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Cancer risk among women treated with levonorgestrel-releasing intrauterine system or endometrial ablation for heavy menstrual bleeding

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ACADEMIC DISSERTATION

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For My Family

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List of original publications

This thesis is based on the following publications which are referred to in the text by their Roman numerals:

I.   Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol 2014; 124:292-9.

II.   Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Joensuu H, Pukkala E. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: A nationwide cohort study. Acta Oncol 2016; 55(2):188-92.

III.   Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E. Impact of levonorgestrel-releasing intrauterine system use on the cancer risk of the ovary and fallopian tube. Acta Oncol. 2016; 55(11):1281-84.

IV.   Soini T, Rantanen M, Paavonen J, Grénman S, Mäenpää J, Pukkala E, Gissler M, Hurskainen R. Long-term follow-up after endometrial ablation in Finland: Cancer risks and later hysterectomies. *Published ahead of print in Obstet Gynecol on August, 2017.* DOI: 10.1097/AOG.0000000000002166.

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In addition, this thesis contains some unpublished data.

Abbreviations

AR	androgen receptor
AUB	abnormal uterine bleeding
AVTK	Health Behavior and Health among the Finnish Adult Population Survey
BRCA1	breast cancer susceptibility gene type 1
BRCA2	breast cancer susceptibility gene type 2
BSO	bilateral salpingo-oophorectomy
CBG	corticosteroid-binding globulin
CI	confidence interval
COC	combined oral contraceptive
ER	estrogen receptor
ET	estrogen therapy
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique International Federation of Gynecology and Obstetrics
GR	glucocorticoid receptor
HER2	human epidermal growth factor receptor 2
HMB	heavy menstrual bleeding
HPV	human papilloma virus
HR	hazard ratio
HT	hormone therapy
IARC	International Agency for Research on Cancer
IUD	intrauterine device
LNG-IUS	levonorgestrel-releasing intrauterine system
MR	mineralocorticoid receptor
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PCOS	polycystic ovary syndrome
PFTC	primary fallopian tube carcinoma
PR	progesterone receptor
RR	relative risk
SHBG	sex hormone binding globulin
SIR	standardized incidence ratio

Abstract

Heavy menstrual bleeding (HMB) is a common complaint negatively affecting women's quality of life. Modern intrauterine treatment modalities for HMB, namely levonorgestrel-releasing intrauterine system (LNG-IUS) and endometrial ablation, have changed significantly the management of HMB and resulted in a marked decrease in the number of hysterectomies in many countries. Despite the increasing popularity of these treatments, little is known about the cancer risks among women treated with these methods. Also, some women need a later hysterectomy after endometrial ablation, but factors predisposing to that are insufficiently known. To assess the cancer risk among women treated for HMB with LNG-IUS or endometrial ablation, and to evaluate the risk factors for postablation hysterectomy, we conducted four nationwide register-based cohort studies.

In the LNG-IUS user studies, a cohort of all Finnish women who had received reimbursement for LNG-IUS for the treatment of HMB at age 30−49 years during 1994−2007 (n = 93 843) were identified from the Medical Reimbursement Register. In the endometrial ablation study, we identified all Finnish women who had undergone endometrial ablation at age 30−49 years in 1997−2014 from the Hospital Discharge Register (n = 5 484).

In all studies, the study subjects were followed for the cancer of interest with the aid of the Finnish Cancer Registry. The risk of cancer was compared with that of the background population. In the endometrial ablation study, postablation hysterectomy rate was compared with that of the control cohort (n = 26 938) extracted from the Population Register Centre. A multivariate Poisson regression model was used to evaluate the risk factors for postablation hysterectomy.

The data on deaths and emigrations during the follow-up in all studies, and the information on live deliveries in the endometrial ablation study, were received from the Population Register Centre. Information on surgical procedures were obtained in all studies from the Hospital Discharge Register. The study subjects were followed from the index date to the end of the study, emigration, or death, whichever occurred first. Depending on the cancer, additional censoring was done at the date of hysterectomy, bilateral/unilateral salpingectomy, or salpingo-oophorectomy.

The use of LNG-IUS for HMB was associated with an increased risk of breast cancer (standardized incidence ratio, SIR 1.19, 95% confidence interval (CI) 1.13−1.25). In absolute numbers, this means 2-4 excess cases of breast cancer per 1 000 LNG-IUS users followed for ten years. The LNG-IUS users with two or more LNG-IUS purchases, had 40% higher breast cancer incidence than the

general population (SIR 1.40, 95% CI 1.24–1.57). The risk 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) was increased among LNG-IUS users. After two or more LNG-IUS purchases, the SIR for invasive lobular cancer was 73% higher than in the general population (SIR 1.73, 95% CI 1.37–2.15). Most invasive breast cancers among LNG-IUS users were localized but after 5 years of follow-up, the risk of non-localized breast cancers was also statistically significantly higher among LNG-IUS users than in the general population.

The risk of endometrial cancer among LNG-IUS users was significantly decreased compared with the background population (SIR 0.46, 95% CI 0.33–0.64). In absolute numbers, this means 3-6 prevented endometrial cancers per 10 000 LNG-IUS users followed for ten years. After two or more LNG-IUS purchases, the risk was 75% lower than among the general population (SIR 0.25, 95% CI 0.05–0.73).

Among LNG-IUS users, the risk of ovarian cancer was up to 41% lower compared with the general population (SIR 0.59 (95% CI 0.47–0.73). In absolute numbers, this means 3-6 prevented invasive ovarian cancers per 10 000 LNG-IUS users followed for ten years. The risk was decreased for all epithelial ovarian cancers, most clearly for mucinous carcinoma (SIR 0.49, 95% CI 0.24–0.87). LNG-IUS use was also associated with a decreased risk of borderline ovarian tumors (SIR 0.76, 95% CI 0.57–0.99). The risk of primary fallopian tube carcinoma was not increased among LNG-IUS users (SIR 1.22, 95% CI 0.49–2.50). Of all other cancers, LNG-IUS users had significantly lower risk of lung cancer (SIR 0.68, 95% CI 0.49–0.91) and pancreatic cancer (SIR 0.50 (95% CI 0.28–0.81).

Among women with endometrial ablation, the incidence of endometrial cancer was not increased compared with the background population (SIR 0.56, 95% CI 0.12–1.64). The risk of breast cancer after endometrial ablation was similar to that of the general population (SIR 0.86, 95% CI 0.67–1.09).

A hysterectomy was performed for 19.8% of women treated with endometrial ablation during the follow-up (mean 7.3 years, maximum 18 years). The risk factors for postablation hysterectomy were leiomyomas, young age, and a history of two or more cesarean deliveries or sterilization.

In conclusion, the use of LNG-IUS for HMB was associated with elevated risk of breast cancer but decreased risk of both endometrial and ovarian cancer. If the increased breast cancer risk among LNG-IUS users is caused by LNG-IUS itself or by other risk factors particularly characteristic to women with HMB is not yet known. Endometrial ablation is a good alternative for selected women with HMB as most treated women can avoid postablation hysterectomy. Also, cancer risks after endometrial ablation seem to be comparable with those of the general population. Both these intrauterine methods for treatment of HMB

are effective, but an individual risk–benefit assessment is important to do when deciding the treatment for HMB.

Yhteenveto

Runsaat kuukautiset ovat yleinen ongelma, joka vaikuttaa haitallisesti naisen elämänlaatuun. Uudet hoitomenetelmät, hormonikierukka ja kohdun limakalvon tuhoaminen (endometriumablaatio), ovat merkittävästi muuttaneet runsaiden kuukautisten hoitoa, mikä on huomattavasti vähentänyt kohdunpoistoja monessa eri maassa. Huolimatta näiden uusien hoitokeinojen lisääntyneestä käytöstä, niiden vaikutuksesta naisen myöhempään syöpäriskiin on vasta vain vähän tietoa. Kaikki eivät myöskään saa riittävää apua vuotoihinsa hormonikierukalla tai endometriumablaatiolla. Niitä tekijöitä, jotka ennakoivat lisääntynyttä riskiä joutua myöhempään kohdunpoistoon endometriumablaation jälkeen ei vielä kunnolla tunneta. Tämän väitöskirjatyön tavoitteena oli tutkia runsaiden kuukautisten hoitoon hormonikierukkaa käyttäneiden tai endometriumablaatiolla hoidettujen naisten myöhempää syöpäriskiä sekä arvioida, mitkä tekijät ennakoivat lisääntynyttä riskiä endometriumablaation jälkeiseen kohdunpoistoon. Tutkimukset suoritettiin kansallisina rekisteritutkimuksina.

Hormonikierukkaa ja syöpäriskiä koskevissa töissämme keräsimme tiedot Kelan lääkekorvausrekisteristä kaikista suomalaisista naisista, jotka olivat 30-49 -vuotiaina käyttäneet hormonikierukkaa runsaiden kuukautisten hoitoon vuosina 1994-2007 (93 843 naista). Endometriumablaatiotyössämme keräsimme tiedot niistä suomalaisista naisista, joille oli 30-49 -vuotiaana tehty endometriumablaatio (5 484 naista). Kaikissa osatöissämme vertasimme tutkimusväestön syöpäsairastuvuutta vastaavan ikäiseen taustaväestöön Suomen Syöpärekisterin tietojen avulla. Endometriumablaatiotyössämme kohdunpoistoriskiä tutkittiin vertailemalla endometriumablaation jälkeen tehtyjä kohdunpoistoja Väestörekisterikeskuksesta poimitun vertailuväestön (26 938 naista) kohdunpoistolukuihin. Kohdunpoiston riskitekijöitä analysoitiin Poissonin monimuuttuja-analyysillä.

Tiedot tutkimusaineistoomme kuuluneiden naisten kuolemista, maasta poismuutosta sekä elävänä syntyneistä lapsista saatiin Väestörekisterikeskuksesta. Tiedot kirurgisista toimenpiteistä saatiin Terveyden ja hyvinvoinnin laitoksen Poistoilmoitusrekisteristä. Seuranta-aika alkoi indeksipäivästä ja jatkui tutkimuksen sulkuaikaan, maasta poismuuttoon tai kuolemaan, riippuen mikä näistä tapahtui ensin. Syöpätyyppikohtaisesti seuranta lopetettiin myös kohdunpoistoon, toisen tai molempien munasarjojen ja/tai munatorvien poistoon.

Hormonikierukkaa runsaiden vuotojen hoitoon käyttäneillä naisilla todettiin lisääntynyt riski sairastua rintasyöpään (SIR 1.19, 95% luottamusväli 1.13-1.25). Tämä tarkoittaa 2-4 ylimääräistä rintasyöpää 1000 hormonikierukan käyttäjän joukossa 10 vuoden seuranta-aikana. Naisilla, jotka olivat ostaneet

vähintään kaksi kertaa hormonikierukan, oli 40% korkeampi rintasyöpäsairastuvuus kuin muilla naisilla (SIR 1.40, 1.24-1.57). Riski oli kohonnut sekä lobulaariseen (SIR 1.33, 1.20-1.46) että duktaaliseen rintasyöpään (SIR 1.20, 1.14-1.25). Vähintään kaksi hormonikierukkaa ostaneilla oli 73% korkeampi riski lobulaariseen rintasyöpään kuin taustaväestöllä (SIR 1.73, 1.37-2.15). Suurin osa hormonikierukan käyttäjien rintasyövistä todettiin paikallisina, mutta viiden vuoden seuranta-ajan jälkeen myös levinneen rintasyövän riski oli suurempi kuin muilla naisilla.

Hormonikierukan käyttäjillä oli taustaväestöä selvästi pienempi kohdunrungon syöpäriski (SIR 0.46, 0.33-0.64). Tämä tarkoittaa 3-6 ehkäistyä kohdunrungon syöpää 10 000 hormonikierukan käyttäjän joukossa 10 vuoden seurannassa. Vähintään kaksi hormonikierukkaa ostaneilla kohdunrungon syöpäriski oli 75% pienempi kuin muilla naisilla (SIR 0.25, 0.05-0.73).

Munasarjasyövän riski oli hormonikierukan käyttäjillä 41% pienempi kuin taustaväestöllä (SIR 0.59, 0.47-0.73), mikä tarkoittaa 3-6 ehkäistyä munasarjasyöpää 10 000 hormonikierukan käyttäjän joukossa 10 vuoden seurannassa. Hormonikierukan käyttäjillä oli pienentynyt riski kaikkiin epiteliaalisiin munasarjasyöpiin, mutta selvimmin musinoosiin karsinoomaan (SIR 0.49, 0.24-0.87). Hormonikierukan käyttäjillä oli myös muita vähemmän munasarjojen rajalaatuisia (borderline) kasvaimia (SIR 0.76, 0.57-0.99). Munatorvisyövän riski ei ollut hormonikierukan käyttäjillä lisääntynyt (SIR 1.22, 0.49-2.50). Hormonikierukan käyttäjillä oli pienentynyt riski sairastua keuhkosyöpään (SIR 0.68, 0.49-0.91) ja haimasyöpään (SIR 0.50, 0.28-0.81).

Endometriumablaation jälkeen ei todettu lisääntynyttä riskiä kohdunrungon syöpään (SIR 0.56, 0.12-1.64). Myös rintasyöpäriski oli endometriumablaatiolla hoidetuilla taustaväestöä vastaava (SIR 0.86, 0.67-1.09).

19.8% :lle tehtiin kohdunpoisto endometriumablaation jälkeen seuranta-aikana (keskiarvo 7.3 vuotta, maksimi 18 vuotta). Kohdunpoiston riskitekijöitä olivat kohdun myoomat, nuori ikä, aiemmat keisarileikkaukset tai sterilisaatio.

Johtopäätöksenä voidaan todeta, että hormonikierukkaa runsaiden kuukautisten hoitoon käyttäneillä naisilla oli lisääntynyt riski sairastua rintasyöpään, mutta vähentynyt riski kohdunrungon- ja munasarjasyöpään. Sitä, johtuuko lisääntynyt rintasyöpäriski juuri hormonikierukasta, vai näillä naisilla esiintyvistä muista tekijöistä, ei vielä tiedetä. Endometriumablaatio on hyvä hoitokeino osalle potilaista, sillä suurin osa endometriumablaatiolla hoidetuista ei tarvitse myöhempää kohdunpoistoa. Molemmat näistä runsaiden kuukautisten kohdunsisäisistä hoitomuodoista ovat tehokkaita, mutta riskien ja hyötyjen punnitseminen yksilöllisesti on tärkeää ennen hoitopäätöstä.

Introduction

Heavy menstrual bleeding (HMB) is a common problem affecting 30% of women in their reproductive years (Fraser et al. 2015). Due to modern and effective family planning, each woman experiences approximately 400 episodes of menstrual bleeding during her lifetime in developed countries (Maybin and Critchley 2015). Without effective treatment of heavy menstruation, excessive blood loss can cause anemia, have a major negative impact on a woman's quality of life, and cause socioeconomic consequences. Due to this worldwide common and demanding gynecological condition, efficient and safe treatment options are continuously needed.

