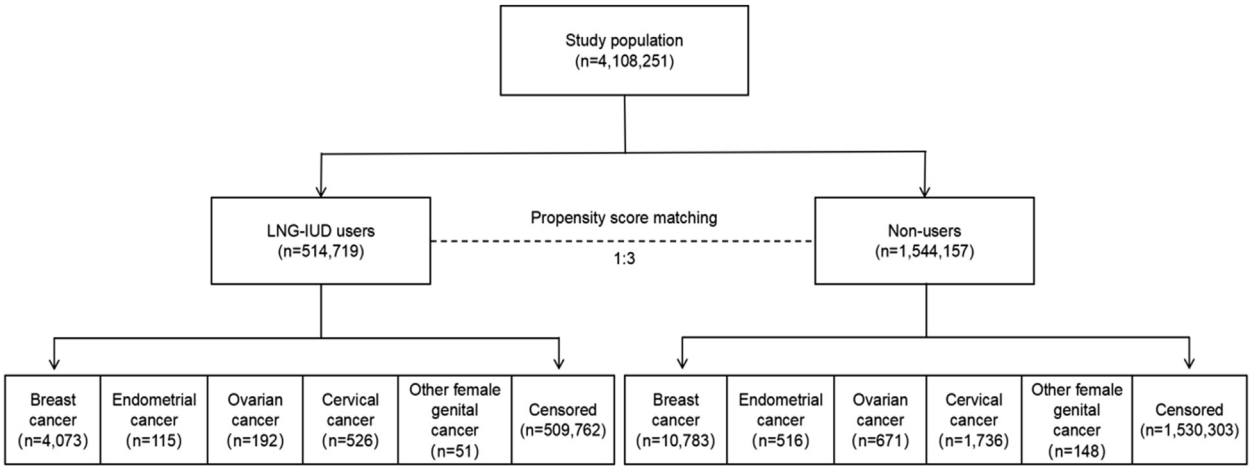
These individuals were further linked to the Swedish Cancer Registry to identify those who had been diagnosed with cancers, by using the 10th International Classification of Diseases (ICD) codes of C50 for breast cancer, C53 for cervical cancer, C54.1 for endometrial cancer, C56 for ovarian cancer, and C51−C52, C54.0, C54.2−C54.9, C55, and C57 for other gynecologic cancers. By further linking to the Cause of Death Register, we could identify individuals who had died during the follow-up period.

The follow-up was started on the date of the first prescription of LNG-IUD for LNG-IUD users or the index date for their comparisons (the same date as the corresponding LNG-IUD user), ended at the first date of diagnosis of gynecologic and breast cancers, date of death from any cause, and the end of the study period (December 31, 2018), whichever came first.

Assessment of covariates

By retrieving data from the National Patient Register, Statistics Sweden's Total Population Register and Population Housing Census, and Swedish Multiple Generation Register, we extracted information on potential confounding factors, including age, highest education (1−9, 10−11, and ≥12 years),[23] income (lowest, middle-low, middle-high, and highest), parity (0, 1, 2, 3, and ≥4), age at the birth of the first child (never, ≤30 years, 31−40 years, and >40 years), history of endometriosis (yes/no),

FIGURE 1
Flowchart of participants involved in this national cohort study



LNG-IUD, levonorgestrel-releasing intrauterine device.

history of uterine leiomyoma (yes/no), history of hormonal therapy (yes/no), family history of cancer (having at least 1 first-degree relative diagnosed with cancer, yes/no), obesity (identified from the National Patient Register using ICD code E66, yes/no), COPD (yes/no) as a proxy for smoking, and CCI (0, 1, 2, and ≥3). As comorbidity is an important factor affecting the health condition and risk of cancer, we calculated the CCI based on a total of 17 categories.[24]

Statistical analysis

Continuous covariates were expressed as mean±standard deviation, while categorical covariates were presented as counts and percentages. The propensity score was calculated using a logistic regression model to estimate the probability of LNG-IUD use. Subsequently, the propensity score was utilized to match women who used LNG-IUD with those who did not (with a caliper width of 0.1).[25] Standardized mean differences (SMDs) were usually used to assess the balance of the covariates between the study group and the control groups after propensity score matching.[26,27] Additionally, we calculated the *P* value to explore whether these covariates were balanced after the matching (Supplemental Table). Competing risk Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of gynecologic and breast cancers associated with LNG-IUD use to control the competing risk of other types of cancer. Besides relative risk (HR) calculation, the association between exposure to IUD and breast cancer was assessed through the evaluation of absolute risk reduction (ARR).

