Original Research

Cancer Risk in Women Using the Levonorgestrel-Releasing Intrauterine System in Finland

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OBJECTIVE: To examine the association between premenopausal use of the levonorgestrel-releasing intrauterine system and cancer incidence in Finland with a special focus on endometrial adenocarcinoma.

METHODS: All Finnish women aged 30–49 years using a levonorgestrel-releasing intrauterine system for treatment of menorrhagia in 1994–2007 (n=93,843) were identified from the National Reimbursement Registry and linked to the Finnish Cancer Registry data. The incidence of cancers in levonorgestrel-releasing intrauterine system users was compared with that in the general population.

RESULTS: A total of 2,781 cancer cases were detected in levonorgestrel-releasing intrauterine system users during the follow-up of 855,324 women-years. The standardized incidence ratio (observed-to-expected ratio) for endometrial adenocarcinoma was 0.50 (95% confidence interval [CI] 0.35–0.70; 34 observed compared with 68 expected cases) after the first levonorgestrel-releasing intrauterine system purchase and 0.25 (95% CI 0.05–0.73; three observed compared with 12 expected cases) after two purchases. The standardized incidence ratio for ovarian cancer was 0.60 (95% CI 0.45–0.76; 59 observed compared with 99 expected cases), for pancreatic cancer 0.50 (95% CI 0.28–0.81; 15 observed compared with 30 expected cases), and for lung cancer 0.68 (95% CI 0.49–0.91; 43 observed compared with 63 expected cases). The standardized incidence ratio for breast cancer among all levonorgestrel-releasing intrauterine system users was 1.19 (95% CI 1.13–1.25; 1,542 observed compared with 1,292 expected cases).

CONCLUSION: The levonorgestrel-releasing intrauterine system may have a protective effect against endometrial malignant transformation. Using the levonorgestrel-releasing intrauterine system for treatment of menorrhagia during reproductive years was associated with a lower incidence of endometrial, ovarian, pancreatic, and lung cancers than expected. Levonorgestrel-releasing intrauterine system use was associated with a higher than expected incidence of breast cancer.

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Globally, breast cancer is the most common malignancy with approximately 1.68 million new cases diagnosed annually. Endometrial cancer is the most frequent gynecologic cancer in developed countries with approximately 319,000 new cases annually worldwide. Half these cancers arise in the Western world.[1] Both physiologic and malignant transformations of breast and endometrial cells are regulated by sex hormones.[2,3]

The levonorgestrel-releasing intrauterine system was primarily developed for contraception, but the indications have later extended to treatment of menorrhagia and protection from endometrial hyperplasia

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Table 1. Cohort of Levonorgestrel-Releasing Intrauterine System Users, Follow-Up 1994–2009

	Follow-Up From the 1st Levonorgestrel-Releasing Intrauterine System			Follow-Up From the 2nd Levonorgestrel-Releasing Intrauterine System		
Age (y)	n	Women-Years	Patients With Cancer	n	Women-Years	Patients With Cancer
30–34	20,998	47,196	45	290	365	0
35–39	28,220	168,763	216	4,151	10,335	16
40–44	25,954	250,431	575	5,643	33,547	97
45–49	18,671	240,504	1,030	4,150	40,962	198
50–54	0	148,430	915	0	23,211	143
Total	93,843	855,324	2,781	14,234	108,420	454

Number of all women classified according to age at the purchase of the first levonorgestrel-releasing intrauterine system, women-years classified according to age at follow-up, and patients with cancer classified according to age at diagnosis.

during estrogen therapy. This hormonal intrauterine system releases continuously high intrauterine concentrations of levonorgestrel, causing endometrial decidualization and atrophic changes.[4] These endometrial effects have made this system a promising alternative for treatment of endometrial hyperplasia,[5] which is a potential precursor of endometrial cancer. The risk for endometrial cancer is reported to be decreased during postmenopausal use of hormonal intrauterine system in combination with estradiol,[6] but the risk for breast cancer is reported to be increased.[7]

There are only two studies published on the breast cancer risk of premenopausal levonorgestrel-releasing intrauterine system users, and neither reports an increased risk.[8,9] The relationship between levonorgestrel-releasing intrauterine system use and the incidence of other cancers remains unknown.

Our primary aim in this nationwide cohort study was to test the hypothesis that the incidence of endometrial adenocarcinoma is decreased among premenopausal levonorgestrel-releasing intrauterine system users. Our second aim was to assess the risks of other common cancers among premenopausal levonorgestrel-releasing intrauterine system users.

