

## Use of the levonorgestrel-releasing intrauterine system in breast cancer patients

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**Objective:** To study the recurrence of breast cancer among patients who were using the levonorgestrel-releasing intrauterine system (LNG IUS).

**Design:** A retrospective, controlled cohort analysis.

**Setting:** Six Belgian hospitals.

**Patient(s):** We identified 79 breast cancer patients who used the LNG IUS, and we selected a control group of 120 patients with no history of LNG IUS use and who were closely matched for age at diagnosis, tumor stage, tumor grade, and treatment modalities. Two subgroups were identified: [1] breast cancer patients who continued using the LNG IUS after diagnosis and [2] breast cancer patients who began using an LNG IUS after treatment for breast cancer.

**Intervention(s):** Patient's data were collected and survival analysis was performed.

**Main Outcome Measure(s):** Breast cancer recurrence rate.

**Result(s):** There was a recurrence rate of 21.5% (17/79) among LNG IUS users and of 16.6% (20/120) among the control group (adjusted hazard ratio, 1.86; 95% confidence interval, 0.86–4.00; no statistically significant difference). Subgroup analysis showed that women using the LNG IUS (n = 38) at the time of breast cancer diagnosis (and who continued its use) had a statistically significantly increased risk of recurrence (adjusted hazard ratio, 3.39; 95% confidence interval, 1.01–11.35) compared with patients in the control group. There was 47.4% (18/38) nodal involvement in this subgroup, and all patients who recurred had metastatic disease.

**Conclusion(s):** Overall, we did not find an increased risk of breast cancer recurrence associated with use of the LNG-IUS. However, in a subgroup analysis of women who developed breast cancer while using an LNG IUS and who continued to use the LNG IUS, we found a higher risk of recurrence of borderline statistical significance. Additional research is needed to confirm or refute these findings. (Fertil Steril® 2007; ■: ■-■. ©2007 by American Society for Reproductive Medicine.)

**Key Words:** LNG IUS, breast cancer, recurrence, Mirena, survival, levonorgestrel

There are several clinical indications for the use of the levonorgestrel-releasing intrauterine system (LNG IUS) in breast cancer patients. In premenopausal breast cancer survivors, it can be used for contraception or for heavy menstrual bleeding problems. In breast cancer patients who are using tamoxifen, the LNG IUS may be beneficial in preventing endometrial changes. In postmenopausal breast cancer patients, a randomized controlled trial of 122 patients showed that the LNG IUS has a protective effect, preventing tamoxifen-induced uterine effects and decreasing the need for repeated investigations for

postmenopausal bleeding (1). In breast cancer survivors who have severe climacteric symptoms, several investigators have suggested that the combination of systemic estrogens in combination with the LNG IUS should be an option to consider (2, 3).

A recent epidemiologic study in Finland found no increase in the incidence of breast cancer in LNG IUS users compared with in nonusers (4). This study was based on a questionnaire sent to LNG IUS users, of whom 77.6% responded. The breast cancer incidence of 17,360 LNG IUS users between 30 and 54 years was compared with data from the Finnish cancer registry.

In animal models, the carcinogenicity of levonorgestrel was tested in rats using parenteral administration and in dogs and monkeys by oral administration (5). The administration of high doses of levonorgestrel to beagle dogs resulted

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in an increased number of mammary nodules, of which a majority were benign adenomas. Because beagles metabolize Ps differently than human beings, the relevance of these results for women is unclear. In the rhesus monkey and rat models, levonorgestrel did not induce palpable mammary nodules or lead to a higher incidence in tumors, respectively.

Given that the LNG IUS does not lead to a higher incidence of breast cancer cases, the question emerges of whether the LNG IUS should be used in patients who have been diagnosed with or completed treatment for breast cancer (6). It is not known whether LNG IUS users who are diagnosed with breast cancer should have their LNG IUS removed. The present article is the first to evaluate the safety of LNG IUS in relation to breast cancer recurrence. It includes two groups of patients: [1] breast cancer patients who continued using the LNG IUS after diagnosis and [2] breast cancer patients who began using an LNG IUS after treatment for breast cancer.