Hysterectomy was the treatment of choice for HMB in earlier decades, but its complication risks and costs are not acceptable, as conservative treatments are equally efficient in most cases (Hurskainen et al. 2001). It is also notable that half the women treated with hysterectomy for HMB are found to have a normal uterus (Duckitt 2015). Alongside these facts, a more conservative treatment approach for HMB has emerged especially in the last two decades.

The primary choices to treat HMB are either medical treatment or mini-invasive surgery. Medical management options are combined oral contraceptive (COC) pills, tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs), or the use of a levonorgestrel-releasing intrauterine system (LNG-IUS).

LNG-IUS was launched in the 1990s for contraception but soon its effectiveness on HMB was noticed and HMB became an indication for LNG-IUS use. The use of LNG-IUS has increased markedly during the last decades (Heikinheimo and Fraser 2017). Since its launch, over 43 million LNG-IUSs have been sold globally (information from Bayer Oy, Turku, Finland). In Finland, currently approximately one-fifth of fertile-aged women use an LNG-IUS (information from Bayer Oy, Turku, Finland).

The effect of LNG-IUS is based on its local intrauterine delivery of a potent progestin, levonorgestrel, into the lining of the uterine cavity, the endometrium. Levonorgestrel reduces endometrial cells and decreases

menstrual bleeding so markedly that most women do not have menstruation during use of LNG-IUS (Guttinger and Critchley 2007). The effectiveness of LNG-IUS on heavy menstruation has made LNG-IUS the first-line option for the treatment of HMB in many countries (Current Care Guidelines 2009, Lethaby et al. 2015, Bitzer et al. 2015, Davies and Kadir 2017, Heikinheimo and Fraser 2017), and it has been reflected as significantly declined rates of hysterectomies. In Finland, the rate of hysterectomies for HMB has decreased by over 50% during the last two decades (Finnish National Institute for Health and Welfare).

Despite the effectiveness of hormonal treatment for menstrual blood loss, one concern is the possible effect on later cancer risk. Lately, in particular, the role of progestogens on the cancer risk has been cleared. The carcinogenic effect of progestogens seems to depend on the tissue and progestogen type used. Also, the progestogen concentration and duration of delivery, as well as the age of the woman may have an impact on cancer risk. In breast tissue, progestogens can act as mitogens and a long-term use of progestogens, both in the form oral hormonal contraception or postmenopausal hormone therapy (HT), is associated with an increased risk of breast cancer (CGHFBC 1996, IARC 2012, Stanczyk et al. 2013, Lambrinoudaki 2014, Bassuk and Manson 2015). An increased risk of breast cancer has also been reported in postmenopausal LNG-IUS users (Lyytinen et al. 2010). In contrast to breast tissue, progestogens have an antiproliferative effect in the endometrium and ovaries (Diep et al. 2015). Whether the breast tissue and other organs react similarly for exogenous progestogens in both fertile-aged and postmenopausal women, is not well known. Although the effect of LNG-IUS is based on the high intrauterine levonorgestrel concentration, some levonorgestrel is also released into the systemic circulation (Luukkainen et al. 1990, Hidalgo et al. 2009, Seeber et al. 2012). The effect of premenopausally used LNG-IUS on the risk of cancers, especially endometrial and breast cancer, is insufficiently known (Backman et al. 2005, Dinger et al. 2011, Heikkinen et al. 2016a).

To avoid the risks of major surgery associated with hysterectomy, and to avoid the side effects of hormones, mini-invasive treatment for HMB using endometrial ablation has emerged in the last two decades (Kumar et al. 2016).

Endometrial ablation is suitable only for women who do not desire future pregnancies. In endometrial ablation, the endometrium is largely destroyed. In the 1980s, hysteroscopic methods (laser, freezing, and electroresection) were used, but in the last two decades, safer non-hysteroscopic methods using microwaves, radiofrequencies, free heated liquid, or thermal balloon have replaced the older methods (Kumar et al. 2016).

The long-term effect of endometrial ablation on menstrual bleeding is comparable with that of LNG-IUS in most women, but some women still need subsequent hysterectomy after endometrial ablation. How the destruction of endometrium affects later cancer risk, especially risk of uterine and gynecological cancers, is sparsely studied. Also, the incidence of breast cancer among women treated with endometrial ablation is unknown.

All this encouraged us to study the cancer risks among women suffering from heavy menstruation and treated with either LNG-IUS or endometrial ablation. We also wanted to evaluate the need for later hysterectomy, as well as the factors predicting for hysterectomy after endometrial ablation. We were able to study these topics using data of excellent quality and high coverage from Finnish health registers.

Review of the literature

Heavy menstrual bleeding

Heavy menstrual bleeding (HMB) represents the most common form of abnormal uterine bleeding (AUB) in women of reproductive age (Munro et al. 2011, Whitaker and Critchley 2016). Without effective treatment, HMB limits normal activities, significantly impairs the quality of life (Hurskainen et al. 2001, Heliövaara-Peippo et al. 2013), and forms a significant cost burden for both the patient and the healthcare system (Jensen et al. 2012).

Historically, HMB has been defined as an objective blood loss over 80 mL per cycle (Hallberg et al. 1966). However, this definition has been questioned due to the difficulty in assessing menstruation blood loss objectively. Also, it has been suggested that HMB is a manifestation caused by heterogeneous etiologies and thus represents more a symptom, rather than a diagnosis (Munro et al. 2011).

To standardize the terminology of AUB used in clinical practice and research, a new classification of AUB was launched by the International Federation of Gynecology and Obstetrics (FIGO) in 2011 (Munro et al. 2011). However, this classification is still not widely used by clinicians, nor has it had an impact on the diagnosis codes. In the new FIGO terminology, previously used "menorrhagia" has been replaced by "heavy menstrual bleeding" to describe excessive menstruation (Munro et al. 2011). According to the new classification, HMB is a symptom that can exist irrespective of the frequency, duration, or regularity of menstrual bleeding (Munro et al. 2011). Also, the new classification of HMB is based on a woman's subjective perception of excessive menstrual bleeding and its negative impact on the quality of her life (Munro et al. 2011, NICE 2016). According to this classification, AUB is categorized by its causes as related or unrelated to uterine structural abnormalities and is classified by one or more letters that indicate the cause. The acronym PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia;

Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified) is composed of the first letters of the causes of AUB (Munro et al. 2011). The PALM group includes structural abnormalities which can be visualized or histologically diagnosed. The COEIN group consists of nonstructural causes of AUB.

HMB can result from a multifactorial cause or solely from an endometrial cause. In up to 20% of cases, excessive menstrual blood loss is caused by a systemic disorder of coagulation (AUB-C) (Davies and Kadir 2017), most often by von Willebrand disease (Shankar et al. 2004). Ovulatory dysfunction associated with chronic unopposed estrogen, commonly caused by obesity or polycystic ovary syndrome (PCOS) (ACOG 2013, Nandi et al. 2014, Hapangama and Bulmer 2016), is a frequent cause of irregular HMB (AUB-O). The mechanism of HMB can also be a primary disorder of the endometrium (AUB-E). In AUB-E, abnormalities occur in endometrial hemostasis, such as an altered local production of endometrial prostaglandins and cytokines, decreased endometrial vasoconstriction, increased destruction of the extracellular matrix, or delayed local repair response in the endometrium (Maybin and Critchley 2015).

Medical treatment of heavy menstrual bleeding

HMB can be treated either medically or surgically. The management of HMB depends on the woman's age, desire to preserve fertility, and the possible findings of pelvic pathology. In the absence of significant pelvic pathology, medical management of HMB (LNG-IUS, progestogen-containing oral preparations, and oral hemostatic therapies) can be considered as the primary choice (RCOG 2008, Current Care Guidelines 2009, NICE 2016).

Levonorgestrel-releasing intrauterine system (LNG-IUS)

Initial study and design of LNG-IUS took place in the 1970s−1980s (Nilsson et al. 1981) and the first LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) was approved for contraception in Finland in 1990 (Luukkainen et al. 1990), and later in other countries. Very soon the effectiveness of LNG-IUS for HMB was noted (Andersson et al. 1994, Lähteenmäki et al. 1998), and since 1991 LNG-IUS has been approved for treatment of HMB in Finland (information from Bayer Oy, Turku, Finland). LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) is currently authorized to be marketed in 128 countries. In 124 countries, LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) is registered for use for idiopathic menorrhagia (information from Bayer Oy, Turku, Finland). In most of these countries, LNG-IUS is also used for endometrial protection during estrogen therapy (ET) (Depypere and Inki 2015). LNG-IUS is the most effective medical treatment for HMB and is currently recommended as the first-line treatment for HMB in many countries (Current Care Guidelines 2009, Lethaby et al. 2015, Bitzer et al. 2015, Davies and Kadir 2017, Heikinheimo and Fraser 2017). The effectiviness of LNG-IUS on HMB has increased the popularity of its use (Heikinheimo and Fraser 2017). Since launch, more than 43 million LNG-IUSs have been sold globally (information from Bayer Oy, Turku, Finland). In Finland, currently approximately one-fifth of fertile-aged women use LNG-IUS (information from Bayer Oy, Turku, Finland).

During the last decade, two newer LNG-IUSs with less levonorgestrel have been launched (Jaydess® and Kyleena®, Bayer Oy, Turku, Finland). However, still only one LNG-IUS is approved for the treatment of HMB and for endometrial protection during ET (Mirena®, Bayer Oy, Turku, Finland), and the other LNG-IUSs (Jaydess® and Kyleena®, Bayer Oy, Turku, Finland) are approved only for contraceptive use.

In this thesis, the focus is solely on the LNG-IUS used for HMB (Mirena®, Bayer Oy, Turku, Finland) (Figure 1).

Figure 1. Levonorgestrel-releasing intrauterine system (Mirena®). Photo and permission of use from Bayer Oy.

Structure of LNG-IUS and mechanism of action

LNG-IUS consists of a T-shaped polyethylene frame with a hormone reservoir containing 52 mg levonorgestrel (Mirena®, Bayer Oy, Turku, Finland). Progestin is released continuously into the uterine cavity at an initial rate of 20 µg/day, and the rate of levonorgestrel release declines to 10 µg/day after 5 years of use. For comparison, the LNG-IUSs containing less progestin, and used solely for contraception, release 6 µg/day (Jaydess®) or 9 µg/day (Kyleena®) levonorgestrel, respectively.

The effect of LNG-IUS is mediated by the action of a high local concentration of levonorgestrel within the endometrium. In the user of LNG-IUS, the concentration of levonorgestrel in the endometrium is over 100-fold that in the systemic circulation (Nilsson et al. 1982). The local delivery of levonorgestrel into the endometrium results in a highly effective suppression of endometrial proliferation, which is histologically seen as an inactive endometrium with thin epithelium and decidualized stroma. These changes result in highly effective contraception and an over 90% decrease in menstrual bleeding (Andersson and Rybo 1990, Hurskainen et al. 2001, Mansour 2012).

Despite the local intrauterine release of levonorgestrel from the LNG-IUS, some levonorgestrel is continuously also released into the systemic circulation, with mean plasma levels of levonorgestrel between 100–200 pg/mL (Luukkainen et al. 1990), but significant variations have been reported (Heikinheimo et al. 2006). Systemic levonorgestrel concentration of the LNG-IUS user is approximately 5–10 times lower than that of an oral levonorgestrel contraceptive user, and approximately 2-fold lower than that of a levonorgestrel contraceptive implant user (Orme et al. 1983, Sivin 2003).

Health benefits of LNG-IUS

In addition to the reduction in menstrual bleeding, and efficient contraception, LNG-IUS has many established health benefits (Bahamondes et al. 2015). LNG-IUS provides effective protection from endometrial hyperplasia during ET (Depypere and Inki 2015). In patients with HMB, LNG-IUS has been reported to alleviate HMB-related pain and increase the quality of life (Heliövaara-Peippo et al. 2013). LNG-IUS has also been reported to relieve premenstrual symptoms among women with HMB (Leminen et al. 2012), and be effective against dysmenorrhea and pelvic pain caused by endometriosis (Dunselman et al. 2014) or adenomyosis (Ozdegirmenci et al. 2011).

Adverse effects of LNG-IUS

During the first months after LNG-IUS insertion in fertile-aged women, transient intermittent or prolonged uterine bleeding or spotting is reported by up to 35% (Hurskainen et al. 2001, Mansour 2012) and some experience hormonal side effects such as acne, nausea, mood changes, or breast tenderness (Andersson et al. 1994, Mansour 2012, Lethaby et al. 2015). Uterine perforation is an infrequent but possible complication associated with insertion of LNG-IUS (incidence 0.4/1000 sold IUSs) (Kaislasuo et al. 2012). Expulsion of LNG-IUS occurs in 0.8–20% of cases (Mansour 2012, Bitzer et al. 2015, NICE 2016). An increased incidence of transient functional ovarian cysts has been reported among LNG-IUS users (Inki et al. 2002, Mansour 2012, Lethaby et al. 2015).

The long-term effects of levonorgestrel exposure from LNG-IUS use on the risk of cancers, especially breast cancer (Backman et al. 2005, Lyytinen et al. 2010, Dinger et al. 2011, Heikkinen et al. 2016a) or gynecological cancers (Jaakkola et al. 2011, Koskela-Niska et al. 2015), are insufficiently known. The issue about LNG-IUS and cancer risk will be discussed later in the section "Hormonal treatment of heavy menstrual bleeding, and cancer risk."

Other medical treatments

Other medical treatments of HMB include various progestogen-containing oral preparations (COCs and oral progestins), antifibrinolytic drugs, and NSAIDs, used alone or in combination (Bitzer et al. 2015, Maybin and Critchley 2016, Davies and Kadir 2017, Heikinheimo and Fraser 2017).

The effectiveness and adverse effects of various treatments for HMB are shown in Table 1.

Table 1. *Effectiveness and adverse effects of various treatments for heavy menstrual bleeding.*

Treatment	Reduction in menstrual blood loss (%)	Additional benefits	Potential adverse effects
Hormonal preparations			
Combined hormonal preparations			
Ethinylestradiol-containing COC[1–3]	35–50	Contraception, regulation of menstruation, relief of dysmenorrhea symptoms	Mood changes, headache, nausea, spotting, thromboembolism
Estradiol valerate-dienogest COC[4,5]	60	Contraception, regulation of menstruation, relief of dysmenorrhea symptoms	Mood changes, headache, nausea, spotting, thromboembolism
Progestin-only preparations			
Extended cycle progestin (menstrual cycle day 5–26 or continuously)[6,7]	80		Progestogenic side effects, need for contraception
LNG-IUS[3,8,9]	86–97	Contraception, relief of dysmenorrhea symptoms	Progestogenic side effects, irregular bleeding
Non-hormonal preparations			
Tranexamic acid[10]	26–60		Diarrhea, indigestion, headache
NSAID[11,12]	10–51	Relief of dysmenorrhea symptoms	Gastrointestinal bleeding/ulceration
Surgical treatments			
Endometrial ablation[13,14]	70	Mini-invasive surgical approach, outpatient setting, short need for sick leave	Residual menstruation, need for further contraception, risk of later hysterectomy. Surgical complications (e.g., infection, hemorrhage, perforation; in 0.3–2%).
Hysterectomy[15]	100		Surgical complications (e.g., infection, thromboembolism, organ perforation; in 12–19%)

COC = combined oral contraceptive, LNG-IUS = levonorgestrel-releasing intrauterine system, NSAID = non-steroidal anti-inflammatory drug.