We simultaneously analyzed the effect of the interaction of LNG-IUD and family history of gynecologic and breast cancers. Multiplicative interaction was assessed by the ratio of odds ratio (OR) ($OR_{combined}/[OR_{IUD}{}^{*}OR_{family\ history}]$), which was assessed by adding the multiplicative interaction term to the regression model as indicator variables. Additive interaction was calculated as the relative excess risk for interaction.[28] We also stratified the analyses based on age and menopausal state to evaluate the specific effects of LNG-IUD on the risk of gynecologic and breast cancers.

All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Figure 1 shows the flowchart of the study design. A total of 2,058,876 females were included in the analysis for the association of LNG-IUD use with gynecologic and breast cancers. The demographic and clinical factors among LNG-IUD users and the matched controls are presented in Table 1. SMD being less than 0.1 indicates a good balance between the 2 groups. All the variables listed in Table 1 were adjusted for in the final multivariable regression model.

Associations between LNG-IUD use and female cancer risk among all women are shown in Table 2. After an accumulated 3,283,629 years of follow-up, the incidence rate of breast cancer among LNG-IUD users was 12.40 per 10,000 person-years, which was higher than comparisons who did not use LNG-IUD (incidence rate, 10.94 per 10,000 person-years). LNG-IUD use was associated with a higher risk of breast cancer, with an adjusted HR of 1.13 (95% CI, 1.10−1.17). Among women who used LNG-IUD, the ARR was 1.46 cases per 10,000 person-years (95% CI 1.03−1.90), suggesting that a total of 751 cases could have been avoided if these women had not used LNG-IUD after 10 years of follow-up.

Meantime, we observed that the incidence rate of endometrial cancer among LNG-IUD users was (0.35 per 10,000 person-years) lower than comparisons who did not use LNG-IUD (incidence rate, 0.52 per 10,000 person-years). LNG-IUD use significantly reduces the risk of endometrial cancer ($P<.001$), with an adjusted HR of 0.67 (95% CI, 0.56−0.80). The risk of cervical and ovarian cancers was lower among LNG-

TABLE 1
Baseline demographic and clinical characteristics between LNG-IUD users and nonusers

Characteristic	LNG-IUD users (*n*=514,719)		Nonusers (*n*=1,544,157)		SMD
	Mean	SD	Mean	SD	
Age at index	33.94	9.09	33.98	9.16	0.007
	No.	**%**	**No.**	**%**	
Highest education level, y					0.002
1–9	57,135	11.1	171,634	11.1	
10–11	240,464	46.7	720,745	46.7	
≥12	217,120	42.2	651,778	42.2	
Income					0.003
Lowest	75,567	14.7	224,848	14.6	
Middle-low	124,370	24.2	372,926	24.1	
Middle-high	146,281	28.4	439,496	28.5	
Highest	168,501	32.7	506,887	32.8	
Parity					0.001
0	157,254	30.6	470,648	30.5	
1	66,621	12.9	198,806	12.9	
2	198,582	38.6	597,401	38.7	
3	74,553	14.5	224,201	14.5	
≥3	17,709	3.4	53,101	3.4	
Age at birth of first child					0.002
Never	157,254	30.6	470,648	30.5	
≤30	279,896	54.4	841,511	54.5	
31–40	75,914	14.7	227,271	14.7	
>40	1655	0.3	4727	0.3	
History of endometriosis					0.002
No	504,560	98.0	1,516,313	98.2	
Yes	10,159	2.0	27,844	1.8	
History of uterine leiomyoma					0.001
No	504,775	98.1	1,515,788	98.2	
Yes	9944	1.9	28,369	1.8	
History of hormonal therapy					0.001
No	505,334	98.2	1,518,389	98.3	
Yes	9385	1.8	25,768	1.7	
Obesity					0.001
No	499,692	97.1	1,501,543	97.2	
Yes	15,027	2.9	42,614	2.8	
COPD					0.002
No	480,575	93.4	1,443,656	93.5	
Yes	34,144	6.6	100,501	6.5	

