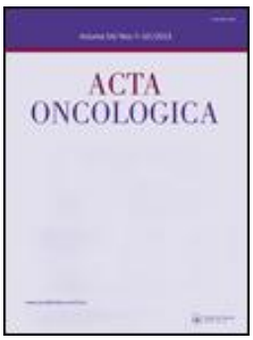

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ORIGINAL ARTICLE

Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study

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ABSTRACT

Background. Prolonged steroid hormone therapy increases the risk of breast cancer, especially the risk of lobular cancer, but the effect of the levonorgestrel-releasing intrauterine system (LNG-IUS) use is controversial. In this study we aimed to test the hypothesis that risk for lobular breast cancer is elevated among LNG-IUS users.

Material and methods. We identified from the national Medical Reimbursement Registry of Finland the women aged 30–49 who had used LNG-IUS for the treatment or prevention of menorrhagia in 1994–2007, and from the Finnish Cancer Registry breast cancers diagnosed before the age of 55 and by the end of 2012.

Results. A total of 2015 women had breast cancer diagnosed in a cohort of 93 843 LNG-IUS users during follow-up consisting of 1 032 767 women-years. The LNG-IUS users had an increased risk for both ductal breast cancer [standardized incidence ratio (SIR) 1.20, 95% confidence interval (CI) 1.14–1.25] and for lobular breast cancer (SIR 1.33, 95% CI 1.20–1.46), as compared with the general female population. The highest risk was found in LNG-IUS users who purchased the device at least twice, whose SIR for lobular cancer was 1.73 (95% CI 1.37–2.15).

Conclusions. The results imply that intrauterine administration of levonorgestrel is not only related to an excess risk of lobular breast cancer but also, in contrary to previous assumptions, to an excess risk of ductal breast cancer.

Breast cancer is globally the most common cancer and the leading cause of cancer death among women [1]. Breast cancer incidence varies substantially by region and has increased in many countries over recent decades [1,2]. It is well documented that progestogens can act as a mitogen in breast tissue and a prolonged use of exogenous progestins is associated with an increased risk of breast cancer [3]. Menopausal estrogen-progestin hormone therapy (HT) increases the risk of breast cancer and the risk varies depending on the progestin used [4]. Progestin administration without estrogens may also increase the risk of breast cancer in premenopausal women [5] as well as the use of oral contraceptives (OC) [6].

Several studies have suggested that the relationship between exogenous HT and breast cancer risk depends on the histological and biological subtype of breast cancer. Of all breast cancers, approximately 80% are ductal, 15% lobular, and the remaining 5% consist of uncommon histologies [7]. Menopausal estrogen-progestin HT increases the risk of lobular breast cancer whereas in general, little or no effect is

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found in the incidence of ductal breast cancer [8]. An increased risk for lobular breast cancer has been reported also among users of OC [9].

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a progestin-releasing device that is widely used for menorrhagia. High levonorgestrel concentrations are achieved in the endometrium with the LNG-IUS, but levonorgestrel is also released into the systemic circulation [10]. Postmenopausal use of LNG-IUS has been reported to increase the risk of breast cancer [11]. However, the role in the premenopausal settings is controversial. Two studies found no increased risk [12,13], whereas we found LNG-IUS use to be associated with a slightly but significantly elevated risk for breast cancer with a standardized incidence ratio (SIR) of 1.19 based on 1542 breast cancers detected in the cohort [14].

In the present nationwide study with a larger number of incident cases we wanted to explore the risk of breast cancer associated with LNG-IUS further, and, in particular, its associations with the histological subtypes of breast cancer.

Material and methods

We collected a file including all Finnish women who received reimbursement for the LNG-IUS purchase prescribed for treatment of menorrhagia at the age of 30–49 in 1994–2007 (n = 93 843). The data about LNG-IUS use were extracted from the national Reimbursement Register of the Social Insurance Institution, Finland, which contains data about the reimbursed purchases of LNG-IUS since 1994. The dates of death and emigration were taken from the national Population Register Centre of Finland. Since 1967, the Population Register Centre has issued all citizens and permanent residents of Finland a unique personal identity code which is used as the identification code in all national registers in Finland. The data linkages between registries were done using the unique personal identity code. The cancer cases of the LNG-IUS cohort were identified from the Finnish Cancer Registry which receives notifications of cancer cases from Finnish hospitals, pathology laboratories, and death certificates, covering virtually 100% of diagnosed cancers in Finland since 1953. The data on different histological types of breast cancer in the Finnish Cancer Registry is coded according to the ICD-O-3 system. For this study we achieved information about all cases of: 1) invasive ductal breast cancer; 2) invasive lobular breast cancer; and 3) other histological types of breast cancer. We also received information on cases of ductal carcinoma in situ of breast (DCIS). The Finnish Cancer Registry also provided data on the clinical staging (localized vs. non-localized) of breast cancer at the diagnosis.