## MATERIALS AND METHODS

To study the safety of LNG IUS use by breast cancer patients, we collected data on breast cancer patients who were using the LNG IUS from June 2005 until April 2006. Six centers participated in this retrospective cohort analysis. In three centers with breast cancer units, electronic databases were available for query searches. In all six centers, patients were selected from among patients who presented in breast cancer follow-up programs. Inclusion criteria were that the patient [1] ought to have had a diagnosis of invasive breast cancer and [2] ought to have used an LNG IUS during a subsequent disease-free period. Disease-free survival was defined as survival time that was free of distant metastasis, local recurrence, and contralateral breast cancer. Thus, patients were excluded from analysis who had their LNG IUS inserted after recurrence or who had distant metastasis at the time of LNG IUS insertion. Patients who had *in situ* carcinoma also were excluded. Information regarding breast cancer characteristics, the use of LNG IUS, treatment, and follow-up data were collected in a database. All LNG IUS used were Mirena by Schering (Diegem, Belgium) and released 20  $\mu\text{g}$  of levonorgestrel daily.

A control group was closely matched for age at initial diagnosis, tumor grade, tumor histology, tumor TNM classification, and treatment options. Because almost all patients in the LNG IUS group were premenopausal (97.4%) at the time of initial diagnosis, an existing database of premenopausal breast cancer patients was used for the matching procedure. This existing database included 277 patients with invasive breast cancer along with follow-up data, and information about the use of contraception, so all patients using LNG IUS could be excluded from the control group before the matching procedure. The matching procedure was performed by blinding the investigator (X.B.T.) to the survival follow-up data, but with baseline characteristics available. After age matching was performed, the P receptor status

was matched. Because of its high prognostic value, the nodal involvement status was adjusted to have comparable percentages with preservation of the matching. After this adjustment, 120 patients remained in the control cohort.

After unblinding the survival and follow-up data, Kaplan-Meier curves were used to obtain disease-free survival curves. Whenever a patient had an LNG IUS removed during follow-up, that patient was censored from the analysis on the date of removal. Adjusted hazard ratios were calculated by using Cox-regression correction for age at diagnosis, tumor grade, tumor histology, tumor TNM classification, treatment modalities, and hormone sensitivity. The SPSS statistical package (version 13.0; SPSS, Chicago, IL) was used for these analyses.

Patients were divided into subgroups A and B. Subgroup A contained patients who were using their LNG IUS at the time of diagnosis and continued using this LNG IUS. Subgroup B were patients who had their LNG IUS inserted after a breast cancer diagnosis. The LNG IUS was inserted in these patients after completion of their breast cancer treatment or while they were using adjuvant anti-hormonal therapy.

For subgroups A and B, adjusted hazard ratios were calculated by using the control cohort, with Cox regression analysis correcting for the same factors.

According to Belgian regulations, institutional review board approval was not obtained because the study involved only existing records. We did not conduct any additional patient interviews.

## RESULTS

Data collected from six centers revealed 86 patients who used an LNG IUS and had a history of breast cancer. Seven patients were excluded from analysis because they had their LNG IUS inserted after a distant metastasis had been identified or after recurrence. A control group of 120 patients could be closely matched. A summary of patient and tumor characteristics at the time of initial diagnosis is presented in Table 1. The mean follow-up periods were also comparable in both groups (2.8 y in the LNG IUS group and 2.9 y in the control group). The periods during which the initial breast cancers were diagnosed ranged from June 1991 to October 2005 for the LNG IUS cohort, vs. January 1993 to August 2004 for the control cohort.

In 5%, the LNG IUS was placed after ultrasonographic endometrial thickening was observed. The endometrium was examined histologically in these patients before the LNG IUS was placed. Other indications for insertion of LNG IUS were contraception in 63%, menorrhagia in 10%, and unknown in 22%.