(continued)

TABLE 1
Baseline demographic and clinical characteristics between LNG-IUD users and nonusers *(continued)*

Characteristic	LNG-IUD users (*n*=514,719)		Nonusers (*n*=1,544,157)		SMD
	Mean	SD	Mean	SD	
CCI					0.007
0	466,492	90.6	1,404,126	90.9	
1	42,457	8.3	125,627	8.1	
2	4617	0.9	11,946	0.8	
≥3	1153	0.2	2458	0.2	
Family history of cancer					<0.001
No	324,891	63.1	974,389	63.1	
Yes	189,828	37.9	569,768	37.9	

CCI, Charlson Comorbidity Index; *COPD*, chronic obstructive pulmonary disease; *LNG-IUD*, levonorgestrel-releasing intrauterine device; *SD*, standard deviation; *SMD*, standard mean difference.

IUD users with an adjusted HR of 0.91 (95% CI, 0.84−0.99) and 0.86 (95% CI, 0.75−0.99), respectively.

The results of stratified analyses are listed in Figures 2 and 3. When stratified by age and menopausal status, the risk of gynecologic and breast cancers remained largely consistent among LNG-IUD uses. In some groups, the results were nonsignificant, likely due to the small number of cases.

In Table 3, we analyzed the relationship between LNG-IUD use, family history of cancer, and female cancer risk. We found that both LNG-IUD use and a family history of cancer were associated with an increased risk of breast cancer. Additionally, the risk was even higher among those women who used LNG-IUD and had a family history of cancer (adjusted HR, 2.07, 95% CI, 1.71−2.51).

TABLE 2
Cox proportional hazard model with a competing risk analysis of LNG-IUD use with female cancer risk

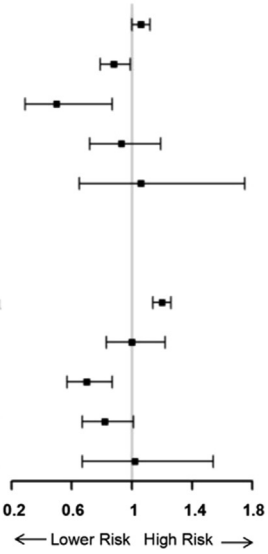
Cancer sites	Individuals, number	Person-years	Number of outcome	IR, per 10,000 person-year	Crude			Adjusted[a]		
					HR	95% CI	*P* value	HR	95% CI	*P* value
Breast cancer										
Nonusers	1,544,157	9,854,948	10,783	10.94	Ref			Ref		
LNG-IUD users	514,719	3,283,629	4073	12.40	1.13	1.10−1.17	<.001	1.13	1.10−1.17	<.001
Cervical cancer										
Nonusers	1,544,157	9,854,948	1736	1.76	Ref			Ref		
LNG-IUD users	514,719	3,283,629	526	1.60	0.91	0.84−0.99	.031	0.91	0.84−0.99	.032
Endometrial cancer										
Nonusers	1,544,157	9,854,948	516	0.52	Ref			Ref		
LNG-IUD users	514,719	3,283,629	115	0.35	0.67	0.56−0.80	<.001	0.67	0.56−0.80	<0.001
Ovarian cancer										
Nonusers	1,544,157	9,854,948	671	0.68	Ref			Ref		
LNG-IUD users	514,719	3,283,629	192	0.58	0.86	0.75−0.99	.034	0.86	0.75−0.99	.038
Other female genital cancer										
Nonusers	1,544,157	9,854,948	148	0.15	Ref			Ref		
LNG-IUD users	514,719	3,283,629	51	0.16	1.03	0.79−1.36	.813	1.03	0.79−1.36	.812

CI, confidence interval; *HR*, hazard ratio; *IR*, incidence rate; *LNG-IUD*, levonorgestrel-releasing intrauterine device.

[a] Adjusted for propensity score calculated by age at index, education, income, chronic obstructive pulmonary disease, obesity, parity, hormonal therapy, Charlson Comorbidity Index, age at birth of first child, history of endometriosis, history of uterine leiomyoma, and family history of cancer.