Data from: [1]Larsson et al. 1992, [2]Fraser and Kovacs 2003, [3]Shaaban et al. 2011, [4]Fraser et al. 2011, [5]Fraser et al. 2012, [6]Irvine et al. 1998, [7]Lethaby et al. 2015, [8]Andersson and Rybo 1990, [9]Kaunitz et al. 2009, [10]Leminen and Hurskainen 2012, [11]Bitzer et al. 2015, [12]Bradley and Gueye 2016, [13]Kumar et al. 2016, [14]Moulder and Yunker 2016, [15]Brummer et al. 2011.

Surgical treatment of heavy menstrual bleeding

Surgical treatment of HMB is an option for those women who do not improve with medical treatment or where such treatment is contraindicated, or for those with significant pelvic pathology. According to guidelines of many countries, mini-invasive surgery with endometrial ablation is currently considered the primary surgical option due to the risks of hysterectomy (NICE 2016, Laberge et al. 2015). In Finland, a guideline for the treatment of HMB recommends the use of endometrial ablation only if there are contraindications for hysterectomy (Current Care Guidelines 2009). However, the Finnish guideline will be updated in the near future.

Endometrial ablation

Mechanism and techniques of endometrial ablation

Endometrial ablation is a minimally invasive procedure where the full thickness of endometrium, including the deep basal glands of the uterus, is destroyed with energy (e.g., heat), and the uterus is preserved (Lethaby et al. 2013). The indication for endometrial ablation is HMB due to benign causes in women who have completed childbearing (Kumar et al. 2016). Contraindications for endometrial ablation include active pelvic infection, endometrial hyperplasia, uterine cancer, and pregnancy or desire of future pregnancies. Endometrial ablation is also contraindicated in postmenopausal women (Laberge et al. 2015, Kumar et al. 2016). Amenorrhea rate is up to 70% (Lethaby et al. 2013, Kumar et al. 2016) (Table 1), and satisfaction rate of 77–96% (Kumar et al. 2016).

Endometrial ablation was introduced in the late 1980s. The first-generation endometrial ablation techniques included hysteroscopic laser or freezing ablations, and transcervical endometrial resection (with rollerball or loop). From the late 1990s, newer second-generation non-hysteroscopic endometrial ablation techniques including thermal balloon, microwave, free-fluid, and

radiofrequency techniques have replaced the older methods (Lethaby et al. 2013). These non-hysteroscopic endometrial ablations can be performed in an outpatient setting under local anesthesia, are easy to learn, and have shorter operating and recovery times and a better safety profile (Kumar et al. 2016).

The efficacy in reducing menstrual bleeding and patient satisfaction rates are similar in the first- and second-generation endometrial ablations in up to 10 years of follow-up (Lethaby et al. 2013). The cost-effectiveness has been reported to be better in the second-generation endometrial ablations compared with the first-generation techniques or hysterectomy (Garside et al. 2004, Miller et al. 2015). Compared with LNG-IUS, endometrial ablation has been reported to be inferior in cost-effectiveness (Health Quality Ontario 2016) but has similar patient satisfaction and greater reduction in menstrual bleeding than LNG-IUS at 2 years (Marjoribanks et al. 2016).

In Finland, endometrial ablation is not common, but in many other countries, endometrial ablation is much more common. Currently, approximately 500 endometrial ablations are performed annually in Finland (Figure 2). In England, up to 75% of surgical treatments for HMB were endometrial ablations during 2009–2012 (RCOG 2014).

Figure 2. The annual number of hysterectomies for heavy menstrual bleeding and endometrial ablations in Finland during 1997–2015. Data from the Hospital Discharge Register of the Finnish National Institute for Health and Welfare.
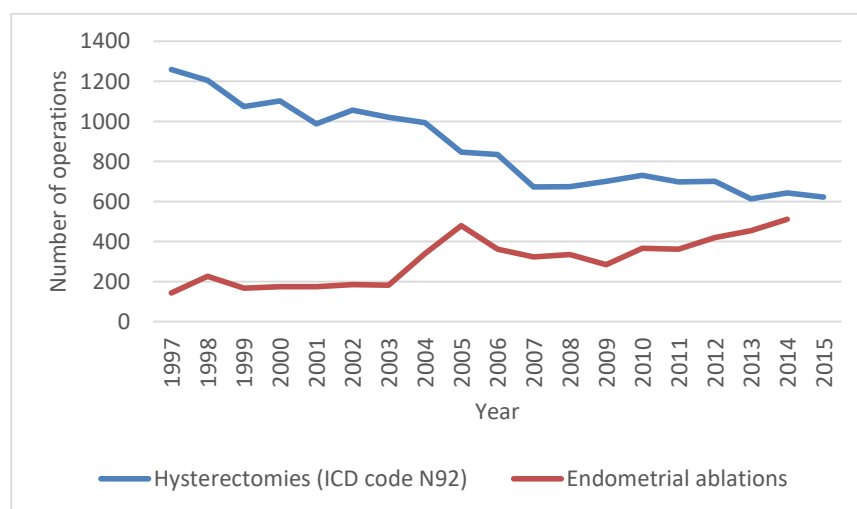
Complications and adverse effects of endometrial ablation

Despite the simplicity of the non-hysteroscopic endometrial ablation procedure, some complication risks exist. The most common intraoperative complications with the second-generation techniques are cervical lacerations, nausea and vomiting, and pelvic pain or cramping (NICE 2016). A rare but serious complication is uterine perforation with possible visceral injury or hemorrhage (NICE 2016). The incidence of uterine perforation with the first-generation endometrial ablation techniques is 1.5% (Kumar et al. 2016) but it is significantly lower with the newer non-hysteroscopic techniques (relative risk [RR] 0.32, 95% confidence interval [CI] 0.1–1.0) (Lethaby et al. 2013, Lethaby et al. 2015). Postoperatively, a prolonged transient vaginal discharge frequently occurs (NICE 2016). Incidence of endometritis is 1.4–2% (Sharp 2012, Kumar et al. 2016). Pregnancy rate after endometrial ablation has been reported to be 0.7–1.4% (Yin 2010, Sharp 2012, Moulder and Yunker 2016). Postablation pregnancies have high risks such as fetal anomalies and abnormal placentation due to uterine cavity scarring and distortion (Yin 2010). Due to the major pregnancy complication risks, sterilization is highly recommended before endometrial ablation.

Small areas with viable endometrium may be retained after endometrial ablation, which is evidenced by residual menstrual bleeding in some cases. These patients may also experience cyclical pain caused by obstructed menstruation (hematometra) in the scarred uterus. In some cases, endometrial ablation fails to relieve a woman's symptoms, and later operation is needed. A repeat endometrial ablation is not usually recommended due to uterine distortion and the lack of data on safety (Laberge et al. 2015). In most cases, hysterectomy is the next step after failed endometrial ablation. The postablation hysterectomy rate has been reported to be 13–21% (Longinotti et al. 2008, El-Nashar et al. 2009, Cooper et al. 2011, Shavell et al. 2012, Bansi-Matharu et al. 2013, Dood et al. 2014, Wishall et al. 2014).

The risk factors predisposing to postablation hysterectomy are not well known, but young age at endometrial ablation (Longinotti et al. 2008, El-

Nashar et al. 2009, Shavell et al. 2012, Bansi-Matharu et al. 2013), previous cesarean sections (Shavell et al. 2012, Wishall et al. 2014), and leiomyomas (Bansi-Matharu et al. 2013, Wishall et al. 2014) have been associated with an increased hysterectomy risk. However, the effect of the sizes or locations of leiomyomas on the risk of endometrial ablation failure is insufficiently known. Also, the possible differences in the long-term efficacy of various second-generation devices are not well known.

Due to the regenerated or retained areas of endometrium after endometrial ablation, the risk of later endometrial malignancy exists but the magnitude of the risk is unknown. The issue of endometrial ablation and cancer risk will be discussed later in the section "Surgical treatment of heavy menstrual bleeding, and cancer risk."

Hysterectomy

Back in 2002, almost half of the hysterectomies worldwide were performed due to HMB (Lethaby et al. 2013). However, due to the increasing popularity of conservative treatments for HMB, especially LNG-IUS and endometrial ablation, the number of hysterectomies has fallen in many countries (Wright et al. 2013, Jokinen et al. 2015, Gante et al. 2017). In the USA, the number of hysterectomies for benign indications decreased by 36% in 2002–2010 (Wright et al. 2013). In Finland, over 11 000 hysterectomies were performed annually 20 years ago. Today, the total number of hysterectomies is over 50% less than in 1997. Also, hysterectomies for HMB have decreased by 50% during the same period (Finnish National Institute for Health and Welfare) (Figure 3).
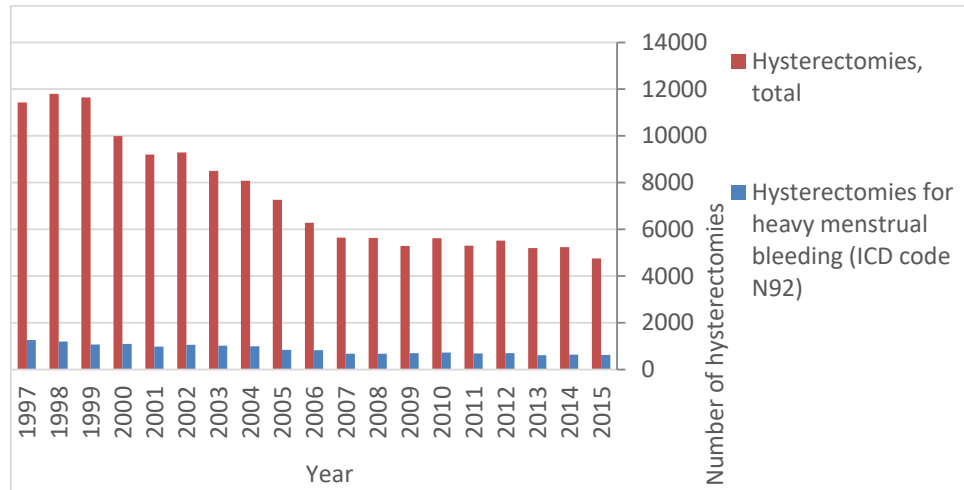
Hysterectomy relieves menstrual bleeding by 100% and has a high satisfaction rate, but it carries risks, is costly, and has a long recovery time. In a Finnish randomized controlled trial, hysterectomy was associated with a postoperative complication rate of 29% (Hurskainen et al. 2001), and a significantly inferior cost-effectiveness compared with LNG-IUS use in up to 10 years of follow-up (Heliövaara-Peippo et al. 2013). A large prospective study in Finland reported a total complication rate of 12–19% in hysterectomies, and a major complication (such as injury to bowel or vascular structure) rate of 3–4% (Brummer et al. 2011). The long-term adverse effects of hysterectomy are increased risk of pelvic organ prolapse (Lykke et al. 2016) and urinary incontinence (Altman et al. 2007, Cooper et al. 2011, Heliövaara-Peippo et al. 2010). Also, hysterectomy has been associated with an increased risk of impaired ovarian function with early menopause (Halmesmäki et al. 2004, Farquhar et al. 2005) and the effects of hysterectomy on cardiovascular functions are unknown (Marjoribanks et al. 2016). It is widely recommended that major surgical treatment of HMB should be reserved for women unresponsive to medical treatment of HMB or those with significant uterine pathology (Current Care Guidelines 2009, NICE 2016).

Cancer among women

Epidemiology of cancers among women

Globally, over 6.7 million new cancers are diagnosed annually among the female population. In Finland, 16 100 new cancers are diagnosed among women (www.cancerregistry.fi). Cancer is the leading cause of death worldwide among fertile-aged women. In developed countries, such as Finland, the incidence of female cancers has been increasing due to changes in lifestyle (i.e., decreased parity, increased obesity, and increased alcohol consumption), population-based cancer screenings, and prolonged life expectancy resulting in a greater proportion of women in older age groups (Figure 4).

Figure 4. New cancer cases (incidence) among all Finnish women during 1955–2014. Data from the Finnish Cancer Registry.

© Finnish Cancer Registry 2017-03-20
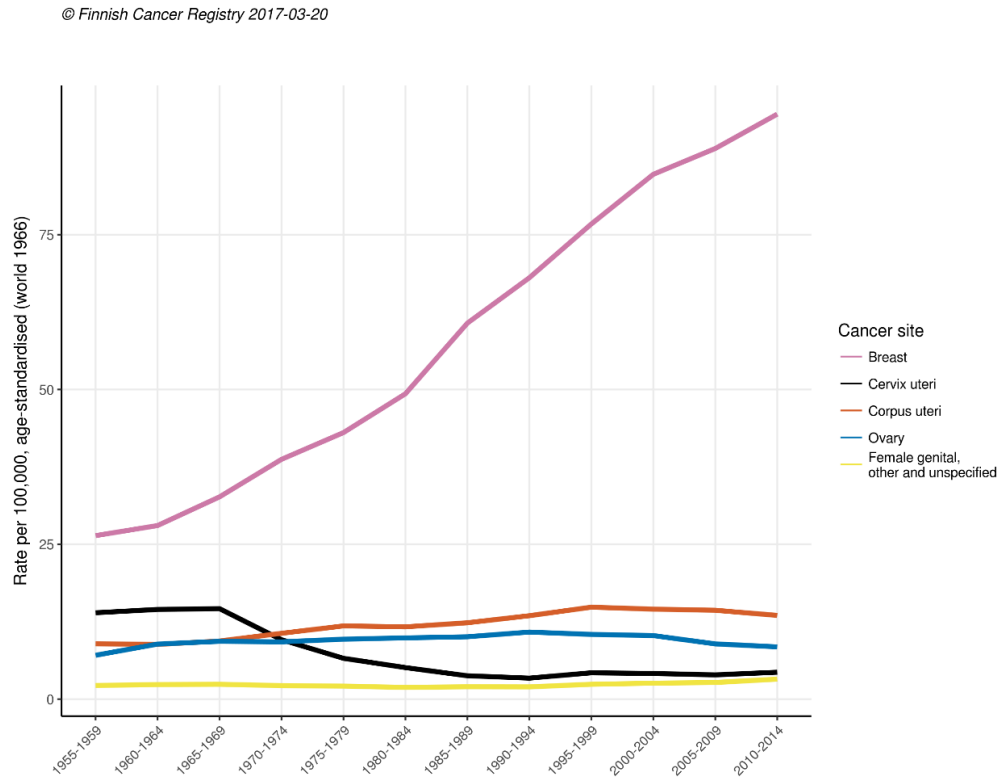
Breast cancer

Breast cancer is the most frequently diagnosed cancer among women. Worldwide, a total of 1.7 million new breast cancers are diagnosed every year. In developed countries, the cumulative lifetime incidence of breast cancer is approximately 10–12% (Ferlay et al. 2012, Rojas and Stuckey 2016) meaning that 1 in 8–10 women is diagnosed with breast cancer during their lifetime (Ferlay et al. 2012, Rojas and Stuckey 2016). In 2014, a total of 5008 new breast cancers were diagnosed in Finland, with an incidence of 95.7/100 000 women-years, adjusted for age of the World Health Organization's world standard population (Figure 4). In addition, a total of 406 precursors of invasive cancer – in situ carcinoma tumors of the breast – were diagnosed in 2014 in Finland. Most breast cancers occur among women aged 60–64 years, but 25% of new cases are diagnosed in women under 50 years (Figure 5) (www.cancer.fi).