MATERIALS AND METHODS

In this observational nationwide cohort study, we collected a database of all Finnish women who in 1994–2007 were between the ages of 30 and 49 years (n=93,843) and had received reimbursement for the levonorgestrel-releasing intrauterine system for treatment of heavy menstrual bleeding. The study data were obtained from administrative registers in Finland. The data linkages were done using the unique personal identity code issued by The Finnish Population Register Centre since 1967 to all citizens and permanent residents of Finland and used as the identification key in all national registers. The data on levonorgestrel-releasing intrauterine system reimbursements were extracted from the national Reimbursement Register of the Social Insurance Institution, which contains data on purchases of the levonorgestrel-releasing intrauterine system since 1994. The register uses the anatomical therapeutic chemical classification system.

The data on cancer cases were extracted from the Finnish Cancer Registry, which receives notifications of all cancer cases from hospitals and pathology laboratories, covering virtually 100% of diagnosed cancers in Finland since 1953.[10] Since 1961, reporting of new cancer cases is mandatory by law in Finland. Cancer notifications submitted to the Finnish Cancer Registry are stored in a database, and regular quality crosschecks are done between the cancer register data and other administrative registers (Central Population Register, Statistics Finland) to ensure the correctness of data. The data of cancer risk-related confounders (ie, smoking, alcohol consumption, physical activity, diet, socioeconomic status) were derived from a series of cross-sectional national health behavior surveys. A nationwide random sample from the Finnish population aged 15–64 years has been drawn annually during 1978–2002 with some 5,000 Finnish people receiving a mailed questionnaire each year. The annual samples for the survey were drawn from the Finnish Population Register. Among women, the response rate has varied between 75% and 86%.[11] Women aged 30–49 years who had returned the questionnaire in the health behavior survey were analyzed (4,056 levonorgestrel-releasing intrauterine system users and 25,801 nonusers). Information on socioeconomic status was obtained from the census files of Statistics Finland. Information on health behaviors was self-reported. We calculated women-years at risk, in 5-year age groups, starting from the first purchase of the levonorgestrel-releasing intrauterine system and

Table 2. Observed and Expected Numbers of Cancer Cases and Standardized Incidence Ratios (With 95% Confidence Intervals) Among Finnish Women Who Bought the Levonorgestrel-Releasing Intrauterine System During 1994–2007 in Those Ages 30–49 Years, by Cancer Type, 1994–2009*

	1 or More Purchases of a Levonorgestrel-Releasing Intrauterine System[†]				
Cancer Type	Observed	Expected	Standardized Incidence Ratio	95% CI	Observed–Expected
All sites	2,781	2,593.1	1.07	1.03–1.11[§]	188
Stomach	45	40.9	1.10	0.80–1.47	4
Colon and rectum	154	131.4	1.17	0.99–1.36	23
Liver	6	8.7	0.69	0.25–1.50	−3
Gallbladder, bile ducts	7	7.9	0.88	0.35–1.81	−1
Pancreas	15	30.3	0.50	0.28–0.81[‖]	−15
Lung, trachea	43	63.0	0.68	0.49–0.91[‖]	−20
Melanoma of skin	129	119.5	1.08	0.90–1.27	10
Breast	1,542	1,292.2	1.19	1.13–1.25[§]	250
Cervix uteri	60	66.8	0.90	0.69–1.15	−7
Adenocarcinoma of cervix uteri	22	18.6	1.18	0.74–1.79	3
Vulva	8	9.9	0.81	0.35–1.59	−2
Vagina	4	3.0	1.32	0.36–3.38	1
Corpus uteri (all types)	56	94.3	0.59	0.45–0.77[§]	−38
Endometrial adenocarcinoma	37	79.6	0.46	0.33–0.64[§]	−43
Uterine sarcomas	18	12.5	1.44	0.86–2.28	6
Other uterine	0	1.1	0.00	0.00–3.27	−1
Ovary, all types	59	98.9	0.60	0.45–0.76[§]	−40
Mucinous cystadenocarcinoma ovari	8	18.5	0.43	0.19–0.85[¶]	−11
Kidney	40	41.0	0.98	0.70–1.32	−1
Bladder, ureter, urethra	12	12.3	0.98	0.51–1.70	0
Brain, nervous system	175	168.3	1.04	0.89–1.19	7
Thyroid gland	138	126.1	1.09	0.92–1.28	12
Non-Hodgkin's lymphoma	81	75.8	1.07	0.85–1.32	5
Hodgkin lymphoma	13	10.9	1.19	0.63–2.03	2
Multiple myeloma	11	11.7	0.94	0.47–1.68	−1
Leukemia	34	36.6	0.93	0.64–1.29	−3
Not included					
Ovarian borderline tumor	40	52.4	0.76	0.54–1.03	−12