FIGURE 2
Hazard ratios and 95% CIs of female cancer risk associated with LNG-IUD use stratified by age at index

	No. of individuals	Follow-up years	No. of outcome	IR, per 10,000 person-years	Adjusted HR (95% CI)	P value
Age ≤ 40 years						
Breast cancer	375531	2220808	1603	7.22	1.06(1.00-1.12)	0.046
Cervical cancer	375531	2220808	392	1.77	0.88(0.79-0.99)	0.028
Endometrial cancer	375531	2220808	15	0.07	0.50(0.29-0.87)	0.014
Ovarian cancer	375531	2220808	77	0.35	0.93(0.72-1.19)	0.549
Other female genital cancer	375531	2220808	21	0.09	1.06(0.65-1.75)	0.811
Age > 40 years						
Breast cancer	139188	1062821	2407	22.65	1.20(1.14-1.26)	<0.001
Cervical cancer	139188	1062821	134	1.26	1.00(0.83-1.22)	0.972
Endometrial cancer	139188	1062821	100	0.94	0.70(0.57-0.87)	0.002
Ovarian cancer	139188	1062821	115	1.08	0.82(0.67-1.01)	0.059
Other female genital cancer	139188	1062821	30	0.28	1.02(0.67-1.54)	0.932

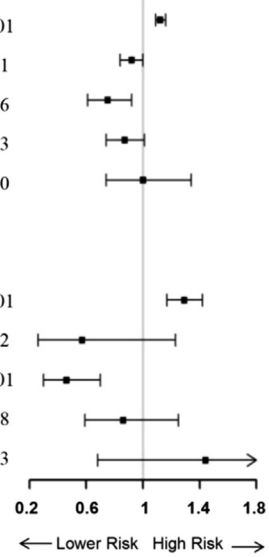


Adjusted for age, education level, income, parity, age at the birth of the first child, history of endometriosis, history of uterine leiomyoma, history of hormonal therapy, obesity, chronic obstructive pulmonary disease, Charlson Comorbidity Index, and family history of cancer.

CI, confidence interval; *HR*, hazard ratio; *IR*, incidence rate; *LNG-IUD*, levonorgestrel-releasing intrauterine device.

FIGURE 3
Hazard ratios and 95% CIs of female cancer risk associated with LNG-IUD use stratified by menopausal state

	No. of individuals	Follow-up years	No. of outcome	IR, per 10,000 person-years	Adjusted HR (95% CI)	P value
Premenopausal cancer						
Breast cancer	513679	3143415	3662	11.65	1.12(1.09-1.16)	<0.001
Cervical cancer	513679	3143415	520	1.65	0.92(0.84-1.00)	0.041
Endometrial cancer	513679	3143415	92	0.29	0.75(0.61-0.92)	0.006
Ovarian cancer	513679	3143415	165	0.52	0.87(0.74-1.01)	0.063
Other female genital cancer	513679	3143415	44	0.14	1.00(0.74-1.34)	0.990
Postmenopausal cancer						
Breast cancer	42207	140214	411	29.31	1.29(1.17-1.42)	<0.001
Cervical cancer	42207	140214	6	0.43	0.57(0.26-1.23)	0.152
Endometrial cancer	42207	140214	23	1.64	0.46(0.30-0.70)	<0.001
Ovarian cancer	42207	140214	27	1.93	0.86(0.59-1.25)	0.418
Other female genital cancer	42207	140214	7	0.50	1.44(0.68-3.08)	0.343



Adjusted for age, education level, income, parity, age at the birth of the first child, history of endometriosis, history of uterine leiomyoma, history of hormonal therapy, obesity, chronic obstructive pulmonary disease, Charlson Comorbidity Index, and family history of cancer.

CI, confidence interval; *HR*, hazard ratio; *IR*, incidence rate; *LNG-IUD*, levonorgestrel-releasing intrauterine device.

