

ORIGINAL ARTICLE

## Impact of levonorgestrel-releasing intrauterine system use on the cancer risk of the ovary and fallopian tube

Tuuli Soini<sup>a</sup>, Ritva Hurskainen<sup>a</sup>, Seija Grénman<sup>b,c</sup>, Johanna Mäenpää<sup>d,e</sup>, Jorma Paavonen<sup>f,g</sup> and Eero Pukkala<sup>h,i</sup>

<sup>a</sup>Department of Obstetrics and Gynecology, Hyvinkää Hospital, Hyvinkää, Finland; <sup>b</sup>Department of Obstetrics and Gynecology, Turku University Hospital, Turku, Finland; <sup>c</sup>University of Turku, Turku, Finland; <sup>d</sup>School of Medicine, University of Tampere, University of Tampere, Finland; <sup>e</sup>Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland; <sup>f</sup>Department of Obstetrics and Gynecology, Helsinki University Hospital, Helsinki, Finland; <sup>g</sup>University of Helsinki, Helsinki, Finland; <sup>h</sup>School of Health Sciences, University of Tampere, University of Tampere, Tampere, Finland; <sup>i</sup>Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

### ABSTRACT

**Background:** Levonorgestrel-releasing intrauterine system (LNG-IUS) is used for contraception and heavy menstrual bleeding. A long-term hormone therapy can modify the risk of gynecologic cancers. Little is known about the impact of LNG-IUS use on the risk for invasive and borderline ovarian tumor subtypes or for primary fallopian tube carcinoma. We examined the associations of LNG-IUS use with these tumors.

**Material and methods:** We identified from the national Medical Reimbursement Registry of Finland the women aged 30–49 years who had used LNG-IUS for menorrhagia in 1994–2007, and from the Finnish Cancer Registry ovarian cancers and primary fallopian tube carcinomas diagnosed before the age of 55 and by the end of 2013.

**Results:** A total of 77 invasive ovarian cancers and seven primary fallopian tube carcinoma cases were diagnosed in a cohort of 93 843 LNG-IUS users during the follow-up of 1 083 126 women-years. The LNG-IUS users had decreased risk for both invasive ovarian cancer [standardized incidence ratio (SIR) 0.59, 95% confidence interval (CI) 0.47–0.73] and for borderline ovarian tumors (SIR 0.76, 95% CI 0.57–0.99) as compared to the background population. The risk of primary fallopian tube carcinoma was not increased (SIR 1.22, 95% CI 0.49–2.50). Decreased risks for mucinous (SIR 0.49, 95% CI 0.24–0.87), endometrioid (SIR 0.55, 95% CI 0.28–0.98), and serous ovarian carcinomas (SIR 0.75, 95% CI 0.55–0.99) were seen in LNG-IUS users.

**Conclusions:** LNG-IUS use associated with decreased risk for both invasive and borderline ovarian tumors. The incidence of primary fallopian tube carcinoma did not significantly differ between LNG-IUS users and the background population.

### ARTICLE HISTORY

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Ovarian cancer is the fifth most common cancer in women in the developed world and the most lethal of gynecological cancers [1]. Most cases of ovarian cancer are diagnosed at an advanced stage with poor prognosis despite aggressive treatment. Primary fallopian tube carcinoma (PFTC) is a rare disease, constituting up to 1.8% of gynecological malignancies [2]. Despite vigorous research, effective screening method still does not exist for these cancers. Therefore, understanding the pathogenesis of these malignancies is crucial for enabling all possible preventive efforts.

Approximately 90% of primary ovarian cancers are of epithelial origin [1]. Epithelial ovarian cancer includes different histopathological types: high grade serous, low grade serous, endometrioid, clear cell and mucinous carcinomas [1]. According to the recent data, ovarian cancer seems to be a heterogeneous disease arising from different tissue origins and has diverging risk factors [3]. Emerging data show that high grade serous carcinomas originate from the fimbriated end of the fallopian tube and low grade serous carcinomas from the ovarian epithelium [4]. Endometrioid and clear cell

ovarian cancer are suggested to be of endometrial origin, especially endometriosis [3], whereas mucinous ovarian tumors are believed to originate from the gastrointestinal tract [5].

Many of established risk factors for ovarian cancer are reproductive or hormone-related. Oral contraception, tubal ligation, and pregnancies are protective factors against ovarian cancer whereas nulliparity, postmenopausal hormone therapy (HT), and family history of ovarian cancer increase the risk [1,6,7].