Figure 5. Diagnosed new breast cancers in Finland by age group during 2010–2014. Data from the Finnish Cancer Registry.
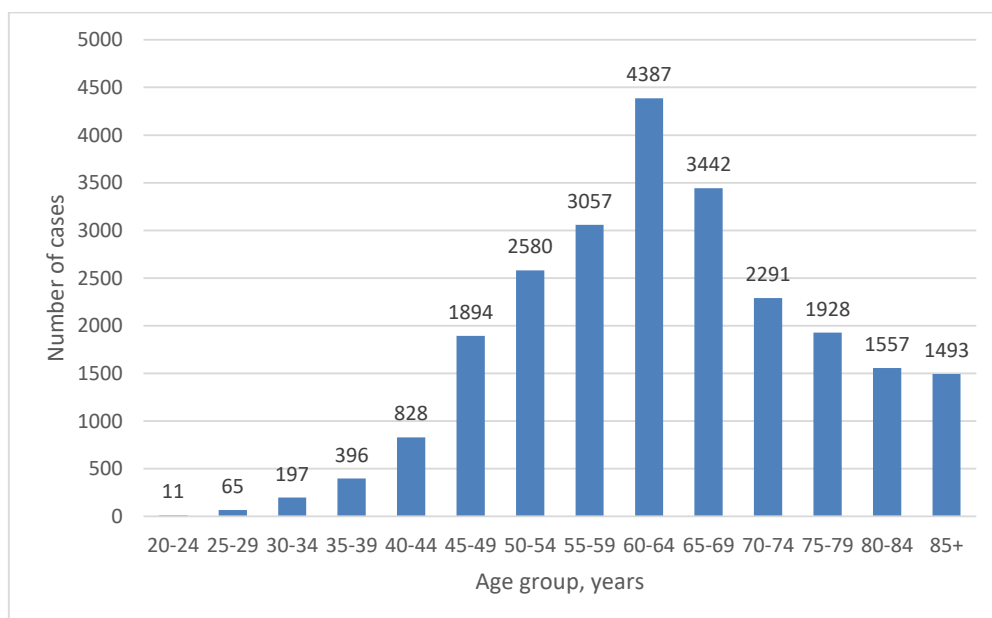
Postmenopausal breast cancer incidence has been growing in Finland and in other countries (Ferlay et al. 2012) but incidence among those under 65 years of age has been stable in Finland (Ferlay et al. 2012). Due to effective population-based screening programs with mammographies, and improved treatments, survival of breast cancer has improved in recent decades (Sant et al. 2015). In Finland, the relative 5-year survival rate was 93% for women aged both under and over 55 years in 2012–2014 (www.cancer.fi). Despite improved survival, breast cancer remains the leading cause of cancer death among premenopausal women, which has been suggested to be attributable to more aggressive disease characteristics, later stage of disease at diagnosis, and lack of population-based screening (Ferlay et al. 2012, Azim and Partridge 2014) (Figure 6).

Figure 6. Cancer deaths among women aged under 55 years in Finland during 2010–2014 (www-dep.iarc.fr/NORDCAN).

Finland (2014)
Number of cancer deaths - Female, age 0-54
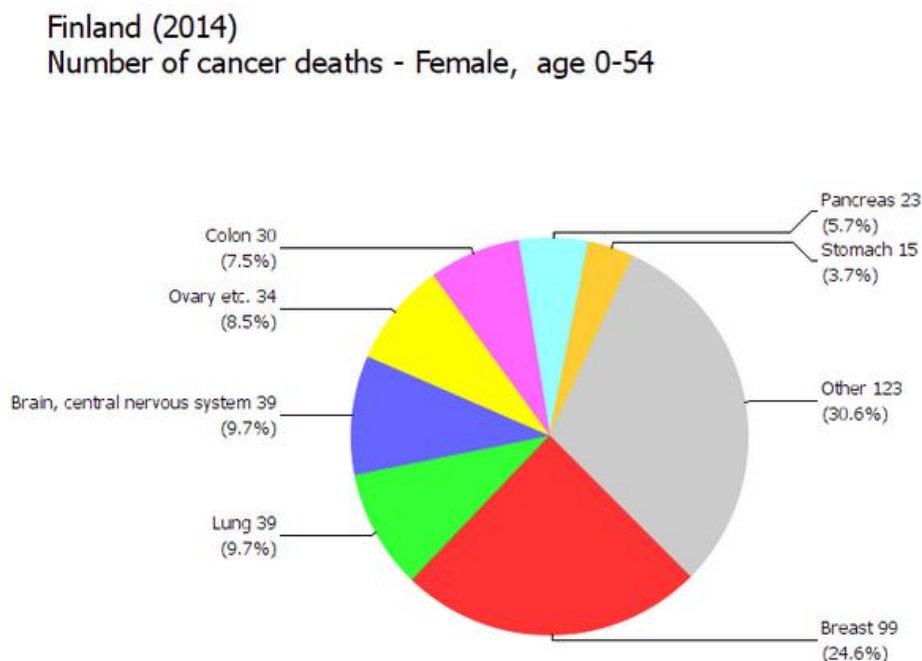
NORDCAN © Association of the Nordic Cancer Registries (13.3.2017)

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Breast cancer is a heterogeneous disease with many histological subtypes: up to 80% of invasive breast cancers are of ductal histology, 15% lobular, and the remaining 5% other less common histologies (Tavassoli 2003). Since the 2000s, in addition to histological subtypes, breast cancer tumors are considered to consist of at least four different molecular subtypes: luminal A (estrogen receptor [ER] or progesterone receptor [PR] positive, or both, human epidermal growth factor receptor 2 [HER2] negative, low proliferation), luminal B (ER or PR positive, or both, HER2 negative, high proliferation), HER2-enriched, and basal-like tumors (HER2 negative, and ER and PR negative; triple-negative breast cancer) (Perou et al. 2000, Sorlie et al. 2001). Young women tend to more frequently have more aggressive breast tumors including basal-like, HER2 positive, and tumors with higher grade than in postmenopausal women (Azim and Partridge 2014).

Breast cancer is a hormone-related cancer and is associated with many genetic, reproductive, and lifestyle factors (Rojas and Stuckey 2016). Many of the protective or risk factors are associated with endogenous or exogenous hormones (Rojas and Stuckey 2016). There is consistent evidence that long-term HT including progestogen and COCs increases the risk of breast cancer (IARC 2012, Gierisch et al. 2013, Bassuk and Manson 2015, Chlebowski et al. 2015). In general, parity and breastfeeding are protective factors, whereas young age at menarche, and late menopause increase the risk of breast cancer (Rojas and Stuckey 2016). The highest risk of breast cancer is among women with first-degree relatives with breast cancer (Nelson et al. 2012, Rojas and Stuckey 2016). Also, lifestyle factors such as alcohol consumption, sedentary lifestyle, and smoking are associated with increased risk of breast cancer (Rojas and Stuckey 2016). Obesity is a significant risk factor for postmenopausal breast cancer, but no effect or a decrease in risk is seen for premenopausal breast cancer (Benedetto et al. 2015). Up to 10% of breast cancers are due to mutations in breast cancer susceptibility genes. Mutations in breast cancer susceptibility genes type 1 or 2 (BRCA1 or BRCA2 genes) result in a cumulative lifetime risk of breast cancer of 49–57% (Chen and Parmigiani 2007).

Endometrial cancer

Endometrial cancer is the fourth most common cancer following breast, colon, and lung cancers, and the most common gynecological cancer among women in developed countries (www.cancer.fi) (Ferlay et al. 2012). Annually, 850 new endometrial cancers are diagnosed in Finland (www.cancer.fi) (Engholm et al. 2016). The age-adjusted annual incidence of endometrial cancer in Finland is 13.2/100 000 women-years (Figure 4). Most cases are diagnosed in women over 60 years but 5% occur in women under 50 years (www.cancer.fi) (Figure 7). In the USA, the incidence of endometrial cancer at young ages is significantly higher; 24% of new cases occurred in women under 55 during 2009–2013 (SEER 2013). The incidence of endometrial cancer has alarmingly increased at all ages in developed countries, mainly due to longevity and the epidemic of obesity (Renehan et al. 2010, Kamal et al. 2016). The incidence of endometrial cancer is predicted to increase by 30% among women over 65 years by the year 2025 in Finland (Ferlay et al. 2012).

Figure 7. Diagnosed new gynecological cancers in Finland, 2010–2014. Data from the Finnish Cancer Registry.
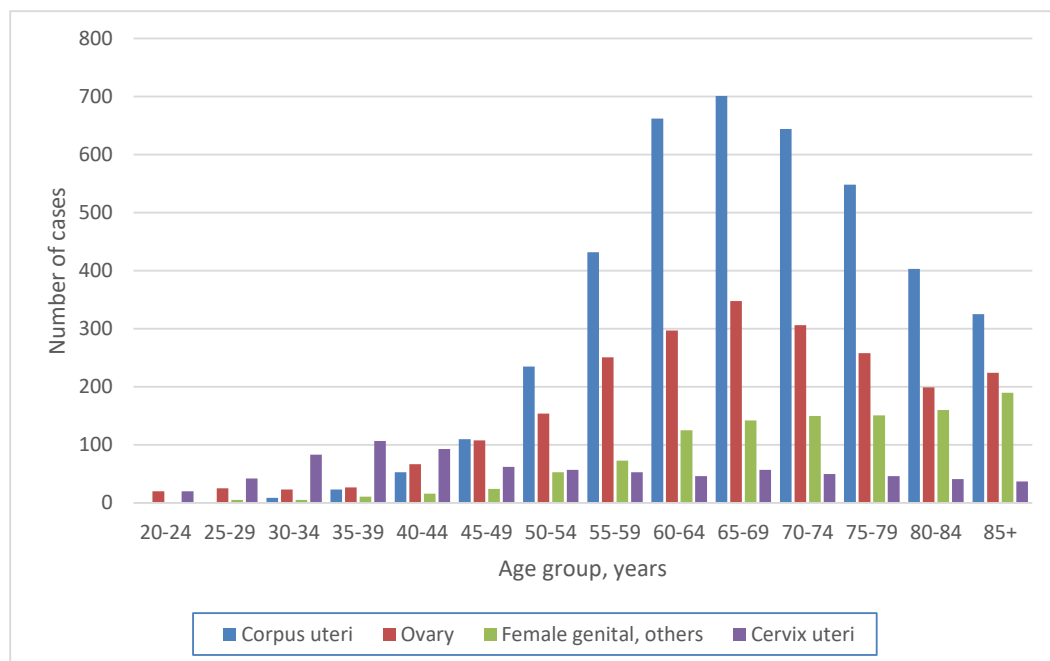
Endometrial cancers are divided into well-, moderately-, and poorly differentiated estrogen-related type 1 cancer, and more aggressive, non-estrogen dependent type 2 cancer (Bokhman 1983). Type 1 cancers account for 60−70% of new cases and are usually low grade with endometrioid histology, arise from endometrial hyperplasia, and have better prognosis (Murali et al. 2014). Type 2 endometrial carcinomas occur typically in older women and are usually higher grade with non-endometrioid histology, and have a poor prognosis (Tran and Gehrig 2017). The increased incidence of endometrial cancer is mostly due to the increased numbers of type 1 cancer, while the incidence of type 2 cancer has not significantly changed (Duong et al. 2011). Endometrial cancer commonly presents with postmenopausal bleeding or AUB in younger women. The incidence of endometrial cancer among premenopausal women with AUB is unknown.

Unopposed exogenous or endogenous estrogen exposure is an established risk factor and the most conspicuous driver of type 1 endometrial cancer. Obesity, PCOS, and anovulatory menstrual cycles are states with chronic unopposed estrogenic effect and are associated with an elevated risk of endometrial cancer (Schindler 2009, Kamal et al. 2016). Estrogen overload without adequate progestogen effect in the endometrium results in endometrial proliferation and eventually hyperplastic changes in the endometrium. Endometrial hyperplasia with atypia and endometrial intraepithelial neoplasia are precursors of endometrial cancer with significant risk of progression to carcinoma (Kurman et al. 1985, Lacey and Chia 2009, Sanderson et al. 2016). Other risk factors include early menarche, nulliparity, late menopause, and postmenopausal tamoxifen use (Saso et al. 2011, Kamal et al. 2016). A risk population for endometrial cancer are women with Lynch syndrome (hereditary nonpolyposis colon cancer). They have a lifetime risk of endometrial cancer of up to 71%, with average age of 49 at cancer diagnosis (Singh and Resnick 2017).

Endometrial cancer has a good prognosis if diagnosed early. The 5-year survival for stage I endometrial cancer is approximately 92%, but for stages III and IV, only 57−66% and 20−26%, respectively (Murali et al. 2014).

Ovarian cancer

Ovarian cancer is the fifth most common cancer in women in the developed world and the most lethal of gynecological cancers (Ferlay et al. 2012, Torre et al. 2017) (Figure 6). In Scandinavian countries, the incidence of ovarian cancer is the highest in the world (Engholm et al. 2016, Torre et al. 2017). In 2014, the incidence of ovarian cancer in Finland was 9.5/100 000 women-years (Figure 4). A total of 421 ovarian cancers and 191 precursors of ovarian cancer (borderline ovarian tumors) were diagnosed in Finland (www.cancer.fi). Most ovarian cancers are diagnosed among women aged 65–69 years (www.cancer.fi) (Figure 7).

Ovarian cancers are classified as epithelial, sex cord stromal, and germ cell tumors (Jayson et al. 2014). Epithelial ovarian cancer is the most predominant form of ovarian cancer (80–90%) and is divided into different histopathological classes: serous (68–71% of all epithelial carcinomas), clear cell (12–13%), endometrioid (9–11%), mucinous (3%), mixed (6%), and transitional (1%) carcinomas (McCluggage 2011). Since 2014, serous ovarian carcinoma has been further divided into high-grade and low-grade subtypes (Kurman et al. 2014, Prat and FIGO Committee on Gynecologic Oncology 2014), which are considered as distinct tumors with different etiology, morphology, and behavior (McCluggage 2011). The origin of high-grade serous ovarian carcinoma is proposed not to be in the ovary but in the fimbriae of the fallopian tubes (serous tubal intraepithelial carcinoma of the fallopian tube) (Crum et al. 2012).