TABLE 3
Cox proportional hazard model with competing risk analyses for LNG-IUD use, family history of cancer, and female cancer risk

Cancer sites	Individuals, number	Person-years	Number of outcome	IR, per 10,000 person-year	Adjusted[a]			*P* for multiplicative interaction	Additive interaction	
					HR	95% CI	*P* value		RERI (95% CI)	*P* value
Breast cancer								.066	0.19 (0.07, 0.31)	.002
No LNG-IUD+no family history	974,389	5,560,700	4355	7.83	Ref					
LNG-IUD only	324,891	1,854,202	1592	8.59	1.09	1.04–1.15	<.001			
Family history only	569,768	4,294,248	6428	14.97	1.78	1.47–2.16	<.001			
LNG-IUD+family history	189,828	1,429,427	2481	17.36	2.07	1.71–2.51	<.001			
Cervical cancer								.508	−0.04 (−0.14, 0.06)	.462
No LNG-IUD+no family history	974,389	5,560,700	966	1.74	Ref					
IUD only	324,891	1,854,202	301	1.62	0.93	0.84–1.05	.237			
Family history only	569,768	4,294,248	770	1.79	0.89	0.50–1.57	.667			
LNG-IUD+family history	189,828	1,429,427	225	1.57	0.78	0.44–1.39	.403			
Endometrial cancer								.920	−0.17 (−0.53, 0.20)	.370
No LNG-IUD+no family history	974,389	5,560,700	186	0.33	Ref					
LNG-IUD only	324,891	1,854,202	43	0.23	0.67	0.50–0.91	.010			
Family history only	569,768	4,294,248	330	0.77	1.45	0.83–2.54	.192			
LNG-IUD+family history	189,828	1,429,427	72	0.50	0.96	0.53–1.75	.900			
Ovarian cancer								.291	−0.50 (−1.11, 0.11)	.108
No LNG-IUD+no family history	974,389	5,560,700	262	0.47	Ref					
LNG-IUD only	324,891	1,854,202	82	0.44	0.95	0.76–1.17	.608			
Family history only	569,768	4,294,248	409	0.95	2.90	1.49–5.64	.002			
LNG-IUD+family history	189,828	1,429,427	110	0.77	2.35	1.19–0.42	.013			
Other female genital cancer								.139	−0.46 (−0.86, −0.05)	.028
No LNG-IUD+no family history	974,389	5,560,700	63	0.11	Ref					
LNG-IUD only	324,891	1,854,202	27	0.15	1.29	0.88–1.89	.199			
Family history only	569,768	4,294,248	85	0.20	1.09	0.26–4.53	.902			
LNG-IUD+family history	189,828	1,429,427	24	0.17	0.93	0.22–3.99	.917			

CI, confidence interval; *HR*, hazard ratio; *IR*, incidence rate; *LNG-IUD*, levonorgestrel-releasing intrauterine device; *RERI*, relative excess risk.

[a] Adjusted for PS calculated by age at index, education, income, chronic obstructive pulmonary disease, obesity, parity, hormonal therapy, Charlson Comorbidity Index, age at birth of first child, history of endometriosis, and history of uterine leiomyoma.

A significant interaction was observed for breast cancer at the additive scale ($P<.001$), indicating a relative 19% excess risk for interaction, which could be translated as 1.63 additional cases per 10,000 person-years. However, no significant interaction was observed for endometrial, cervical, and ovarian cancers in the additive interactions ($P>.05$).

Comment

Principal findings

In this population-based nationwide cohort study, we found that the incidence of breast cancer was significantly higher among patients who use the LNG-IUD as compared to the matched nonuse LNG-IUD group. Conversely, LNG-IUD use reduced the risk of endometrial, cervical, and ovarian cancers. The significant interaction on an additive scale demonstrates that LNG-IUD use and family history of cancer synergistically raise the risk for breast cancer. It is noteworthy that the increased risk of breast cancer among LNG-IUD users was small, and we could not fully exclude confounding bias.

Results in the context of what is known

The results support that LNG-IUD use only slightly increased the risk of breast cancer in younger women, but the risk was significantly higher in postmenopausal women, which was consistent with previous reports,[29−31] even though not all of them have taken into account other possible confounding factors. A systematic review demonstrated an increased risk of breast cancer in LNG-IUD users, especially in postmenopausal and longer-using women.[32] This may be because younger women tend to use the LNG-IUD for contraception, whereas perimenopausal/postmenopausal women tend to use it for abnormal bleeding and heavy menstrual bleeding,[33] which is more common in obese women, who are at increased risk of breast cancer due to prolonged anovulation or abnormal ovulation.[34] However, a meta-analysis suggested that no evidence of increased breast cancer risk was observed among users of the LNG-IUD.[35] Clinical heterogeneity and differences in statistical methods across study types may have some influence on the conclusions of the study. Based on our findings, a total of 751 cases could be prevented if these women did not use LNG-IUD after 10 years of follow-up.