CI, confidence interval.
* Follow-up until age 55 y.
† Follow-up started from the first purchase of levonorgestrel-releasing intrauterine system.
‡ Follow-up started from the second purchase of levonorgestrel-releasing intrauterine system.
§ $P<.001$.
‖ $P<.01$.
¶ $P<.05$.

ending on December 31, 2009, or on emigration, the 55th birthday, bilateral or unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, hysterectomy, or death, whichever occurred first. We obtained information on surgical procedures since 1986 from the Hospital Discharge Register of the National Institute of Health and Welfare. This register has summary information on patients discharged from public and private hospitals since 1969 with coverage of almost 100%.[12] The data accuracy and completeness of the Finnish Hospital Discharge Register data have been reported to be good.[13] To analyze the effect of duration of levonorgestrel-releasing intrauterine system use on cancer risks, we also analyzed study participants with at least two levonorgestrel-releasing intrauterine system purchases. In these analyses, the follow-up started from the second purchase of a levonorgestrel-releasing intrauterine system.

We calculated the expected numbers of cancers by multiplying the number of woman-years in each 5-year age group by the corresponding cancer incidence among all Finnish women during the same period.

2 or More Purchases of a Levonorgestrel-Releasing Intrauterine System[‡]				
Observed	Expected	Standardized Incidence Ratio	95% CI	Observed–Expected
454	377.6	1.20	1.09–1.31[§]	76
7	5.7	1.22	0.49–2.51	1
24	19.7	1.22	0.78–1.81	4
2	1.3	1.58	0.19–5.69	1
2	1.1	1.77	0.21–6.37	1
3	4.6	0.66	0.14–1.91	−2
3	9.6	0.31	0.06–0.91[¶]	−7
19	17.1	1.11	0.67–1.73	2
271	193.2	1.40	1.24–1.57[§]	78
6	7.9	0.76	0.28–1.65	−2
2	2.2	0.91	0.11–3.30	0
3	1.4	2.13	0.44–6.21	2
0	0.5	0.00	0.00–7.40	−1
5	14.0	0.36	0.12–0.83[¶]	−9
3	11.9	0.25	0.05–0.73[‖]	−9
2	1.7	1.17	0.14–4.22	0
0	0.1	0.00	0.00–35.65	0
7	13.7	0.51	0.20–1.04	−7
0	2.4	0.00	0.00–1.51	−2
10	6.1	1.63	0.78–3.00	4
3	1.7	1.75	0.36–5.10	1
25	23.4	1.07	0.69–1.57	2
21	16.9	1.25	0.77–1.90	4
10	11.0	0.91	0.44–1.67	−1
2	1.1	1.77	0.21–6.41	1
2	1.7	1.19	0.14–4.29	0
2	5.3	0.38	0.05–1.37	−3
5	7.1	0.71	0.23–1.65	−2

Standardized incidence ratio was calculated by dividing the number of observed cancer cases by the number of expected cancer cases. Ninety-five percent confidence intervals (CIs) for the standardized incidence ratios were based on the assumption that the number of observed cases represents a Poisson distribution.[14] A standardized incidence ratio with $P<.01$ was considered statistically significant.

All statistical analyses in the health behavior survey data were performed using StataMP 11.[15] Logistic regression analyses (odds ratios [ORs] with 95% CIs) were conducted to assess the association between individual health behavior factors and use of the levonorgestrel-releasing intrauterine system. This study was approved by the institutional review boards of Hyvinkää Hospital and Helsinki University Hospital. The Finnish National Centre for Welfare and Health, after consulting the data protection authority, approved the use of the confidential national register data in this research.

RESULTS

During the study period 1994–2009, a total of 93,843 levonorgestrel-releasing intrauterine system users were followed for 855,324 women-years at risk, and 2,781 cancer cases were diagnosed among levonorgestrel-releasing intrauterine system users during the follow-up (Table 1). Altogether, 14,234 women had purchased at least two levonorgestrel-releasing intrauterine systems, and 454 incident cancer cases were diagnosed after the second purchase (Table 1).

The observed number of cancer cases among all levonorgestrel-releasing intrauterine system users was 7% higher than the expected number (Table 2).