The different epithelial ovarian tumor subtypes are suggested to arise from different tissue origins and their etiologies and risk factors vary. The theories of general mechanisms behind the ovarian cancer are incessant ovulation theory (Fathalla 1972), the gonadotropin theory (Stadel 1975, Cramer and Welch 1983), the retrograde menstruation or inflammatory theory (Cramer and Xu 1995), fallopian tube as an origin theory (Crum et al. 2007), and the newest, dual pathway theory (Kurman and Shih 2010). According to the dual pathway theory, ovarian cancer is divided into two groups according to tumor

behavior and morphology. Type 1 tumors consist of low-grade serous, low-grade endometrioid, clear cell, mucinous, and transitional (Brenner) tumors. Type 1 tumors are indolent and slowly growing tumors arising from borderline tumors and have a good prognosis (Kurman and Shih 2010). Type 2 tumors consist of high-grade serous carcinomas, undifferentiated carcinomas, and malignant mixed mesodermal tumors (carcinosarcomas). Type 2 tumors are highly aggressive, rapidly growing, and are usually diagnosed at an advanced stage (Kurman and Shih 2010).

Several protective and risk factors for ovarian cancer exist, but these may differ according to the subtypes of ovarian cancer. The most established protective factors are the use of COC, parity, tubal ligation, salpingectomy, and hysterectomy (Hinkula et al. 2006, Cibula et al. 2011, Havrilesky et al. 2013, Falconer et al. 2015, Madsen et al. 2015). The risk factors for ovarian cancer include advanced age, family history of ovarian cancer, HT use, nulliparity, and infertility (Adami et al. 1994, Ness et al. 2002, Koskela-Niska et al. 2013b, Jervis et al. 2014). Also, endometriosis has been suggested as a risk factor for ovarian cancer (Heidemann et al. 2014). However, some subtypes of ovarian cancer differ according to their risk factors. One of these is mucinous ovarian cancer, incidence of which seems not to be decreased by COCs (Schuler et al. 2013) but is reported to be decreased by postmenopausal ET use (Koskela-Niska et al. 2013b). Populations at significantly high risk of ovarian cancer are BRCA1 or BRCA2 mutation carriers who have a 40–60% lifetime risk of epithelial ovarian cancer (Mavaddat et al. 2013, Jayson et al. 2014).

Unfortunately, the vast majority of ovarian cancers are diagnosed at an advanced stage (Finnish Cancer Registry). A delayed diagnosis results from lack of effective screening and nonspecific symptoms of ovarian cancer, which include abdominal pain/bloating and distention, urinary urgency, alterations in bowel function, or an abdominal mass (Puistola and Leminen 2013, Jayson et al. 2014). Despite advances in treatment, ovarian cancer has the poorest prognosis of all gynecological cancers, with an overall 5-year survival of 45% (Engholm et al. 2016).

Due to the highest prevalence of epithelial ovarian tumors, I focus on these in this thesis.

Primary fallopian tube carcinoma

Primary fallopian tube carcinoma (PFTC) is a rare and aggressive malignancy, constituting approximately 1% of gynecological malignancies (Kalampokas et al. 2013) with worldwide incidence of 0.36/100 000 women-years (Kalampokas et al. 2013). In Finland during 2010–2014, the incidence of PFTC was 0.7/100 000 women-years with 205 new cases (Finnish Cancer Registry). PFTC most commonly occurs in women aged 40–65 years (mean 55 years) and 75% of PFTCs are postmenopausal (Kalampokas et al. 2013). PFTC is a distinct malignancy but the differentiation of PFTC from epithelial ovarian cancer is sometimes difficult due to similar histological appearance (Kalampokas et al. 2013).

The etiology and risk factors of PFTC are not well known, but multiparity and use of COCs are associated with decreased risk (Riska et al. 2007, Riska and Leminen 2007, Kalampokas et al. 2013). Nulliparity, long-term postmenopausal HT, also in the form of LNG-IUS, have been reported to increase the risk of PFTC (Riska and Leminen 2007, Koskela-Niska et al. 2015). The effect of premenopausal LNG-IUS use on the risk of PFTC is not known.

Symptoms of PFTC are nonspecific and mostly similar to those in ovarian cancer. However, PFTC is usually diagnosed at an earlier stage than ovarian cancer, as PFTC results in tubal distention and associated abdominal pain, as well as bloody-watery discharge (Horng et al. 2014). Due to the rarity of PFTC, optimal management of PFTC is still uncertain, and survival following PFTC is poor (Horng et al. 2014).

Cervical cancer

Cervical cancer is the fourth most common female cancer worldwide with 527 600 new cervical cancers in 2012 (Ferlay et al. 2012). Globally, large variations in the incidence of cervical cancer exist due to differences in human papilloma virus (HPV) prevalence, and striking disparities in the availability of protective vaccination against cervical cancer and screening programs (Torre et al. 2017). Approximately 85% of cervical cancers are diagnosed in low- or middle-income countries (Ferlay et al. 2015). In 2014, a total of 175 new cervical cancers were diagnosed in Finland. The overall incidence of cervical cancer in Finland in 2014 was 4.7/100 000 women-years, adjusted for age of world standard population (www.cancerregistry.fi) (Figure 4).

Other cancers

Cancers of the colon and rectum (colorectal) are the second most common female cancer worldwide with 614 300 new cases annually in 2012 (Ferlay et al. 2012). There is substantial variation in incidence globally, with the highest rates occurring in high-income countries (Ferlay et al. 2012). In 2014, a total of 989 colon cancers and 428 rectosigmoid cancers were diagnosed among women in Finland (www.cancerregistry.fi).

Globally, lung cancer is the third most common cancer among women, with 583 100 new cases in 2012 (Ferlay et al. 2012). Lung cancer is one of the most preventable cancers, as smoking is the most important risk factor. Also, air pollutants have a significant role in the carcinogenesis of lung cancer (Torre et al. 2015). In Finland, a total of 937 lung cancers were diagnosed among Finnish women in 2014. In 2014, the incidence of lung cancer was 13.3/100 000 women-years, adjusted for age of world standard population (www.cancerregistry.fi).

In the same year, a total of 601 pancreatic cancers were diagnosed among women in Finland (www.cancerregistry.fi) and the incidence of pancreatic cancer among Finnish women was 7.6/100 000 women-years, adjusted for age

of world standard population (www.cancerregistry.fi). Pancreatic cancer is one of the deadliest cancers (Ilic and Ilic 2016), and the risk faced by women in Finland of dying from pancreatic cancer is third highest in the world (Ferlay et al. 2012, Ilic and Ilic 2016). The 5-year survival was 8% among women during 2010–2014 in Finland (Engholm et al. 2016). Tobacco smoking is a known risk factor for pancreatic cancer, and also certain other risk factors (e.g., obesity, alcohol, and diabetes) have been identified, but the causes of this cancer are still insufficiently known (Ilic and Ilic 2016).

Treatment of heavy menstrual bleeding, and cancer risk

Hormonal aspects of carcinogenesis – the role of progestogens

In addition to the actions of estrogen and progestogens in the normal physiology of reproductive organs, they have an impact on carcinogenesis. Estrogen acts via ER-α and ER-β, and progestogens via two PRs – PR-A and PR-B – existing in mammary glands, the female reproductive tract (Chuffa et al. 2017), and in other tissues such as in the pancreas (Robles-Diaz and Duarte-Rojo 2001), lung (Siegfried and Stabile 2014), and colon (Singh et al. 1993). Imbalances in the actions of sex hormones as well as the altered function of sex hormone receptors in female organs are associated with various diseases such as AUB, and cancers of reproductive organs (Diep et al. 2015, Maybin and Critchley 2015, Chuffa et al. 2017). An excessive estrogen effect in the endometrium without effective progestogen action increases the risk of endometrial carcinogenesis (Kamal et al. 2016). Likewise in the endometrium, progestogens have protective effects on ovaries by decreasing the proliferative effects of estrogen, by suppressing ovulations (Ivarsson et al. 2001, Chuffa et al. 2017), and by inducing cell differentiation and apoptosis in ovarian cells (Bu et al. 1997, Diep et al. 2015, Chuffa et al. 2017). In contrast to their effect on the uterus and ovaries, progestogens can have a proliferative effect on the mammary gland (Aupperlee et al. 2005, Garcia y Narvaiza et al. 2008).

All hormonal treatments for HMB are based on progestins and their actions on the endometrium. Progestins used in the medical treatment of HMB vary significantly. Synthetic progestins can be structurally related either to progesterone or testosterone (e.g., levonorgestrel) and their binding affinity to hormone receptors varies (Carp 2015) (Table 2). The pharmacological differences of progestins may explain their various actions depending on the tissue. Also, the delivery mode (per oral, parenteral), continuity of administration (cyclic, continuous), metabolism, and hormonal milieu in the target tissue may have an impact on the risk of malignant transformation.

All progestogens mediate their actions by binding to the PRs in the cellular nucleus and activate PR signaling pathways, leading to changes in gene transcription and protein expression in the target cell. In mammary tissue, the proliferative effect of progestogens is mediated on both PR-positive and PR-negative breast cells. Progestogens directly bind to and stimulate PR-positive breast cells to produce and secrete cytokines and growth factors (e.g., receptor activator of nuclear factor κB ligand, and Wnt) which have a proliferative effect on adjacent PR-negative mammary cells (paracrine signaling) (Diep et al. 2015). It has been proposed that the increased breast cancer risk during postmenopausal HT is caused not only by direct proliferative effect of progestin on PR-positive precursor lesions, but also by expansion of PR-negative mammary stem/progenitor cells (Joshi et al. 2010, Asselin-Labat et al. 2010).

In addition, the actions of progestogens are mediated via androgen receptors, glucocorticoid receptors, and mineralocorticoid receptors but the binding affinities of different progestogens vary significantly (Stanczyk et al. 2013) (Table 2). Compared with other progestins, levonorgestrel has a high affinity for PR, relatively high affinity to androgen receptors, and a high bioavailability of over 90% (Stanczyk et al. 2013).

Table 2. *The binding affinities of different progestogens to various steroid hormone receptors. Modified from the review by Schindler A.E. in the textbook* Progestogens in Obstetrics and Gynecology*, ed. Carp, H.J.A. 2015.*

Progestogen	PR	AR	ER	GR	MR	SHBG	CBG	Albumin bound	Free
Progesterone	50	0	0	10	100	0	36	79.3	2.4
Dydrogesterone	75	0	ND	ND	ND	ND			
Cyproterone acetate	90	6	0	6	8	0	0		
Medroxyprogesterone acetate	115	5	0	29	160	0	0		
Megestrol acetate	65	5	0	30	0	0	0		
Nomegestrol	125	6	0	6	0	0	0		
Promegestone	100	0	0	5	53	0	0		
Drospirenone	35	65	0	6	230	0	0		
Norethisterone	75	15	0	0	0	16	0	60.8	3.7
Levonorgestrel	**150**	**45**	**0**	**1**	**75**	**50**	**0**	**50.0**	**2.5**
Norgestimate	15	0	0	1	0	0	0		
Desogestrel (etonogestrel)	150	20	0	14	0	15	0	65.5	2.5
Gestodene	90	85	0	27	290	40	0	24.1	0.6
Dienogest	5	10	0	1	0	0	0		

AR = androgen receptor (metribolone = 100%), CBG = corticosteroid-binding globulin (cortisol = 100%), ER = estrogen receptor (estradiol-17β = 100%), GR = glucocorticoid receptor (dexamethasone = 100%), MR = mineralocorticoid receptor (aldosterone = 100%), ND = not determined, PR = progesterone receptor (promegestone = 100%), SHBG = sex hormone binding globulin (dihydrotestosterone = 100%).

Hormonal treatment of heavy menstrual bleeding, and cancer risk

Combined oral contraceptives

Breast cancer

A large meta-analysis of 54 studies defined the association between COCs and breast cancer (CGHFBC 1996). In this meta-analysis, the risk of breast cancer in current users of COCs was 24% higher than in never-users (Table 3). The finding of elevated breast cancer risk among COC users was later confirmed by many studies (Kumle et al. 2002, Marchbanks et al. 2002, Kahlenborn et al. 2006, Hunter et al. 2010, Gierisch et al. 2013) (Table 3). However, in some studies only a slight increase or no increase in breast cancer risk has been reported (Hankinson et al. 1997, Hannaford et al. 2007, Vessey and Painter 2006, Vessey and Yeates 2013, Iversen et al. 2017) (Table 3). Based on the numerous human studies and experimental animal studies on COCs and

breast cancer risk, the International Agency for Research on Cancer (IARC) has classified COCs as a carcinogenic agent (IARC 2012). In a recent meta-analysis (Gierisch et al. 2013), the risk of breast cancer among ever-users of COCs was elevated by 8% compared with never-users (odds ratio [OR] 1.08, 95% CI 1.00–1.17). However, the excess in breast cancer risk may be transient as the risk seems to disappear after 10 or more years since cessation of COC use (CGHFBC 1996, Urban et al. 2012, Iversen et al. 2017).

The progestin component of COCs varies and may have an impact on cancer risk but only a few studies have provided information on specific formulations. In the Nurses' Health Study II (Hunter et al. 2010), a tri-phasic preparation with levonorgestrel was associated with an increased risk of breast cancer (RR 3.05, 95% CI 2.00–4.66). In the Women's Care Study (Marchbanks et al. 2002, Marchbanks et al. 2012), no increase in risk was observed for levonorgestrel-containing preparations but the number of women was sparse. To evaluate possible carcinogenic effects of different progestins in COCs, more studies on currently used COC formulas are needed.

Table 3. *Studies on combined oral contraceptive use and risk of breast cancer.*

Study	Study design, size of cohort, cases/controls	Study period/Follow-up	RR/OR/HR (95% confidence interval)
Oxford (CGHFBC 1996)	Meta-analysis 53 297/100 239	1976–1992	1.24 (1.15–1.33) current/recent use 1.16 (1.08–1.23) 1–4 y since last use 1.07 (1.02–1.13) 5–9 y since last use 1.01 (0.96–1.05) > 10 y since last use
The Nurses' Health Study I (Hankinson et al. 1997)	Cohort 3 383	1976–1992	1.11 (0.94–1.32) 0.96 (0.65–1.43) > 5 y use
Women's Care (Marchbanks et al. 2002)	Cohort 4 575/4 682	1994–1998	1.0 (0.8–1.1) 1.3 (1.0–1.7) premenopausal breast cancer
Women's Lifestyle and Health Study (Kumle et al. 2002)	Cohort 103 027	1991–1999	1.2 (1.1–1.4) former users 1.6 (1.2–2.0) current/recent users
Oxford Family Planning Association (Vessey and Painter 2006, Vessey and Yeates 2013)	Cohort 17 032	1968–1974	1.0 (0.8–1.1), follow-up until end of 2004 1.0 (0.9–1.1), follow-up until end of 2010
Mayo Clinic (Kahlenborn et al. 2006)	Meta-analysis	1980–2004	1.19 (1.09–1.29) ever-users
RCGP (Hannaford et al. 2007, Iversen et al. 2017)	Cohort 46 000	1968–1969	0.98 (0.87–1.19), follow-up until end of 2004 1.04 (0.91–1.17), follow-up until end of 2012
The Nurses' Health Study II (Hunter et al. 2010)	Cohort 116 413	1989–2001	1.12 (0.95–1.33) past use 1.33 (1.03–1.73) current use 1.16 (0.80–1.69) 0–8 y use 1.42 (1.05–1.94) > 8 y use
Johannesburg Cancer Case-Control Study (Urban et al. 2012)	Case-control 1 664/1 492	1995–2006	1.66 (1.28–2.16) all current/recent users vs never-users 1.57 (1.03–2.40) only oral contraceptive users 1.11 (0.91–1.36) > 10 y since last use
The Agency for Healthcare Research and Quality Evidence Report (Gierisch et al. 2013)	Meta-analysis 317 341	2000–2012	1.08 (1.00–1.17) ever-users vs never-users 1.21 (1.04–1.41) 0–5 y since last use 1.17 (0.98–1.38) 5–10 y since last use 1.13 (0.97–1.31) 10–20 y since last use 1.02 (0.88–1.18) > 20 y since last use

HR = hazard ratio, OR = odds ratio, RR = relative risk

Endometrial cancer

A decreased risk of endometrial cancer among COC users has been widely reported (Weiss and Sayvetz 1980, Schlesselman 1997, Vessey and Painter 2006, Hannaford et al. 2007, Dossus et al. 2010, Iversen et al. 2017). According to a recent meta-analysis (Gierisch et al. 2013), the risk of endometrial cancer among ever-users of COC was estimated to be approximately halved compared with non-users (OR 0.57, 95% CI 0.43–0.77). The protective effect of COCs against endometrial cancer has been reported to persist over 20 years (Schlesselman 1997, Iversen et al. 2017). Based on robust data, IARC has concluded that COCs are a protective agent against endometrial cancer (IARC 2012).