Figure 1 shows the Kaplan-Meier survival curve of the control group vs. the LNG IUS group. There were 21.5% (17/79) recurrences in the LNG IUS group and 16.6% (20/120) recurrences in the control group. A Cox regression was performed as described in Materials and Methods. An

**TABLE 1****Characteristics of patients in the LNG cohort and the control cohort.**

Parameter	LNG cohort	Control cohort
n	79	120
Age at diagnosis (y)	39.8	40.0
Tumor histology		
Ductal	88.6	92.5
Lobular	7.6	4.2
Tumor grade		
I	17.6	21.6
II	41.9	45.0
III	40.5	33.3
Estrogen sensitivity	61.5	73.7
Progesterone sensitivity	63.6	62.6
Tumor classification		
T1	61.5	57.5
T2	29.5	34.2
T3	3.8	4.2
T4	5.1	4.2
N0	62.0	65.0
N1	32.9	30.0
N2	5.1	5.0
Breast-conserving surgery	50.6	55.8
Mastectomies	49.4	44.2
Radiotherapy	88.6	90
Chemotherapy	67.1	67.5
Neoadjuvant chemotherapy	6.3	5
Anti-hormonal therapy	59.5	59.2

*Note:* Data are percentages unless otherwise indicated.

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adjusted hazard ratio was 1.86 (95% confidence interval, 0.86–4.00), with a *P* value of .11. The crude hazard ratio was 1.47 (95% confidence interval, 0.77–2.80), with a *P* value of .24.

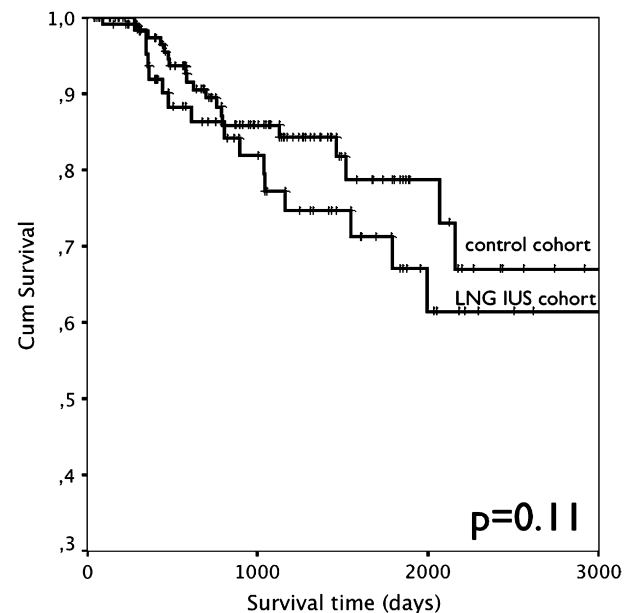
While we were collecting data on patients who fulfilled the inclusion criteria, we noted two types of patients in the LNG IUS cohort. First, there were patients who were using their LNG IUS at the time of diagnosis and continued using this LNG IUS (subgroup A, *n* = 38). Second, there were patients who had their LNG IUS inserted after a breast cancer diagnosis. The LNG IUS was inserted in these patients after completion of their breast cancer treatment or while they were using adjuvant anti-hormonal therapy (subgroup B, *n* = 41).

The same Kaplan-Meier curves and Cox regression analyses were performed in the subgroups, comparing them with the control group. The adjusted hazard ratios were 3.39 (95% CI, 1.01–11.35; *P* = .048) for subgroup A (Fig. 2) and 1.48 (95% CI, 0.62–3.49; *P* = .38) for subgroup B.

The initial baseline characteristics of subgroup A and B patients are described in Table 2. Subgroup A patients had

**FIGURE 1**

Kaplan-Meier survival curve: LNG IUS breast cancer patients vs. control cohort.