Table 3. Observed Numbers of Breast Cancer Cases and Standardized Incidence Ratios (With 95% Confidence Intervals) Among Finnish Women Who Bought the Levonorgestrel-Releasing Intrauterine System During 1994–2007 in Those Aged 30–49 Years, by Age at Follow-Up and Time Since First Purchase, 1994–2009*

	Time Since First Purchase							
	0–0.99 y			1–4.99 y			5–9.99 y	
Age at Follow-Up (y)	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio
30–34	3	0.78	0.16–2.28	8	1.30	0.56–2.55		
35–39	15	1.03	0.58–1.70	28	0.55	0.37–0.79†	26	1.23
40–44	22	0.78	0.49–1.17	124	1.09	0.90–1.28	114	1.09
45–49	40	0.96	0.68–1.30	205	1.08	0.94–1.23	280	1.39
50–54	4	1.21	0.33–3.09	136	1.31	1.10–1.53§	293	1.28
Total	84	0.91	0.73–1.13	501	1.08	0.99–1.17	713	1.28

CI, confidence interval.
* Follow-up from the first purchase of levonorgestrel-releasing intrauterine system until the age of 55 y.
† $P<.001$.
‡ $P<.05$.
§ $P<.01$.

In absolute numbers, a total of 188 excess of cancer cases was detected during follow-up. There was a 20% excess among women with two levonorgestrel-releasing intrauterine system purchases (76 cancer cases more than expected).

The standardized incidence ratio for endometrial adenocarcinoma after at least one levonorgestrel-releasing intrauterine system purchase was 0.46 (95% CI 0.33–0.64; 37 observed compared with 80 expected cases) and 0.25 (95% CI 0.05–0.73; three observed compared with 12 expected cases) after two purchases. The standardized incidence ratio for uterine sarcomas was not lower than in the reference population (Table 2).

The standardized incidence ratio for breast cancer among all levonorgestrel-releasing intrauterine system users was 1.19 (95% CI 1.13–1.25; 1,542 observed compared with 1,292 expected cases). Among users with two levonorgestrel-releasing intrauterine system purchases, the standardized incidence ratio was 1.40 (95% CI 1.24–1.57; 271 observed compared with 193 expected cases). Increased standardized incidence ratios for breast cancer were found, especially in age categories of 45–54 years (Table 3). The standardized incidence ratio increased along with follow-up time.

The standardized incidence ratio for ovarian cancer in general was 0.60 (95% CI 0.45–0.76; 59 observed compared with 99 expected cases) (Table 2).

Compared with the background population, the incidences for lung cancer and pancreatic cancer among the levonorgestrel-releasing intrauterine system users were significantly lower (Table 2). We did not observe significant standardized incidence ratios for the other cancers (Table 2).

We also calculated standardized incidence ratios for women exposed to only one levonorgestrel-releasing intrauterine system. In this analysis, the follow-up ended at the date of the second levonorgestrel-releasing intrauterine system purchase. The standardized incidence ratio for endometrial cancer of users with only one levonorgestrel-releasing intrauterine system was 0.50 (95% CI 0.35–0.70; 34 observed compared with 68 expected cases), whereas the standardized incidence ratio after two or more purchases was 0.25 (95% CI 0.05–0.73; three observed compared with 12 expected cases). The respective standardized incidence ratios for breast cancer were 1.16 (95% CI 1.09–1.22; 1,271 observed compared with 1,099 expected cases) and 1.40 (95% CI 1.24–1.57; 271 observed compared with 193 expected cases).

Four percent of the whole levonorgestrel-releasing intrauterine system user cohort had participated in the national health behavior survey among a random sample from the Finnish population aged 15–64 years during 1978–2002. In that sample, the levonorgestrel-releasing intrauterine system users had a higher socioeconomic position and were more often married as compared with the nonusers. The levonorgestrel-releasing intrauterine system users were less often overweight (body mass index [calculated as weight (kg)/[height (m)]^2] more than 25; 17.1% compared with 20.5%; OR 0.80, 95% CI 0.73–0.87) and were less often smokers (22.1% compared with 25.6%; OR 0.80, 95% CI 0.74–0.87) compared with nonusers.

Time Since First Purchase						
5–9.99 y	More Than 10 y			Entire Follow-Up		
95% CI	Observed	Standardized Incidence Ratio	95% CI	Observed	Standardized Incidence Ratio	95% CI
				11	1.10	0.55–1.96
0.80–1.80				69	0.80	0.62–1.00
0.90–1.30	25	1.40	0.90–2.06	285	1.08	0.96–1.20
1.23–1.55†	92	1.33	1.07–1.63‡	617	1.23	1.13–1.32†
1.14–1.42†	127	1.37	1.14–1.61§	560	1.30	1.20–1.41†
1.19–1.37†	244	1.36	1.19–1.53†	1,542	1.19	1.13–1.25†

On the other hand, they consumed alcohol slightly more often and went to work by car instead of walking or biking.