Numerous studies confirm that the use of LNG-IUD reduces the risk of gynecological cancers, especially endometrial cancer.[36−38] Our study suggests that the LNG-IUD significantly reduces the risk of endometrial cancer (adjusted HR 0.67, 95% CI, 0.53−0.80), regardless of age and menopausal status. Since the LNG-IUD is located inside the uterus, it can prevent endometrial cancer by localized inflammation-like reactions and/or endometrial suppression.[39,40] Moreover, the LNG-IUD locally releases high concentrations of levonorgestrel to counteract endogenous estrogen, leading to endometrial epithelial atrophy and inhibiting endometrial proliferation.[41] This mechanism can also be used to treat endometrial atypia and low-grade endometrial cancer.[42] LNG-IUD is primarily inhibitory to the endometrium and therefore has a reduced risk of endometrial cancer in women of all ages.

Most studies showed that the LNG-IUD also reduces the risk of cervical cancer,[38,43] consistent with our results. The following aspects may explain its mechanism of reducing the risk of cervical cancer; (1) device-related inflammatory responses in the cervical canal that may alter the course of human papillomavirus infection[44]; (2) insertion or removal of the IUD results in local trauma to the cervical tissue, which can lead to localized chronic inflammation and a long-term immune response similar to that seen in patients after colposcopic biopsy[44]; (3) elimination of cervical intraepithelial neoplasia during IUD insertion or removal; (4) LNG-IUD may be capable of increasing the number of Langerhans cells, which can increase localized squamous epithelial immunosurveillance, thus providing a protective effect.[45]

Studies about the relationship between ovarian cancer and LNG-IUD use have shown inconsistent results.[38] A large Norwegian study found that LNG-IUD use significantly reduced the risk of ovarian cancer.[36] In contrast, some studies[46,47] concluded that the use of IUD is not associated with a reduction in the occurrence of ovarian cancer and even increases the risk of ovarian cancer.[48] Our study found that LNG-IUD use slightly reduced the risk of ovarian cancer but when analyzed stratified by age and menopausal status, none of these was statistically significant ($P > .05$) probably due to the small sample size. The mechanism may be that LNG-IUD induces a local inflammatory response and activates local immune cells to attack cancer cells,[49] and the LNG-IUD reduces menstruation, often leading to amenorrhea, and theoretically reduces retrograde menstruation and reduces the likelihood of cancer-causing cells entering the fallopian tubes and abdominal cavity.[37]

Clinical implications

We found an interaction between LNG-IUD use and a family history of breast cancer.[50] Although the LNG-IUD alone slightly increases breast cancer risk, the risk of breast cancer is significantly higher when there is a family history of cancer. Such evidence could guide clinical recommendations, especially for those with a family history of cancer.

Research implications

The association of LNG-IUD with gynecologic and breast cancers has been recognized, although much remains to be explored. Studies have confirmed the strong association between a family history of cancer and breast and gynecological cancers.[17,51−53] However, little has been reported on the interaction between LNG-IUD and a family history of cancer in these cancers. To investigate whether LNG-IUD use in women with a family history of cancer increases the risk of cancer in women, we analyzed the interaction of the 2 factors and found that the interaction between family history of cancer and LNG-IUD use was not significant in gynecological cancers. However, it is of interest to note that although there was no correlation in the final results, both factors together reduced the risk of cancer compared to

having a family history of cancer alone, and this was particularly significant in ovarian cancer, and a synergistic promotion of both has been found in breast cancer. The mechanisms involved are unclear and the biological mechanisms behind this association require more in-depth exploration.