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axillary node involvement in 47.4% of patients, compared with 29.3% of patients in subgroup B (*P* > .05). A higher axillary node involvement probably explains why patients in subgroup A received chemotherapy at a higher rate vs. those in subgroup B (84% vs. 51%). There was no significant difference in hormone receptor expression in tumors of subgroups A and B.

When comparing patients' status at the last follow-up appointment, all patients who recurred in subgroup A had distant metastasis and were all "alive with disease" (100%), whereas recurrences in the control group were labeled as patients with "no evidence of disease" in 35%, as "alive with disease" in 55%, or as "dead of disease" in 10%. In subgroup B, among the patients who recurred, there was no evidence of disease in 70.0%, and 30.0% were alive with disease.

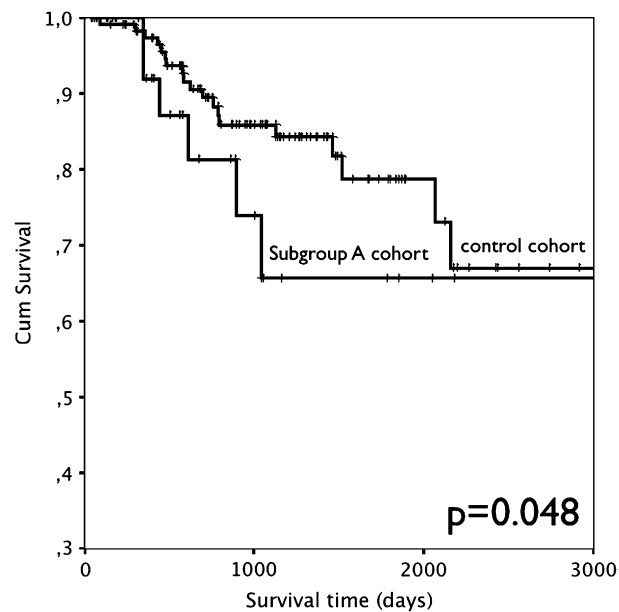
This could mean that subgroup A may have a higher mortality potential because all patients who recurred had metastatic disease. In subgroup B or in the control group, there was a proportion of patients who had local recurrence (70% of the recurrences).

## DISCUSSION

The effect of levonorgestrel has been studied on breast cancer cell lines. Mirkin et al. (7) reported that levonorgestrel increases vascular endothelial growth factor messenger RNA in T47D (P receptor-rich) breast cancer cell lines. In vitro studies have shown that levonorgestrel stimulates cell growth

FIGURE 2

Kaplan-Meier survival curve: LNG IUS breast cancer patients who had a LNG IUS at time of diagnosis and continued using it (subgroup A) vs. control cohort.



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in T47D-A cells, whereas it did not affect cell growth in T47D-S cells. These results with T47D cells show that subclones of cell lines may respond differently to high pharmacological levels of levonorgestrel (8).

In MCF-7 breast cancer cell lines, levonorgestrel stimulated cell growth in all studied subclones (9). In both MCF-7 and T47-A, anti-progestogens such as RU 38486 and Org 31710 could not block these stimulatory effects, whereas antiestrogens such as 4-hydroxytamoxifen and ICI 164,384 could. This suggests that the levonorgestrel stimulatory effect involves the estrogen receptor. Administration of E<sub>2</sub> or levonorgestrel separately stimulates cell growth in MCF-7 and T47-A breast cancer cell lines. However, with combined administration, the E<sub>2</sub>-induced cell growth could be significantly inhibited (8–10).

These in vitro studies suggest that levonorgestrel-only administration can stimulate breast cancer cell growth, and this effect may play a role in cancer angiogenesis by increasing messenger RNA vascular endothelial growth factor.

Whether it is plausible that LNG IUS has an effect on breast cancer depends on whether or not the LNG IUS produces significant systemic exposure. Its contraceptive mechanism mainly is caused by local effects, but the device also has an important systemic effect, and the systemic levels of levonorgestrel should not be ignored (11). Evidence for significant systemic levels are the side effects that are associated with the use of the LNG IUS. Patients using the LNG IUS have a relative risk of hypertension and gall bladder disease

TABLE 2

Characteristics of patients in subgroup A and subgroup B.