DISCUSSION

Our main finding is that levonorgestrel-releasing intrauterine system use for treatment of menorrhagia during reproductive years was associated with a lower incidence of endometrial, ovarian, pancreatic, and lung cancers than expected. Levonorgestrel-releasing intrauterine system use was associated with a higher than expected incidence of breast cancer.

The incidence of endometrial adenocarcinoma after first levonorgestrel-releasing intrauterine system purchase was 54% lower than in the general population, and the reduction was pronounced with continued use. This is in line with a study on postmenopausal women.[6] Risk for endometrial cancer among nonhormonal intrauterine device users is decreased by half,[16] and our results indicate that the risk is even more decreased with the hormonal intrauterine system.

The levonorgestrel-releasing intrauterine system was associated with an increased risk for breast cancer, in contrast to earlier studies. A postmarketing study on 17,360 women using the levonorgestrel-releasing intrauterine system for contraception found no elevation in breast cancer risk.[8] However, the follow-up of 10 years in that study was probably too short and the epidemiologic methodology was also unusual, because the breast cancer incidence of levonorgestrel-releasing intrauterine system users over the entire follow-up period was compared with breast cancer incidence of a single year in 1998. In a retrospective, population-based case–control study with women younger than age 50 years at the time of breast cancer diagnosis, the risk of premenopausal breast cancer was not increased in levonorgestrel-releasing intrauterine system users relative to copper intrauterine device users.[9]

The effects of progestins have been described to be clearly different in the endometrium and in the breast. Progestins inhibit endometrial cell proliferation, but in the breast, the action is more complex.[17,18] Although the mechanism of action of a hormonal intrauterine system is primarily local, a small amount of levonorgestrel is absorbed into the systemic circulation,[19] and significant individual variations have been reported.[20,21] Our finding of an increased standardized incidence ratio for breast cancer after 5 or more years of follow-up may reflect causality between extended progestin exposure and cancer risk, but the results should be interpreted with caution in light of the limitations of the study. Women using a hormonal intrauterine system for menorrhagia may represent a selected group with different characteristics than the reference population.

Our data show a strongly decreased risk for ovarian cancer among levonorgestrel-releasing intrauterine system users. Theories of the general mechanisms behind the reduced ovarian cancer risk are suppression of ovulation[22] and obstructing retrograde transportation of endometrial epithelial cells.[23] The hormonal intrauterine system does not significantly affect ovarian function[24] but frequently causes amenorrhea,[25] which hypothetically reduces transportation of carcinogenic agents into fallopian tubes.

The incidence of cancer of the pancreas and lung was strongly decreased. Part of this can be explained by a lower frequency of smokers in the levonorgestrel-releasing intrauterine system user cohort but not all. Hypothetically, exposure to levonorgestrel may play a role in this. Both the normal and neoplastic pancreas and lung are reported to express steroid hormone

receptors[26,27] and exogenous steroid hormones may modify the risk for these cancers.[27,28] Progesterone receptor expression is also reported to be a strong protective factor for lung cancer.[27]

Strengths of this study are a long follow-up with a large number of women. Up to 15% of fertile women used the levonorgestrel-releasing intrauterine system in Finland during the study period. Up to 60% of purchased levonorgestrel-releasing intrauterine systems were used for menorrhagia (L. Kaikkonen, Bayer Schering Pharma, Turku, Finland, personal communication). In addition, the national registers of Finland have a high level of coverage enabling this type of research.[29] We had complete follow-up for surgical operations, emigration, and death. Thus, biases resulting from selective reporting and recall were eliminated.

We could not adjust for all potential confounding factors such as parity, family history of cancer, lifestyle factors, or use of other exogenous hormones. Whether a larger fraction of the study group than of the reference population was also on estrogen therapy is unknown. If so, the possible joint exposure to both levonorgestrel and estrogen may explain the increased risk of breast cancer among the study group. This potential confounding was minimized by stopping the follow-up at the age of 55 years. The study group was compared with a reference population including also hormonal intrauterine system users and those with previous hysterectomy or salpingo-oophorectomy, which slightly dilutes the risk estimates shown.

This study supports the idea of a protective endometrial effect of the levonorgestrel-releasing intrauterine system, but the increased risk of breast cancer is of concern, and studies with more detailed demographic and epidemiologic data are needed. It is important to always counsel patients about the potential benefits and risks of the hormonal therapies.

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