We calculated women-years at risk, in five-year age groups, starting from the purchase of the LNG-IUS and ending on 31 December 2012, on emigration, the 55th birthday, bilateral or unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, hysterectomy, or death, whichever occurred first. Oophorectomy with or without hysterectomy was selected to be used as an end-point of the follow-up, because oophorectomy is associated with a decreased breast cancer risk [15]. Also salpingectomy was chosen as an end-point of the follow-up as it is frequently performed in addition to oophorectomy. Information about the surgical operations since 1986 was obtained from the Hospital Discharge Register of the National Institute of Health and Welfare, Finland. This register covers almost 100% of the summary information about patients discharged from public and private hospitals since 1969.

The expected number of cancer cases was calculated by multiplying the number of women-years in each five-year age group by the corresponding breast cancer incidence rate among all Finnish women during the same time period. A SIR 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 SIRs were based on the assumption that the number of observed cases represents a Poisson distribution [16]. A SIR with $p < 0.05$ was considered statistically significant.

The study was approved by the Institutional Review Boards of Hyvinkää Hospital and Helsinki University Central Hospital. The Finnish National Centre for Welfare and Health gave, after consulting the data protection authority, a permission to use the confidential national register data.

Results

A total of 2015 new invasive breast cancers were diagnosed in the study cohort consisting of 93 843 LNG-IUS users during a follow-up consisting of a total of 1 032 767 women-years (Table I). The mean follow-up time of the LNG-IUS users was 11.0 years (maximum 19 years). Of the 2015 breast cancers diagnosed, 1598 cases were of the invasive ductal histological type, 376 were invasive lobular cancers, and 41 were other histological types.

The incidence of both invasive lobular cancer (SIR 1.33, 95% CI 1.20–1.46) and ductal cancer (SIR 1.20, 95% CI 1.14–1.25) were higher among the LNG-IUS users as compared to the general

Table I. Cohort of levonorgestrel-releasing intrauterine system (LNG-IUS) users, follow-up 1994–2012.

	Follow-up from the first LNG-IUS purchase		Follow-up from the second LNG-IUS purchase	
Age	n	Women-years	n	Women-years
30 to 34	20 998	47 196	290	365
35 to 39	28 219	172 523	4 151	10 352
40 to 44	25 955	285 032	5 643	35 218
45 to 49	18 670	310 402	4 150	52 677
50 to 54	–	217 615	–	38 305
Total	93 843	1 032 767	14 234	136 917

Number of all women (n) counted by age at the purchase of LNG-IUS; women-years counted by age at the follow-up.

female population (Table II). After two or more purchases of the LNG-IUS the SIR for invasive lobular breast cancer was 1.73 (81 cases; 95% CI 1.37–2.15, $p < 0.001$) and for invasive ductal cancer 1.37 (286 cases; 95% CI 1.21–1.53, $p < 0.001$). Meaningful SIRs for the uncommon histological types (i.e. other types than ductal or lobular cancer) could not be computed due to small numbers.

The SIRs for both invasive lobular cancer and ductal cancer were not elevated during the first few years of follow-up as compared to the general female population, but they were significantly higher after the first five years of follow-up (Table II). The SIRs were slightly higher for localized breast cancer than for non-localized cancer, but also the incidence of non-localized ductal and lobular cancers was statistically significantly higher among the LNG-IUS users than in the control population after the first five years of follow-up (Table II).

An increase in the incidence of DCIS was less evident than for invasive cancer. A borderline significant SIR of 1.17 was observed for DCIS among the LNG-IUS users (Table II).

Discussion

We found that incidence of both invasive ductal and lobular breast cancer was higher in women who used the LNG-IUS as compared with the general female population of similar age. The SIRs were higher in the subgroup of the LNG-IUS users who purchased the LNG-IUS at least twice. These women had 73% higher risk for being diagnosed with lobular breast cancer than women in the general female population. An elevated risk for both ductal and lobular cancer was evident after the first five years of follow-up, the SIRs being slightly higher for lobular than for ductal cancer. These findings suggest a possible causal effect of levonorgestrel on breast cancer promotion. It is interesting that LNG-IUS use seemed to increase the risk for both lobular and ductal breast cancer, although only the lobular type has generally been considered to be associated with the use of estrogen and progestins [8]. The present finding is, however, not the only one implying that also ductal carcinoma may be linked to hormonal manipulation. Cerne et al. found that tumors in HT users were more often ductal than those in controls [17]. Also a large Danish study found that the relative risk of being diagnosed with invasive ductal carcinoma was 2.49 (95% CI 1.76–3.51) among current HT users as compared to never-users [18].