The etiology of PFTC is not well known, but multiparity [8] and use of oral contraceptives have been shown to decrease the risk of PFTC [2,9]. Nulliparity, long-term postmenopausal HT with estrogen and progestin, also in the form of LNG-IUS, have been reported to increase the risk of PFTC [9,10]. The effect of premenopausal LNG-IUS use on the risk of PFTC is not known.

The LNG-IUS is an effective treatment for heavy menstruation [11]. Despite high level of levonorgestrel locally in the endometrium, the levels of levonorgestrel are similarly high in

the fallopian tubes as they are in the myometrium [12]. This high local progestin effect could potentially modify the cancer risk. In our previous study, we found a decreased risk of endometrial cancer among LNG-IUS users, but ovarian cancer risk also seemed to be lower than in the background population [13]. As ovarian cancer has distinct etiologies and malignant transformation in the fallopian tube is linked to ovarian cancer, we wanted to study the effect of LNG-IUS use on the risk of different histologies of ovarian cancer and PFTC by conducting this nationwide cohort study.

## Material and methods

We collected a cohort of all Finnish women who had received reimbursement for the LNG-IUS purchase for the treatment of menorrhagia at the age of 30–49 in 1994–2007 ( $n = 93\,843$ ). The study was based on information from Finnish nationwide health and administrative registers. Data linkages between registers were done using the personal identity code issued to all citizens and permanent residents of Finland by the Finnish Population Centre since 1967 and used as the identification key in all registers. The data about LNG-IUS purchases were received from the national Reimbursement Register of the Social Insurance Institution, Finland, which contains data about the reimbursed LNG-IUSs since 1994. The dates of emigration and death during the follow-up were received from the Population Register Centre of Finland.

The cancer cases of the LNG-IUS cohort were identified from the Finnish Cancer Registry, which receives notifications of all cancer cases diagnosed in Finland since 1953. The data on different histological types of ovarian tumors and PFTC are coded by the Finnish Cancer Registry according to ICD-O-3 system.

We calculated women-years at risk, in five-year age groups, starting from the first LNG-IUS purchase and ending on 31 December 2013, on emigration, on the 55th birthday, bilateral or unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, hysterectomy, or death, whichever occurred first. Information about the surgical procedures since 1986 was obtained from the Hospital Discharge Register of the National Institute of Health and Welfare. This register has summary information about patients discharged from the public and private hospitals since 1969 with coverage of almost 100%.

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 period. A SIR was calculated by dividing the number of observed cancer cases by the expected number of 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 [14]. 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 Hospital. The Finnish National Center for Welfare and Health gave, after

consulting the data protection authority, permission to use the confidential national register data in this research.

## Results

A total of 77 new invasive ovarian cancer cases were diagnosed in the study cohort during the follow-up consisting of a total of 1 083 126 women-years corresponding to an average follow-up of 11.5 years (maximum 20 years) (Table 1). Of all invasive ovarian cancers, 46 cases were serous, 11 cases were mucinous, 11 cases were endometrioid carcinomas, and the rest were other less common cancer types. The risk of ovarian malignancy was significantly decreased in LNG-IUS users (SIR 0.59, 95% CI 0.47–0.73) compared with the background population (Table 2).

Of the histological subtypes of ovarian cancer, the relative risk was lowest for mucinous carcinoma (SIR 0.49, 95% CI 0.24–0.87), and highest for serous carcinoma (SIR 0.75, 95% CI 0.55–0.99). The differences between histology-specific SIRs were not significant (Table 2). After the first five years of follow-up, the SIRs for the invasive mucinous, serous, or endometrioid ovarian cancers did not decrease (Table 2).

During the follow-up, a total of 55 cases of borderline ovarian tumors were diagnosed in LNG-IUS users. The SIR for borderline ovarian tumor was 0.76 (95% CI 0.57–0.99) (Table 2). There were no significant differences between histology-specific SIRs of borderline ovarian tumors.

Seven PFTC cases were diagnosed in the LNG-IUS user cohort during the follow-up. The risk of PFTC in LNG-IUS users did not differ from that in the general population (Table 2).

Eleven cases of invasive ovarian tumors were diagnosed among women with two or more LNG-IUS purchases ( $n = 14\,234$ ). The SIR for ovarian cancer (all types) was 0.57 (95% CI 0.29–1.02) among the women with two or more LNG-IUS purchases.