Ovarian cancer

There is consistent evidence from numerous studies that COCs are associated with significantly decreased risk of ovarian cancer (IARC 2012, Havrilesky et al. 2013) and the risk reduction is positively associated with the length of COC use. The risk is more than halved after 10 years of COC use and the protective effect seems to persist for decades (Collaborative Group on Epidemiological Studies of Ovarian Cancer 2008, Havrilesky et al. 2013). The protective effect of COCs against ovarian cancer is plausible via many proposed mechanisms. COCs suppress ovulations which cause microtrauma in the ovarian epithelium and is one of the proposed mechanisms of ovarian carcinogenesis (Fathalla 1972). With decreased ovulations, the exposure of the epithelium of the fallopian tube to carcinogenic agents in follicular fluid or other microenvironmental changes during ovulations is decreased (Crum et al. 2007).

Primary fallopian tube carcinoma

PFTC is a rare cancer whose etiology is not well known. Hormonal factors may play a role as oral contraceptive use has been associated with decreased risk of PFTC (Riska et al. 2007, Riska and Leminen 2007, Kalampokas et al. 2013).

Cervical cancer

The development of cervical cancer is caused by persistent high-risk HPV infection (Bosch et al. 2002, Cogliano et al. 2005) but co-factors such as sex hormones and Chlamydia trachomatis infection also may have a role in the cervical malignant transformation in HPV-positive women (Paavonen et al. 1979, Munoz et al. 2002, Luostarinen et al. 2004, Brake and Lambert 2005, Ramachandran 2017). Current and long-term COC use is a risk factor for cervical cancer among HPV-positive women (Moreno et al. 2002, Smith et al. 2003, International Collaboration of Epidemiological Studies of Cervical Cancer et al. 2007, Gierisch et al. 2013) but the elevated risk declines 10 years after cessation of COC use (International Collaboration of Epidemiological Studies of Cervical Cancer et al. 2007). However, the true effect of COCs on carcinogenesis may be difficult to assess as women using COCs for longer times may have increased sexual activity and thus more significant HPV exposure compared with other women.

Other cancers

The use of COCs has been associated with a decreased risk of colorectal cancer in numerous studies (Nichols et al. 2005, Bosetti et al. 2009, Gierisch et al. 2013, Iversen et al. 2017). The reported reductions in risk vary between approximately 15% and 20% for ever- versus never-users of COCs respectively (Bosetti et al. 2009, Gierisch et al. 2013), and the protective effect is stronger among current users of COCs (Nichols et al. 2005, Bosetti et al. 2009, Cibula et al. 2010).

LNG-IUS

Breast cancer
At the time of planning this thesis, only one study had been published on LNG-IUS use and breast cancer risk in premenopausal women (Backman et al.

2005). During our work, two other studies were published (Dinger et al. 2011, Heikkinen et al. 2016a) (Table 4).

Backman et al. conducted a post-marketing cohort study with 17 360 women (mean age 35.4 years) using LNG-IUS for contraception in Finland (Backman et al. 2005). In that study, the incidence of breast cancers during 1990–2000 among the LNG-IUS users in each 5-year group of LNG-IUS users was compared with the corresponding breast cancer incidence in the Finnish general population in 1998. The incidence of breast cancer was non-significantly higher among LNG-IUS users aged 30–39 years compared with the background population. Also, in other age groups, no significant associations were observed (Table 4).

In a case-control study from Finland and Germany by Dinger et al. (2011), prior use of copper intrauterine device (IUD) or LNG-IUS was compared between 5 113 women with breast cancer diagnosed before age 50, and 20 452 healthy controls. The use of LNG-IUS was self-reported and cancer diagnoses were obtained from cancer registries. Ever- or current use of LNG-IUS was not associated with increased risk of breast cancer compared with copper IUD use (Table 4).

In the case-control study by Heikkinen et al. (2016a), 5 927 women with breast cancer diagnosed at ages 22–60 years during 2000–2007, and 19 633 healthy controls were studied. Information on LNG-IUS use and potential confounders (e.g., use of hormonal contraception or HT, family history of cancer, alcohol use, body mass index) were obtained via a survey. Among women aged 25–50 years with exclusive use of LNG-IUS, no risk of breast cancer was observed compared with never-users. In women over 50, the risk of breast cancer was increased (Table 4). Also, a prior study reported an increased risk of breast cancer among postmenopausal women (Lyytinen et al. 2010) (Table 4).

Table 4. *Studies on use of the levonorgestrel-releasing intrauterine system and breast cancer risk.*

Study	Study design, size of cohort, cases/controls, age, follow-up	Study period/Follow-up	Country	Age (years)	RR/OR/HR (95% confidence interval)
Backman et al. 2005	Cohort 17 360 30—54 y (mean 35.4) 1990—2000	1990—1993	Finland	30—54	Breast cancer incidences (LNG-IUS users vs background population; per 100 000 women-years) 30—34 y: 27.2 vs 25.5 35—39 y: 74.0 vs 49.2 40—44 y: 120.3 vs 122.4 45—49 y: 203.6 vs 232.5 50—54 y: 258.5 vs 272.6
Lyytinen et al. 2009	Case-control 9956/29 868 50—62 y	1995—2007	Finland	50—62	Estradiol+LNG-IUS: 2.07 (1.78—2.41); 287 cases and 473 controls LNG-IUS only: 1.53 (1.33—1.75); 329 cases and 708 controls
Dinger et al. 2011	Case-control 5113/20 452 < 50 y	2000—2007	Finland and Germany	< 50 y	0.99 (0.88—1.12) ever-use of LNG-IUS vs ever-use of copper IUD 0.85 (0.52—1.39) current use of LNG-IUS vs current use of copper IUD
Heikkinen et al. 2016a	Case-control 5927/19 633 22—60 y	2000—2007	Finland	22—60 y	25-50 y: 1.00 (0.77—1.30); 75 cases and 261 controls 51—64 y: 1.63 (1.26—2.11); 73 cases and 137 controls

HR = hazard ratio, IUD = intrauterine device, LNG-IUS = levonorgestrel-releasing intrauterine system, OR = odds ratio, RR = relative risk.

Endometrial cancer

At the initiation of our study, nothing was known about the effect of LNG-IUS use on the risk of endometrial cancer, and this topic was the major driver of

this thesis. Our hypothesis of the protective effect of LNG-IUS against endometrial carcinogenesis was based on the findings of the antiproliferative effect of progestins in the endometrium, the powerful effect of LNG-IUS against endometrial proliferation (Andersson and Rybo 1990, Mansour 2012), and the studies of decreased endometrial cancer risk among non-hormonal IUD users (Felix et al. 2015). LNG-IUS has also been reported to be an effective treatment for endometrial hyperplasia, a potential precursor of endometrial cancer (Gallos et al. 2013, Yuk et al. 2016).

During our work, a Finnish register-based case-control study reported a decreased risk of endometrial cancer among postmenopausal women using LNG-IUS combined with ET (OR 0.34, 95% CI 0.16–0.72) or alone (OR 0.27, 95% CI 0.13–0.56) (Jaakkola et al. 2011), but the number of LNG-IUS users was low in that study.

Ovarian cancer

During the planning of our study, no reports on LNG-IUS use and ovarian cancer existed. During our work, a Finnish register-based case-control study (Koskela-Niska et al. 2013b) among postmenopausal women reported no increase in risk of ovarian cancer among women using ET with LNG-IUS (23 cases, 64 controls; OR 1.02, 95% CI 0.63–1.66).

Primary fallopian tube carcinoma

At the initiation of this study, no reports on LNG-IUS and PFTC risk existed. During the study, Koskela-Niska et al. reported an increased risk of PFTC among postmenopausal women with HT, also in the form of LNG-IUS (Koskela-Niska et al. 2015).

Cervical cancer

According to a pooled analysis of 26 epidemiological studies, ever-use of IUD was associated with a halved risk of cervical cancer (Castellsague et al. 2011). A study from Brazil with 187 LNG-IUS users and follow-up for 7 years observed no increase in precancerous cervical atypia among LNG-IUS users

(Lessard et al. 2008). However, the incidence of cervical cancer among LNG-IUS users is unknown.

Oral progestins

Progestins, especially norethisterone acetate, are used for HMB, but no reports on exclusive use of oral progestin for HMB and cancer risk exist. The only report on premenopausal use of non-contraceptive oral progestins and cancer risk is on breast cancer risk.

A prospective French E3N cohort study (Fabre et al. 2007) among over 73 000 women aged 40–64 years (mean 51.8 years) and mean follow-up of 9.1 years found no significant association between premenopausal ever-use of oral progestin and risk of breast cancer compared with never-users (RR 1.01, 95% CI 0.93–1.11). However, for progestin use of over 4.5 years, an increase in breast cancer risk was observed (RR 1.44, 95% CI 1.03–2.00). Compared with never-users, each additional year of progestin use increased the risk of breast cancer by 3%, and after discontinuation of use, the risk decreased to baseline (Fabre et al. 2007). A limitation was that information on the indications or the dosages of progestins was not provided.

Surgical treatment of heavy menstrual bleeding, and cancer risk

Hysterectomy and cancer risk

Breast cancer

Hysterectomy reduces HMB by 100% but surgical removal of the uterus has been reported to affect the circulation of blood in the ovaries, resulting in damage to ovarian function. This leads to a decrease in endogenous lifetime sex hormone exposure, which could predispose to later health outcomes such as cardiovascular disease and cancer (Judd et al. 1974, Farquhar et al. 2005, Xiangying et al. 2006). In a study among 66 802 postmenopausal women (Gaudet et al. 2014), a simple hysterectomy preserving ovaries at age under

45 years was associated with a reduced risk of breast cancer (OR 0.80, 95% CI 0.69–0.94). Similar findings have been reported by others (Press et al. 2011). The impact on cancer risk seems to be more pronounced when hysterectomy is performed together with a bilateral salpingo-oophorectomy (BSO). In the Nurses' Health Study (Parker et al. 2009), the risk of breast cancer after hysterectomy with BSO was reduced by 25% at all ages (RR 0.75, 95% CI 0.68–0.84), but the decrease was largest among women under 45 years (RR 0.62, 95% CI 0.53–0.74) compared with those with simple hysterectomy. Similar findings on breast cancer risk have been reported by other studies (Gaudet et al. 2014), but not all (Jacoby et al. 2011). Simple bilateral oophorectomy at age under 45 years has been reported to decrease breast cancer risk by approximately 50% (Schairer et al. 1997, Press et al. 2011) and the protective effect is evident for 10 years after surgery (Schairer et al. 1997).

Ovarian cancer

The effect of hysterectomy on the risk of ovarian cancer is unclear. No effect was seen for ovarian cancer risk at any ages in the study by Gaudet et al. (2014). In contrast, an Italian case-control study reported a decreased risk of ovarian cancer (1 031 cases, 2 411 controls; OR 0.6, 95% CI 0.4–0.9) among women with previous hysterectomy (Chiaffarino et al. 2005).

Other cancers

The effect of hysterectomy on other cancers has been studied less. In the study by Gaudet et al. (2014), no effect on the risks of colorectal cancer, lung cancer, non-Hodgkin lymphoma, or kidney cancer was observed. However, simple hysterectomy was associated with an increased risk of pancreatic cancer (RR 1.48, 95% CI 1.03–2.14).

Endometrial ablation and cancer risk

In endometrial ablation, the endometrium is deeply destroyed, but some endometrial islands may remain. Whether the ablation affects later risk of cancer, especially endometrial cancer, is not well known (Krogh et al. 2009,

Cooper et al. 2011, Dood et al. 2014, Singh et al. 2016). Most studies have reported no significant impact on endometrial cancer risk (Krogh et al. 2009, Cooper et al. 2011, Dood et al. 2014), but one study observed a decreased risk of endometrial cancer after endometrial ablation (Singh et al. 2016) (Table 5). The incidence of breast cancer among women treated with endometrial ablation is unclear, although one previous study has reported a 1.15% incidence of breast cancer among endometrial ablation treated women (Cooper et al. 2011) (Table 5).

Table 5. *Studies on endometrial ablation and cancer risk.*

Study	Study design, size of cohort/cases/controls, age, endometrial ablation type(s), region/country	Study period/ Follow-up	Incidence of cancer / Relative risk (RR)
Krogh et al. 2009	Cohort n = 367 (421 TRCEs) Age 45 ± 6 y Transcervical endometrial resection Denmark	1990—1996 4037 women-years	Endometrial cancer: incidence 3/367
Cooper et al. 2011	Cohort, population-based n = 14 078 25–55 y NA Scotland	1989—2006 median 6.2 (2.7—10.8) y	Incidences: Endometrial cancer: 0.02% Breast cancer: 1.15% Ovarian cancer: 0.04% Cervical cancer: 0.04%
Dood et al. 2014	Cohort n = 4776 median 41.55 (IQR: 37.08—45.61) y NA UK	1994—2010 median 5.5 (3.15—8.04) y	Endometrial cancer: incidence 3/4776; 19.3/100 000 women-years
Singh et al. 2016	Cohort n = 1 521 48 ± 6.3 y 1022 (67.19%) 1st generation EA, 499 (32.81%) ≥ 2nd generation EA UK	1994—2011 median 10 (2—17) y 19 733 women-years	Endometrial cancer: RR 0.0135 (95% CI 0.0007—0.2801), p = 0.0054

EA = endometrial ablation, IQR = interquartile range, NA = not available, TRCE = transcervical endometrial resection

Objectives

This thesis was designed to assess the cancer risks after intrauterine treatment (LNG-IUS or endometrial ablation) for HMB. In particular, the risks of endometrial cancer and breast cancer were the focus of interest. Secondly, we wanted to evaluate the need for hysterectomy among women treated with endometrial ablation. All studies were register-based nationwide cohort studies.