Parameter	Subgroup A	Subgroup B
n	38	41
Age at diagnosis (y)	39.3	40.2
Tumor histology		
Ductal	92.1	85.4
Lobular	5.3	9.8
Tumor grade		
I	16.7	18.4
II	41.7	42.1
III	41.7	39.5
Estrogen sensitivity	60.5	62.5
Progesterone sensitivity	65.8	61.5
Tumor classification		
T1	62.2	61.0
T2	29.7	29.3
T3	5.3	2.4
T4	2.6	7.3
N0	52.6	70.7
N1	42.1	24.4
N2	5.3	4.9
Breast-conserving surgery	47.4	53.7
Mastectomies	52.6	46.3
Radiotherapy	81.6	95.1
Chemotherapy	84.2	51.2
Neoadjuvant chemotherapy	7.9	4.9
Anti-hormonal therapy	71.1	48.8

Note: Data are percentages unless otherwise indicated.

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of 1.8 and 1.5, respectively, and other side effects include skin conditions, headache, upper limb neuropathies, dizziness, nervousness, malaise, minor visual disturbances, respiratory conditions, arthropathies, weight change, anxiety, and nonclinical depression (4, 6, 12).

The Mirena IUS that has been the subject of this study releases a daily dose of 20 µg. The plasma concentration of 150–200 pg/mL of levonorgestrel in premenopausal women who are using Mirena (according to the product monograph, Bayer Healthcare Pharmaceuticals, <http://www.bayerhealth.com>.) has been confirmed in studies by Xiao et al. (13) and Nilsson et al. (14)

However, more recent reports describe higher concentrations of levonorgestrel in LNG IUS users in specific subgroups of LNG IUS users. Serum concentrations of LNG IUS in premenopausal patients who were treated for endometriosis reached 459.2 ± 100 pg/mL after 1 month, 368.2 ± 51.8 pg/mL after 3 months, and 357.3 ± 53.0 pg/mL after

6 months (12). In another population, postmenopausal women using an LNG IUS, the median LNG serum concentrations were 209 pg/mL and 212 pg/mL after 6 and 12 months, respectively (15). These concentrations are comparable to those that are reached among users of the 30- $\mu$ g levonorgestrel-only pill, which has plasma steady-state concentrations of  $312 \pm 211.9$  pg/mL (16, 17).

The plasma levels of combined contraceptives using levonorgestrel are 10-fold higher (1,300–5,500 pg/mL) than is the intrauterine release by LNG IUS (14, 16, 18). A comparable plasma concentration can be reached exceptionally by LNG IUS, as reported by Haimov-Kochman et al. (16). That case report described the pharmacokinetics of an LNG IUS user in whom the device was situated in the peritoneal abdominal cavity after a uterine perforation. Intraperitoneally dislocated LNG IUS resulted in plasma levonorgestrel levels that were 10 times higher than the plasma levels that were observed with LNG IUS in utero (1,530 pg/mL). This suggests that the LNG IUS may release more levonorgestrel depending on the environment or that the systemic uptake of levonorgestrel in the peritoneal cavity is higher.

These studies indicate that there is a significant systemic uptake of levonorgestrel and that in certain subgroups of women, the levels may be comparable to those in women who take levonorgestrel-only pills.

The results of this study indicate that overall, there was no higher recurrence risk in breast cancer patients who were using LNG IUS. Subgroup analysis suggests that the LNG IUS is not associated with an increased risk of recurrence in patients who start using the LNG IUS after completing their breast cancer treatment. These patients had a survival curve similar to that of the matched control group. However, in patients who were using an LNG IUS at the time of diagnosis and who continued using it, the LNG IUS was associated with an increased risk of disease recurrence. All the patients in subgroup A in this study who had a recurrence are alive with metastases. Although not statistically different from the control group, these patients interestingly had 47.3% node involvement at time of initial diagnosis, whereas in subgroup B, node involvement at initial diagnosis was seen in only 29.3% of women. In contrast with subgroup A, in which all patients with disease recurrence have distant metastasis, in subgroup B, 70% of all recurrences were local recurrences, which were susceptible to treatment. This indicates that in our study cohort, subgroup A had less favorable characteristics.