## Discussion

In this large cohort study consisting of 93 843 LNG-IUS users and over one million women-years of follow-up time, we found that risk of ovarian cancer was decreased by 41% in LNG-IUS users compared with the general female population of similar age. The decrease in risk was seen already in the first five years of follow-up and was maintained during the whole follow-up. The decreased incidence of ovarian cancer in the LNG-IUS users was seen in all main histological types. The risk of borderline ovarian tumors was also significantly

**Table 1.** Cohort of levonorgestrel-releasing intrauterine system (LNG-IUS) users, follow-up 1994–2013.

Age	Follow-up from the first LNG-IUS purchase	
	n	Women-years
30–34	20 998	47 196
35–39	28 220	172 575
40–44	25 955	291 267
45–49	18 670	330 091
50–54	–	241 997
Total	93 843	1 083 126

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

**Table 2.** Observed (OBS) and expected (EXP) numbers of ovarian tumors and primary fallopian tube 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, 1994–2013. Follow-up from the first purchase of LNG-IUS until age 55.

Tumor histology	Time since first LNG-IUS purchase															
	0–4.99 years				5–9.99 years				over 10 years				Entire follow-up			
	OBS	EXP	SIR	95% CI	OBS	EXP	SIR	95% CI	OBS	EXP	SIR	95% CI	OBS	EXP	SIR	95% CI
Ovarian cancer (all invasive ovarian cancers)	30	47.4	0.63	0.43–0.90**	27	49.3	0.55	0.36–0.79***	20	33.6	0.59	0.36–0.91*	77	130.4	0.59	0.47–0.73**
Serous carcinoma	18	22.8	0.79	0.47–1.24	16	23.2	0.69	0.39–1.11	12	15.7	0.77	0.40–1.33	46	61.7	0.75	0.55–0.99*
Mucinous carcinoma	5	9.0	0.56	0.18–1.29	3	8.13	0.37	0.08–1.07	3	5.4	0.56	0.12–1.63	11	22.5	0.49	0.24–0.87*
Endometrioid carcinoma	5	7.1	0.71	0.23–1.65	3	8.0	0.38	0.08–1.10	3	4.9	0.62	0.13–1.79	11	19.9	0.55	0.28–0.98*
Clear cell carcinoma	1	2.4	0.42	0.01–2.34	2	3.3	0.61	0.07–2.19		2.7	0.00	0.00–1.38	3	8.3	0.36	0.07–1.05
Ovarian borderline tumors (all tumor types)	22	26.2	0.84	0.53–1.26	16	27.4	0.58	0.33–0.94*	17	18.5	0.92	0.54–1.47	55	72.1	0.76	0.57–0.99*
Serous	8	10.5	0.77	0.33–1.50	5	10.4	0.48	0.16–1.12	5	6.8	0.74	0.24–1.71	18	27.7	0.65	0.39–1.02
Mucinous	9	11.0	0.82	0.38–1.55	10	12.0	0.84	0.40–1.53	2	8.2	0.25	0.03–0.88*	21	31.1	0.68	0.42–1.03
Endometrioid	1	0.1	7.47	0.19–41.6		0.1	0.00	0.00–27.5		0.2	0.00	0.00–23.2	1	0.4	2.34	0.06–13.1
Clear cell		0.0	0.00	0.00–225		0.1	0.00	0.00–71.5		0.0	0.00	0.00–171		0.1	0.00	0.00–41.2
Primary fallopian tube carcinoma	3	2	1.47	0.30–4.29	2	2.2	0.91	0.11–3.93	2	1.5	1.32	0.16–4.77	7	5.8	1.22	0.49–2.50

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

decreased among LNG-IUS users compared with the background population. In a recent study among postmenopausal women, LNG-IUS use did not affect the risk of ovarian cancer, but the number of ovarian cancer cases was only 27 [15].

In this study, LNG-IUS use was associated with 51% decreased risk of mucinous ovarian carcinoma compared with general population. The association of a protective effect of LNG-IUS use was strongest in this ovarian cancer subtype. The decreased risk among LNG-IUS users for mucinous carcinoma was also seen in our previous study with a shorter follow-up [13]. No other reports are available on the effect of the premenopausal LNG-IUS use on the risk of mucinous ovarian cancer. We also found that the incidence of borderline mucinous tumor, considered as precursor of mucinous carcinoma [5], was decreased among LNG-IUS users, although the finding did not quite reach statistical significance. Mucinous ovarian carcinoma is distinct from other epithelial ovarian cancers. Mucinous ovarian carcinoma is suggested to originate from non-ovarian cells and carries different risk factors than other ovarian cancer types [5]. Its risk has been reported not to be affected by oral contraceptives [16,17] but associations with HT use are inconsistent [7,17,18]. Progesterone receptor (PR) expression is lower in mucinous carcinomas than in other ovarian cancer subtypes [19] which may explain its resistance against the protective effect of oral contraceptives. Our finding of lower risk of both mucinous borderline ovarian tumors and mucinous carcinomas in the LNG-IUS users could be mediated by other mechanisms than direct progestin effect of LNG-IUS.