Premenopausal women with the LNG-IUS have low mean serum levonorgestrel concentrations, but individual variations are large [19]. The cancer cell proliferation enhancing effect of progestins does not necessarily increase with increasing serum progestin levels, and the biological effects and potency of different progestins vary [20]. Exogenous hormonal therapy impacts the risk for invasive lobular breast cancer in particular, and, similarly, HT with estrogen alone and combined with progestins as well as OCs increase the risk for invasive lobular breast

Table II. Observed (OBS) numbers of breast cancer cases and standardized incidence ratios (SIR, with 95% confidence interval [CI]) among Finnish women who purchased levonorgestrel-releasing intrauterine system (LNG-IUS) for menorrhagia during 1994–2007 at ages 30–49 years, by time since first purchase, 1994–2012. Follow-up from the first purchase of LNG-IUS until age 55.

Breast cancer category by histology	Time since first LNG-IUS purchase														
	0–0.99 years			1–4.99 years			5–9.99 years			over 10 years			Entire follow-up		
	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI
Lobular	12	0.93	0.48–1.61	72	0.99	0.78–1.25	168	1.40	1.20–1.62***	124	1.59	1.32–1.87***	376	1.33	1.20–1.46***
localised	6	1.09	0.40–2.37	32	1.03	0.71–1.45	73	1.40	1.10–1.76**	57	1.63	1.16–1.57***	168	1.36	1.16–1.57***
non-localised	6	0.86	0.32–1.88	37	0.97	0.68–1.33	86	1.40	1.12–1.73**	55	1.44	1.08–1.87*	184	1.27	1.10–1.46**
Ductal	66	0.90	0.69–1.14	413	1.12	1.02–1.23*	688	1.25	1.16–1.34***	431	1.26	1.14–1.38***	1598	1.20	1.14–1.25***
localised	38	1.04	0.74–1.43	229	1.26	1.10–1.42***	339	1.27	1.14–1.41***	219	1.34	1.17–1.51***	825	1.27	1.19–1.36***
non-localised	24	0.71	0.46–1.05	171	1.01	0.86–1.16	322	1.25	1.12–1.39***	188	1.19	1.03–1.36*	705	1.14	1.06–1.22***
Ductal in situ	3	0.67	0.14–1.95	34	1.13	0.78–1.57	69	1.17	0.91–1.47	52	1.26	0.94–1.65	158	1.17	1.00–1.36

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

cancer [8,9]. In line with these findings, several studies have found a decreasing incidence of lobular breast cancer with decreasing use of HT in the population, but the decreased incidence rates were limited to the postmenopausal female population [21,22].

The strengths of the present study are the large cohort size, long follow-up time (mean follow-up of 11.0 years), and availability of population-based data from nationwide registries which reduces the risk of a selection bias. We could not adjust the risks for the history of mammography screening which is known to enhance detection of small breast cancers [23]. However, the SIRs for DCIS lesions most of which are found at mammography, were slightly smaller than for invasive cancers which suggests that the frequency of mammography examinations did not differ substantially between LNG-IUS users and other women. In Finland, mammography screening is not offered as a national public service to women younger than 50. A surveillance bias, however, cannot be excluded as breast tenderness is frequent among LNG-IUS users [24] which might result in more frequent breast self-examinations or in more frequent health care visits.

We did not have information about the tumor steroid hormone receptor contents or the human epidermal growth factor receptor-2 (HER2) status of the cancers. The incidence of steroid hormone receptor-positive breast cancer is increasing in some western countries while the incidence of receptor-negative breast cancer is decreasing [25]. This may be due to changes in the lifestyle, obesity and parity, but exogenous hormonal treatments may also play a role [26]. Lobular breast cancer is frequently estrogen receptor and progesterone receptor-positive [7], and might be more sensitive to exogenous steroid hormone administration than other histological types of breast cancer [8].

We did not have information about the actual duration of LNG-IUS use or about the effects of its removal on breast cancer incidence. This requires further studies. In studies investigating OC use and breast cancer risk, current or recent OC use increases the risk of breast cancer, but the risk diminishes after the cessation of use [6]. These findings are compatible with a hypothesis that progestins can act as promoters of breast cancer growth, possibly enhancing the growth of small cancer precursor lesions. However, our results should be interpreted with caution, as the women using the LNG-IUS for menorrhagia may represent a selected population with different intrinsic risk factors for breast cancer and its subtypes (e.g. a greater proportion of anovulatory cycles) compared to the background population or women using LNG-IUS for contraception solely.

In conclusion, the results of the present study support our previous finding that the use of LNG-IUS for menorrhagia is associated with an elevated risk for breast cancer. In line with previous studies on hormonal manipulation and breast cancer risk, especially the risk of lobular type was increased. However, the increased risk does not seem to be limited to lobular breast cancer, because also the number of ductal breast cancers was higher than expected.

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