The specific objectives of the study were:

1. To evaluate the overall cancer risk, with a special interest in endometrial cancer and breast cancer among LNG-IUS users (Study I).

2. To assess the risk of most common breast cancer subtypes among LNG-IUS users (Study II).

3. To elucidate the impact of LNG-IUS use on different histological subtypes of ovarian cancer and on the risk of PFTC (Study III).

4. To study the risk of endometrial cancer, other gynecological cancers, and breast cancer after endometrial ablation (Study IV).

Subjects and methods

Permissions

This study was performed with permission from the Finnish National Centre for Welfare and Health (1881/5.05.00/2010; 1165/5.05.00/2016; 880/5.05.00/2016).

Registers used

In Finland, there exist many administrative and health registers which collect nationwide data on health-related information and are mandated by law. This national policy makes these registers very reliable, with information coverage of almost 100%, thus enabling register-based studies. The unique personal identity code issued by the Finnish Population Register Centre to all Finnish citizens and permanent residents since 1967 is used as an identification key in all these national health registers and is used for data linkages between the registers.

The data on LNG-IUS reimbursements (Mirena®, Bayer Oy, Turku, Finland) for treatment of HMB were obtained from the national Medical Reimbursement Register of the Social Insurance Institution, which contains data on LNG-IUS purchases in electronic form since 1994.

The information on cancer diagnoses among study subjects and nationwide cancer incidence (Studies I–IV) was received from the Finnish Cancer Registry. Since 1961, reporting of new cancer cases has been mandatory by law in Finland. The Finnish Cancer Registry covers virtually 100% of diagnosed cancers in Finland since 1953 (Teppo et al. 1994).

The data on gynecological surgical operations (endometrial ablations, hysterectomies, oophorectomies, salpingectomies, etc.) were obtained from the Hospital Discharge Register of the Finnish National Institute for Health

and Welfare (Studies I–IV). The coverage of this register is nearly 100% (Keskimäki and Aro 1991).

Sterilization data (Study IV) were received from the Sterilization Register of the Finnish National Institute for Health and Welfare.

The data on deliveries of live babies of both the study subjects and of the control cohort (Study IV) were obtained from the Finnish Population Register Centre. The information on the mode of deliveries (i.e., vaginal deliveries, cesarean sections) during 1987–2015 were received from the Birth Register of the Finnish National Institute for Health and Welfare.

The information on emigration dates and death dates was obtained from the Finnish Population Register Centre.

In Study I, additional data of self-reported cancer-related confounders (i.e., alcohol consumption, smoking, physical activity, diet, and socioeconomic status) were derived from a series of cross-sectional national health behavior surveys (the Health Behavior and Health among the Finnish Adult Population Survey [AVTK]). AVTK is a nationwide survey conducted by the National Institute for Health and Welfare. In the AVTK, a nationwide random sample from the Finnish Population Register aged 15–64 years was drawn annually during 1978–2002 with some 5000 Finnish people receiving a mailed questionnaire each year. The response rate among women varied between 75% and 86% (Tolonen et al. 2006). The data from women aged 30–49 years who returned the questionnaire were analyzed (n = 4056 LNG-IUS users; n = 25 801 non-users).

Registers used in Studies I-IV are shown in Table 6.

Table 6. *Registers used in Studies I–IV.*

Register	Obtained data	Complete nationwide data available from	Used in Studies
Medical Reimbursement Register (Social Insurance Institution)	Reimbursed LNG-IUSs	1994–	I, II, III
Finnish Cancer Registry	Cancer diagnoses, clinical stage of cancer at diagnosis, and cancer deaths	1953–	I, II, III, IV
Hospital Discharge Register (National Institute for Health and Welfare)	Gynecological surgical operations	1987–	I, II, III, IV
Sterilization Register (National Institute for Health and Welfare)	Sterilization procedures	1987–	IV
Birth Register (National Institute for Health and Welfare)	Dates of deliveries, modes of deliveries	1987–	IV
Finnish Population Register (Finnish Population Register Centre)	Date of emigration, date of death	1972–	I, II, III, IV
	Dates of deliveries of live babies	1972–	IV

LNG-IUS = levonorgestrel-releasing intrauterine system

Study populations

For the studies of LNG-IUS users and cancer risk (Studies I–III), we identified from the Medical Reimbursement Register of the Social Insurance Institution of Finland all Finnish women who had received reimbursement for LNG-IUS for HMB at ages 30–49 years during 1994–2007 (n = 93 843).

In the study of endometrial ablation (Study IV), we identified all Finnish women who in 1997–2014 had undergone endometrial ablation at age 30–49 years. These women were extracted from the Hospital Discharge Register of the Finnish National Institute for Health and Welfare by using NOMESCO Classification of Surgical Procedures code LCA 16 (destruction of the

endometrium). For each endometrial ablation case, five control women born at the same time (± 6 months), living in the same area, and alive at the index date (date of endometrial ablation) were randomly selected from the Finnish Population Register. Endometrial ablation cases and controls with previous cancer diagnosis before the index date were excluded. The final endometrial ablation cohort included 5 484 women, and the control cohort 26 938 women (Figure 8).

Figure 8. Flow chart of women included in Study IV concerning endometrial ablation and cancer risk.
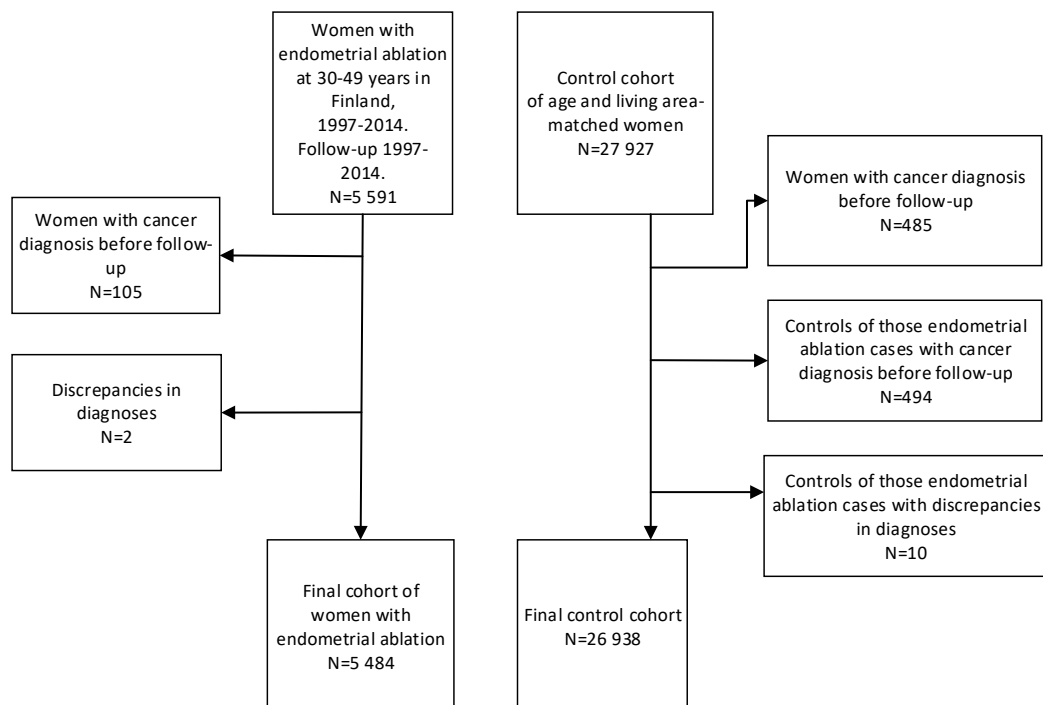
In Study IV, most women had had two prior deliveries before the index date; 38.0% in the endometrial ablation cohort, and 36.9% in the control cohort. Multiparity was also more frequent in the endometrial ablation cohort (Table 7).

Table 7. *Baseline characteristics of all Finnish women treated with endometrial ablation in 1997-2014 at ages 30-49 years, and their control group at the beginning of the follow-up.*

Patient charasteristic	Endometrial ablation	Controls	p
Number of women	5 484	26 938	
Age at the beginning of follow-up, years			
30-34	329 (6.0%)	1 624 (6.0%)	0.955
35-39	1 286 (23.5%)	6 364 (23.6%)	0.789
40-44	2 152 (39.2%)	10 569 (39.2%)	1.000
45-49	1 718 (31.3%)	8 381 (31.1%)	0.772
Parity			
0	282 (5.1%)	4 370 (16.2%)	<0.0001
1	575 (10.5%)	4 373 (16.2%)	<0.0001
2	2 082 (38.0%)	9 951 (36.9%)	0.160
3	1 629 (29.7%)	5 557 (20.6%)	<0.0001
≥4	917 (16.7%)	2 687 (10.0%)	<0.0001

Statistical methods

The standardized incidence ratios (SIRs) were calculated by dividing the observed cancer cases by the numbers expected. The expected number of cancers was calculated by multiplying the number of women-years in each 5-year age group and calendar period by the corresponding cancer incidence among all Finnish women for each primary cancer site. Ninety-five percent CIs were based on the assumption that the number of observed cases represents a Poisson distribution (Rothman et al. 2008).

In Studies I–III, the women-years at risk were calculated starting from the date of the first purchase of LNG-IUS and ending on the study closing date, the 55th birthday, hysterectomy, bilateral/unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, or on emigration, or death, whichever occurred first. In Study IV, the follow-up started from the index date, and ended at the end of 2014, on emigration, or death, whichever occurred first. In Study IV, censoring at the date of hysterectomy in the analyses for uterine cancers, and at the bilateral/unilateral salpingectomy, salpingo-

oophorectomy, or oophorectomy in the analyses for ovarian cancer risk was done. The study closing dates were at the end of 2009 (Study I), the end of 2012 (Study II), the end of 2013 (Study III), or at the end of 2014 (Study IV).

In Study I, multivariate logistic regression models were used to assess, by means of ORs with 95% CIs, the association between individual behavior factors and the use of LNG-IUS.

In Study IV, a multivariate Poisson regression model by means of hazard ratios (HRs) with 95% CIs with women-years as offset was used to evaluate the risk factors for hysterectomy after endometrial ablation. The age of a woman at endometrial ablation, parity, number of cesarean sections, sterilization, and the follow-up time were included in the final model. We used a cause-specific hazard method (Putter et al. 2007) where death was used as a competing event for hysterectomy in the estimation of cumulative risk of hysterectomy.

Results

The main results are presented here, and further data are shown in the original publications.

Cancer risk among LNG-IUS users

Breast cancer (Study I, II)

During the study period, a total of 93 843 LNG-IUS users were followed for 855 324 women-years in Study I, and for 1 032 767 women-years in Study II (Table 8).

Table 8. *Cohorts of levonorgestrel-releasing intrauterine system (LNG-IUS) users (n) in Studies I–II. Follow-up started from the first or second purchase of LNG-IUS.*

Age	Follow-up from the first LNG-IUS			Follow-up from the second LNG-IUS		
	n	Women-years (Study I)[1]	Women-years (Study II)[2]	n	Women-years (Study I)[1]	Women-years (Study II)[2]
30–34	20 998	47 196	47 196	290	365	365
35–39	28 220	168 763	172 523	4 151	10 335	10 352
40–44	25 954	250 431	285 032	5 643	33 547	35 218
45–49	18 671	240 504	310 402	4 150	40 962	52 677
50–54	0	148 430	217 615	0	23 211	38 305
Total	93 843	855 324	1 032 767	14 234	108 420	136 917

n = number of all women counted by age at the purchase of LNG-IUS; women-years counted by age at the follow-up; cancer cases counted by age at diagnosis.

[1] Follow-up 1994–2009.
[2] Follow-up 1994–2012.

In Study I, a total of 2 781 cancers were diagnosed during the study period. The overall cancer incidence was 7% higher among LNG-IUS users than expected (SIR 1.07, 95% CI 1.03–1.11). In Study I, of the 2 781 diagnosed

cancers among LNG-IUS users, 1 542 were breast cancers (250 breast cancer cases more than expected). The risk of breast cancer among all LNG-IUS users was 19% higher than in the background population (SIR 1.19, 95% CI 1.13–1.25). Of the 93 843 LNG-IUS users, 14 234 had two or more LNG-IUS purchases. Among the women with two or more LNG-IUS purchases, the SIR for breast cancer was 1.40 (95% CI 1.24–1.57) (Table 9).

Table 9. *Observed number of cancer cases (OBS) and standardized incidence ratios (SIRs), with 95% confidence interval (CI), among Finnish women with levonorgestrel-releasing intrauterine system (LNG-IUS) purchase at ages 30–49 years, by type of cancer and number of LNG-IUS purchases. Follow-up 1994–2009.*

Cancer type	≥ 1 purchase of LNG-IUS[1]			≥ 2 purchases of LNG-IUS[2]		
	OBS	SIR	95% CI	OBS	SIR	95% CI
All sites	2781	1.07	1.03–1.11***	454	1.20	1.09–1.31***
Stomach	45	1.10	0.80–1.47	7	1.22	0.49–2.51
Colon and rectum	154	1.17	0.99–1.36	24	1.22	0.78–1.81
Liver	6	0.69	0.25–1.50	2	1.58	0.19–5.69
Gallbladder, bile ducts	7	0.88	0.35–1.81	2	1.77	0.21–6.37
Pancreas	15	0.50	0.28–0.81**	3	0.66	0.14–1.91
Lung, trachea	43	0.68	0.49–0.91**	3	0.31	0.06–0.91*
Melanoma of skin	129	1.08	0.90–1.27	19	1.11	0.67–1.73
Breast	1542	1.19	1.13–1.25***	271	1.40	1.24–1.57***
Cervix uteri	60	0.90	0.69–1.15	6	0.76	0.28–1.65
Adenocarcinoma of cervix uteri	22	1.18	0.74–1.79	2	0.91	0.11–3.30
Vulva	8	0.81	0.35–1.59	3	2.13	0.44–6.21
Vagina	4	1.32	0.36–3.38	0	0.00	0.00–7.40
Corpus uteri (all types)	56	0.59	0.45–0.77***	5	0.36	0.12–0.83*
Endometrial adenocarcinoma	37	0.46	0.33–0.64***	3	0.25	0.05–0.73**
Uterine sarcomas	18	1.44	0.86–2.28	2	1.17	0.14–4.22
Other uterine	0	0.00	0.00–3.27	0	0.00	0.00–35.65
Ovary, all types	59	0.60	0.45–0.76***	7	0.51	0.20–1.04
Kidney	40	0.98	0.70–1.32	10	1.63	0.78–3.00
Bladder, ureter, urethra	12	0.98	0.51–1.70	3	1.75	0.36–5.10
Brain, nervous system	175	1.04	0.89–1.19	25	1.07	0.69–1.57
Thyroid gland	138	1.09	0.92–1.28	21	1.25	0.77–1.90
Non-Hodgkin lymphoma	81	1.07	0.85–1.32	10	0.91	0.44–1.67
Hodgkin lymphoma	13	1.19	0.63–2.03	2	1.77	0.21–6.41
Multiple myeloma	11	0.94	0.47–1.68	2	1.19	0.14–4.29
Leukaemia	34	0.93	0.64–1.29	2	0.38	0.05–1.37

* *p* < 0.05; ** *p* < 0.01; *** *p* < 0.001
[1]Follow-up from the first purchase of LNG-IUS.
[2]Follow-up from the second purchase of LNG-IUS.
Only primary cancers are listed.