One hypothesis could be that tumors that develop while being exposed to levonorgestrel are more aggressive. The fact that tumors can have different characteristics after hormonal exposure has been described before. In the Women's Health Initiative trial, the tumors that were found in the combined hormone therapy arm (conjugated equine estrogen + progestin) were larger (mean  $\pm$  SD:  $1.7 \pm 1.1$  cm vs.  $1.5 \pm 0.9$  cm;  $P=.04$ ) and were at more advanced stages (regional or metastatic,  $P=.04$ ) compared with those in the placebo group. Node invasion occurred more frequently (25.9% vs. 15.8%;

$P=.03$ ). There were no differences in the distribution of histology, grade, or estrogen and progesterin receptors between hormone therapy users and the placebo group (19).

There are several limitations to our study. Although we matched for several prognostic and predictive factors, a matched retrospective cohort is not the same as a population sample. The hazard ratio therefore was adjusted for age at diagnosis, tumor grade, tumor histology, tumor TNM classification, treatment modalities, and hormone sensitivity. Although there were no relevant confounders found with the Cox regression analysis, there was still a difference in the calculated crude hazard ratio (1.47) and the adjusted hazard ratio (1.86). This means that both cohorts were not perfectly matched and that there are some confounding. For instance, there was a difference in grade 3 tumors of 7.2% between both cohorts. However, the adjusted hazard ratio represents the risk that was corrected for this difference.

Residual confounding and certain bias may remain because other risk factors that were not available were not included in the analysis. For example, perhaps there is preferential prescribing of the LNG IUS to women who have a high background risk of breast cancer.

Another limitation is that this study included small numbers of patients, especially in the subgroups, and had a limited median follow-up period. In subgroup A, a higher recurrence risk was found among LNG IUS users; however, that finding had a wide confidence interval. And finally, our subgroup analysis was an unplanned analysis, based on the identification of the two subgroups during the data collection period. Thus, our conclusions should be interpreted carefully.

Further research is necessary to evaluate the results found in this cohort analysis, because of its impact on daily practice with breast cancer patients. When diagnosing an LNG IUS user with breast cancer, it is essential to know whether the LNG IUS must be removed. If the risk we found is replicated in other studies, then other contraception options may be considered. When a breast cancer survivor needs contraception, it is important to know that use of an LNG IUS is not associated with a higher rate of disease recurrence.

For premenopausal patients who are using aromatase inhibitors after medical castration, it is particularly important that they have their LNG IUS removed because these patients are hormone hypersensitive (20). However, to prevent tamoxifen-induced endometrial changes, one could consider an LNG IUS. But one should realize that there is not yet enough evidence to conclusively state that the LNG IUS is effective in preventing tamoxifen-induced endometrium adenocarcinoma (21). There should be awareness among physicians involved in breast cancer care that the LNG IUS does result in some systemic hormonal exposure and that women diagnosed with breast cancer should be specifically questioned as to whether they are using an LNG IUS, because it is sometimes overlooked.

To conclude, whereas patients in whom an LNG IUS was inserted after completion of breast cancer treatment did not

have an increased risk to develop disease recurrence, those who developed breast cancer while using an LNG IUS had a higher risk of recurrence that was of borderline statistical significance.

Because this was a retrospective analysis with a number of limitations, a prospective cohort study is being initiated in Belgium to follow premenopausal breast cancer patients, including data on contraceptive use (e.g., duration and type) and other background risk factors that were missing in this study. This should help clarify whether the results of this study were a result of chance or confounding or a result of a treatment effect.

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