The risk for ovarian endometrioid carcinoma was almost halved in LNG-IUS users compared to background population. This is in line with data indicating that endometrioid carcinomas arise from endometriotic cells and that the LNG-IUS is an effective treatment for both endometriosis and menorrhagia [3,11,20]. LNG-IUS use frequently causes amenorrhea which decreases the retrograde flow of menstrual blood including uterine growth factors as well as inflammatory or carcinogenic factors into fallopian tubes [11,21]. Also, ovarian endometrioid carcinoma expresses high levels of PRs which enable to make a hypothesis of a protective effect of progestin [22].

The risk for ovarian clear cell carcinoma, which may also be of endometrial origin [3], was non-significantly decreased in the LNG-IUS users. However, due the rarity of this cancer and the low number of cases, robust conclusions cannot be made.

The risk for ovarian serous carcinoma, the most common subtype of ovarian cancers, was 25% lower in LNG-IUS users than in the general population. In our study cohort, ovarian serous carcinoma cases constituted 60% of all ovarian cancers. Since 2014, ovarian serous carcinoma is distinguished as high grade and low grade subtypes in the classifications by FIGO and WHO [23,24]. High grade serous carcinoma is an aggressively growing cancer which may originate from the distal end of the fallopian tube. High grade serous tumors cause the majority of deaths due to ovarian cancer [25]. Low grade serous ovarian carcinoma is a more indolent type originating from serous borderline tumors and does express high levels of PR [19,22,25]. In this study, serous carcinomas were analyzed as one group because data of tumor grades were not available. Therefore, further analysis of the protective effect of LNG-IUS use in these subtypes of ovarian cancer is indicated.

In this study, the risk of PFTC did not differ between LNG-IUS users and the general population. To our knowledge, no reports have been published on the effect of premenopausal use of LNG-IUS on the risk of PFTC. In a recent study, an elevated risk for PFTC was noticed in postmenopausal women who had used estrogen and LNG-IUS for more than five years (OR 2.84, 95% CI 1.10–7.38) [10]. However, the result was based on only six cases. PFTC is a rare malignancy with a mean incidence age of 55 years [2]. Therefore, it is likely that significant associations between LNG-IUS use and PFTC risk are difficult to detect.

The strengths of this study are large cohort size, long follow-up time, and population-based data from national administrative and health registers. The national registers in Finland have a very high level of coverage enabling this type of research [26]. We had virtually complete information on the LNG-IUS reimbursements, cancer diagnoses, and the deaths during the follow-up. This reduces the risk of selection bias. However, selection bias cannot be totally excluded since the LNG-IUSs were prescribed for menorrhagia. Heavy menstruation with retrograde blood flow into fallopian tubes prior

the use of LNG-IUS might have predisposed these women for a higher risk of ovarian cancer than in the general population. If so, the protective effect of LNG-IUS use on ovarian cancer risk was stronger. A limitation of this study is that we did not have information about the oral contraceptive use or parity. The effect of parity on the risk of mucinous ovarian carcinoma is unclear. In some studies, pregnancies seem not to protect against mucinous carcinomas [27,28], but also an opposite effect has been reported [18]. If the LNG-IUS users had more pregnancies than the background population, the risk estimates could be too low. Also, surveillance bias cannot totally be excluded as ovarian cysts are a known side effect of LNG-IUS [11]. This could lead to more frequent health care visits, closer monitoring and more frequent surgical interventions. In such case, more borderline and invasive ovarian cancers might be diagnosed in LNG-IUS users thus increasing the risk estimates.

In conclusion, our study results suggest decreased risks of both borderline ovarian tumors and invasive ovarian epithelial cancers in LNG-IUS users. These findings are valuable as LNG-IUS is globally used by millions of women and ovarian cancer is the most lethal gynecological malignancy. The mechanisms behind the decreased risk of ovarian cancer among LNG-IUS users might be multifactorial. In the future, more studies are indicated especially on the effect of LNG-IUS on the risk of high grade serous ovarian cancer, the subtype with the worst prognosis, and on the etiology of mucinous ovarian cancer.

## Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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