Strengths and limitations

The major advantage of this study is that it was based on a nationwide population. The cohort study design and large sample size ensured the statistical power and avoided reversal causality. Data collected through a continuously updated national registry can effectively eliminate recall bias and minimize selection bias. All cancer patients included in this study were diagnosed by a clinician and a pathologist, thus further improving the validity of the results. The registry-based data also provided us with information on potential demographic and clinical confounders. A few limitations warrant consideration. First, we were unable to clarify the dose effect of LNG-IUD use duration and different LNG-IUD types on gynecologic and breast cancer, which is crucial for establishing causal associations. This limitation arises from the lack of such detailed information in the nationwide registers used for our study. Second, several potential confounders are missing from this national database, such as smoking, alcohol consumption, and dietary factors. However, we have adjusted for COPD as a proxy for smoking in regression models. We have also adjusted for educational status, which is highly correlated with lifestyle factors that may partially exclude their confounding effects. Besides, we were unable to discern the indication for the utilization of LNG-IUD from the Swedish Prescribed Drug Register. Consequently, we could not completely exclude the possibility of indication bias. Thirdly, these data are observational and the increased risk for breast cancer is small and potentially subject to confounding. Based on that, randomized trials should be considered to reduce the impact of unmeasured confounding.

Conclusions

In conclusion, this population-based cohort study suggests that LNG-IUD use has site-specific effects on gynecologic and breast cancers. Clinical attention should be given to monitoring the development of breast cancer, especially for women with a family history of breast cancer. The increased risk of breast cancer in LNG-IUD users is of small effect size, and the results are limited by the observational study design and subject to potential unmeasured confounding.

Data and materials availability statement

The data based on the Swedish register are not publicly available due to Swedish law and protecting patients' privacy, and the combined set of data used for the analysis presented in this study can only be made available from the appropriate Swedish authorities (the Swedish National Board of Health and Welfare (https://www.socialstyrelsen.se/en) and Statistics Sweden [https://www.scb.se/en]), for researchers who meet the criteria for access to confidential data. ■

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SUPPLEMENTAL TABLE

Baseline demographic and clinical characteristics between LNG-IUD users and nonusers

Characteristic	LNG-IUD users (*n*=514,719)		Nonusers (*n*=1,544,157)		*P* value
	Mean	SD	Mean	SD	
Age at index	33.94	9.09	33.98	9.16	.01
	No.	**%**	**No.**	**%**	
Highest education level, y					.857
1–9	57,135	11.1	171,634	11.1	
10–11	240,464	46.7	720,745	46.7	
≥12	217,120	42.2	651,778	42.2	
Income					.170
Lowest	75,567	14.7	224,848	14.6	
Middle-low	124,370	24.2	372,926	24.1	
Middle-high	146,281	28.4	439,496	28.5	
Highest	168,501	32.7	506,887	32.8	
Parity					.472
0	157,254	30.6	470,648	30.5	
1	66,621	12.9	198,806	12.9	
2	198,582	38.6	597,401	38.7	
3	74,553	14.5	224,201	14.5	
≥3	17,709	3.4	53,101	3.4	
Age at birth of first child					.183
Never	157,254	30.6	470,648	30.5	
≤30	279,896	54.4	841,511	54.5	
31–40	75,914	14.7	227,271	14.7	
>40	1655	0.3	4727	0.3	
History of endometriosis					<.001
No	504,560	98.0	1,516,313	98.2	
Yes	10,159	2.0	27,844	1.8	
History of uterine leiomyoma					<.001
No	504,775	98.1	1,515,788	98.2	
Yes	9944	1.9	28,369	1.8	
History of hormonal therapy					<.001
No	505,334	98.2	1,518,389	98.3	
Yes	9385	1.8	25,768	1.7	
Obesity					<.001
No	499,692	97.1	1,501,543	97.2	
Yes	15,027	2.9	42,614	2.8	
COPD					.002
No	480,575	93.4	1,443,656	93.5	
Yes	34,144	6.6	100,501	6.5	

(continued)

SUPPLEMENTAL TABLE

Baseline demographic and clinical characteristics between LNG-IUD users and nonusers *(continued)*

Characteristic	LNG-IUD users (*n*=514,719)		Nonusers (*n*=1,544,157)		*P* value
	Mean	SD	Mean	SD	
CCI					<.001
0	466,492	90.6	1,404,126	90.9	
1	42,457	8.3	125,627	8.1	
2	4617	0.9	11,946	0.8	
≥3	1153	0.2	2458	0.2	
Family history of cancer					.813
No	324,891	63.1	974,389	63.1	
Yes	189,828	37.9	569,768	37.9	

CCI, Charlson Comorbidity Index; *COPD*, chronic obstructive pulmonary disease; *LNG-IUD*, levonorgestrel-releasing intrauterine device; *SD*, standard deviation.