In Study II, a total of 2015 breast cancers were diagnosed among LNG-IUS users during the follow-up of over one million women-years. The mean follow-up was 11.0 years (maximum 19 years). Of the 2015 breast cancers, 1598 (79.3%) cases were invasive ductal cancers, 376 (18.7%) were invasive lobular cancers, and 41 (2%) had other histologies. The risks 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 increased compared with those of the background population. Among women with two or more LNG-IUS purchases, the SIR for invasive lobular cancer was 1.73 (95% CI 1.37–2.15), and for invasive ductal cancer 1.37 (95% CI 1.21–1.53).

The SIRs for both invasive lobular and ductal cancer were not increased during the first years of follow-up, but a significant elevation in SIRs was noticed after 5 years of follow-up (Figure 9).

Figure 9. The standardized incidence ratios (SIRs) of invasive ductal and lobular breast cancers during the follow-up in Study II. Follow-up 1994–2012. LNG-IUS = levonorgestrel-releasing intrauterine system.
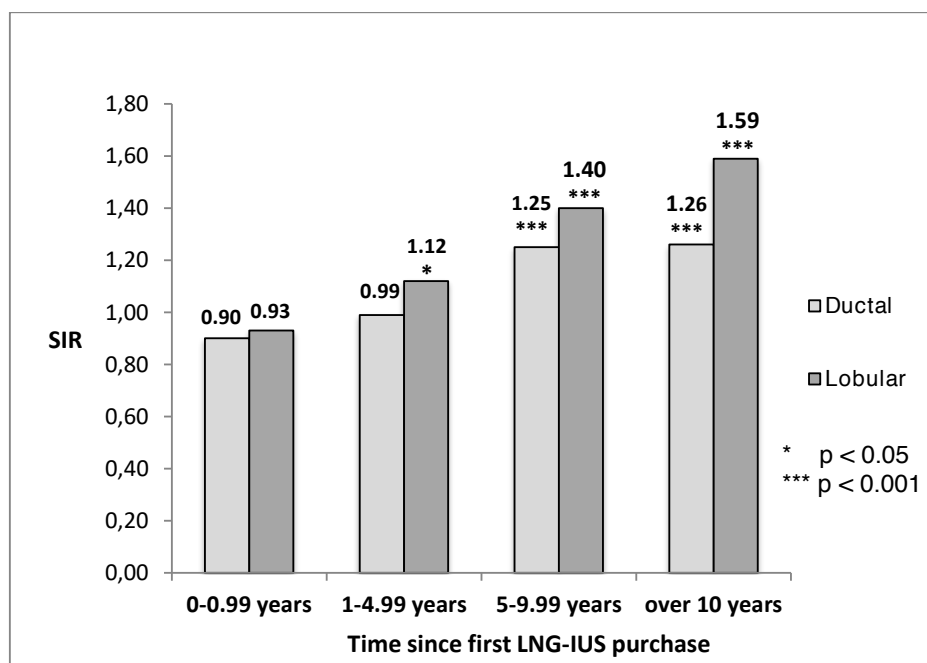
The SIRs were slightly higher for localized breast cancer than for non-localized breast cancer among LNG-IUS users. After 5 years of follow-up, the risks of non-localized ductal and lobular cancers were statistically significantly higher among LNG-IUS users than in the general population (Figure 10).

Figure 10. Standardized incidence ratios (SIRs) of localized and non-localized breast cancers among levonorgestrel-releasing intrauterine system (LNG-IUS) users in Study II. Follow-up 1994–2012.
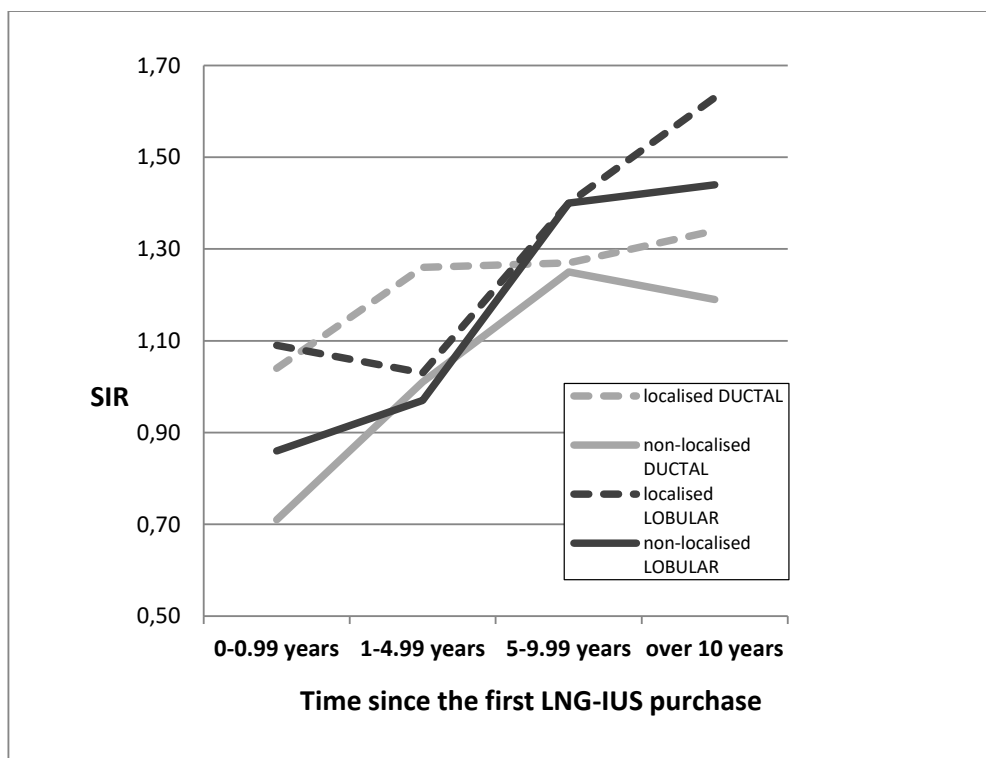
In absolute numbers, 2-4 excess cases of breast cancers were observed among 1 000 Finnish women using LNG-IUS for HMB and followed for 10 years.

Gynecological cancers (Study I, III)

Endometrial cancer (Study I)

A total of 37 endometrial cancers (endometrial adenocarcinoma) were diagnosed among LNG-IUS users during the follow-up of 855 324 women-years in Study I (Table 9). LNG-IUS users had a significantly decreased risk of endometrial cancer compared with the general population (SIR 0.46, 95% CI 0.33–0.64). In absolute numbers, this means 3-6 prevented endometrial cancers per 10 000 LNG-IUS users followed for 10 years. After two purchases of LNG-IUS, the SIR for endometrial cancer was 0.25 (95% CI 0.05–0.73). The decreased risk of endometrial cancer was seen already in the first years of follow-up and was maintained during the whole follow-up (Table 10).

Table 10. *Observed number of endometrial cancers (OBS) and standardized incidence ratios (SIRs), with 95% confidence interval (CI), among Finnish women with levonorgestrel-releasing intrauterine system (LNG-IUS) for heavy menstrual bleeding at ages 30–49 years during 1994–2007. Follow-up 1994–2009.*

| Age at follow-up (years) | Time since the first purchase of LNG-IUS | | | | | | | | | | | |
| | 0—0.99 years | | | 1—4.99 years | | | 5—9.99 years | | | 10 years or over | | |
	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI
30–34	0	0.00	0.00—21.39	0	0.00	0.00—14.04						
35–39	0	0.00	0.00—5.49	1	0.45	0.01—2.47	1	1.36	0.03—7.58			
40–44	0	0.00	0.00—2.83	4	0.80	0.22—2.04	2	0.45	0.05—1.63	0	0.00	0.00—4.83
45–49	2	0.87	0.11—3.14	5	0.51	0.17—1.18	4	0.41	0.11—1.04	1	0.30	0.01—1.68
50–54	0	0.00	0.00—11.55	4	0.41	0.11—1.05	9	0.44	0.20—0.82**	4	0.49	0.13—1.26
Total	2	0.42	0.05—1.51	14	0.52	0.28—0.86**	16	0.45	0.26—0.72***	5	0.41	0.13—0.95*

* *p* < 0.05

** *p* < 0.01

*** *p* < 0.001

Ovarian cancer and primary fallopian tube carcinoma (Study I, III)

In Study I, the SIR for ovarian cancer in general was 0.60 (95% CI 0.45–0.76; 59 observed compared with 99 expected cases) (Table 9). In Study III, a total of 77 invasive ovarian cancers were diagnosed among LNG-IUS users during

the follow-up of 1 083 126 women-years. The risk of ovarian cancer was 41% lower among LNG-IUS users compared with the general population (SIR 0.59 (95% CI 0.47–0.73). Of the invasive ovarian cancers, 46 were serous, 11 mucinous, 11 endometrioid, and 3 were clear cell carcinomas. The rest were other less common types (Table 11).

Of the epithelial ovarian cancers, the RR was lowest for mucinous carcinoma and highest for serous carcinoma among LNG-IUS users (Table 11. The decreased incidence of invasive ovarian cancers was seen during the first 5 years of follow-up (SIR 0.63, 95% CI 0.43–0.90), and was maintained during the whole follow-up. Expressed as absolute numbers, 3-6 invasive ovarian cancers were prevented per 10 000 LNG-IUS users followed for 10 years.

The risk of borderline ovarian tumors was also significantly decreased among LNG-IUS users (SIR 0.76, 95% CI 0.57–0.99). Significant differences between histology-specific SIRs of borderline tumors did not exist (Table 11). Expressed as absolute numbers, five prevented invasive ovarian cancers were observed per 1000 LNG-IUS users followed for 10 years.

A total of seven cases of PFTC were registered among LNG-IUS users during the study period. The risk of PFTC among LNG-IUS users was comparable with that of the background population (Table 11).

Table 11. Observed number of ovarian tumors and primary fallopian tube cancer cases (OBS) and standardized incidence ratios (SIRs), with 95% confidence interval (CI), among Finnish women who purchased levonorgestrel-releasing intrauterine system (LNG-IUS) for heavy menstrual bleeding during 1994–2007 at ages 30–49 years, by time since first purchase. Follow-up 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			10 years or over			Entire follow-up		
	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI	OBS	SIR	95% CI
Ovarian cancer (all invasive ovarian cancers)	30	0.63	0.43–0.90**	27	0.55	0.36–0.79***	20	0.59	0.36–0.91*	77	0.59	0.47–0.73**
Serous carcinoma	18	0.79	0.47–1.24	16	0.69	0.39–1.11	12	0.77	0.40–1.33	46	0.75	0.55–0.99*
Mucinous carcinoma	5	0.56	0.18–1.29	3	0.37	0.08–1.07	3	0.56	0.12–1.63	11	0.49	0.24–0.87*
Endometrioid carcinoma	5	0.71	0.23–1.65	3	0.38	0.08–1.10	3	0.62	0.13–1.79	11	0.55	0.28–0.98*
Clear cell carcinoma	1	0.42	0.01–2.34	2	0.61	0.07–2.19	0	0.00	0.00–1.38	3	0.36	0.07–1.05
Ovarian borderline tumors (all tumor types)	22	0.84	0.53–1.26	16	0.58	0.33–0.94*	17	0.92	0.54–1.47	55	0.76	0.57–0.99*
Serous	8	0.77	0.33–1.50	5	0.48	0.16–1.12	5	0.74	0.24–1.71	18	0.65	0.39–1.02
Mucinous	9	0.82	0.38–1.55	10	0.84	0.40–1.53	2	0.25	0.03–0.88*	21	0.68	0.42–1.03
Endometrioid	1	7.47	0.19–41.6	0	0.00	0.00–27.5	0	0.00	0.00–23.2	1	2.34	0.06–13.1
Clear cell	0	0.00	0.00–225	0	0.00	0.00–71.5	0	0.00	0.00–171	0	0.00	0.00–41.2
Primary fallopian tube carcinoma	3	1.47	0.30–4.29	2	0.91	0.11–3.93	2	1.32	0.16–4.77	7	1.22	0.49–2.50

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Other cancers (Study I)

In addition, LNG-IUS users had a significantly lower risk of lung cancer (SIR 0.68, 95% CI 0.49–0.91) and pancreatic cancer (SIR 0.50 (95% CI 0.28–0.81). The risk of cervical cancer among LNG-IUS users did not differ from that of the background population (Table 9).

Cancer risk after endometrial ablation

Endometrial ablations in Finland

Before the detailed results for cancer risks and hysterectomies after endometrial ablations (Study IV), I present some results of the background data characterizing the endometrial ablations performed in Finland during 1997–2014.

During the study period 1997–2014, a total of 5591 endometrial ablations were performed in Finland. The number of endometrial ablations has been growing during the 2000s in Finland (Figure 11).

Figure 11. Number of endometrial ablations in Finland during 1997–2014.
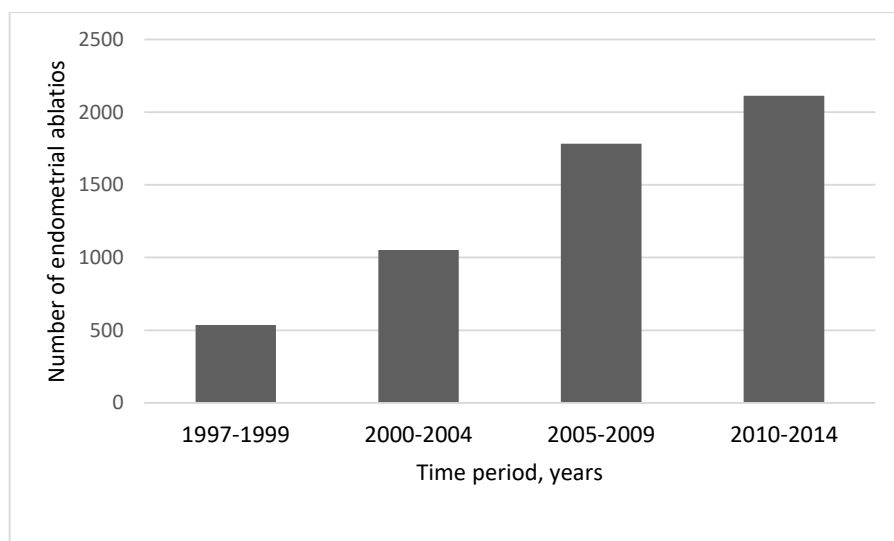
There were differences between the hospital districts in the incidences of performed endometrial ablations during 1997–2014 in Finland. The highest incidence of endometrial ablation was in the hospital district of Satakunta (28/100 000 women-years), and the lowest was in Ahvenanmaa (1/100 000 women-years) (Figure 12).

Figure 12. Incidence of endometrial ablations by hospital district in Finland, 1997–2014.
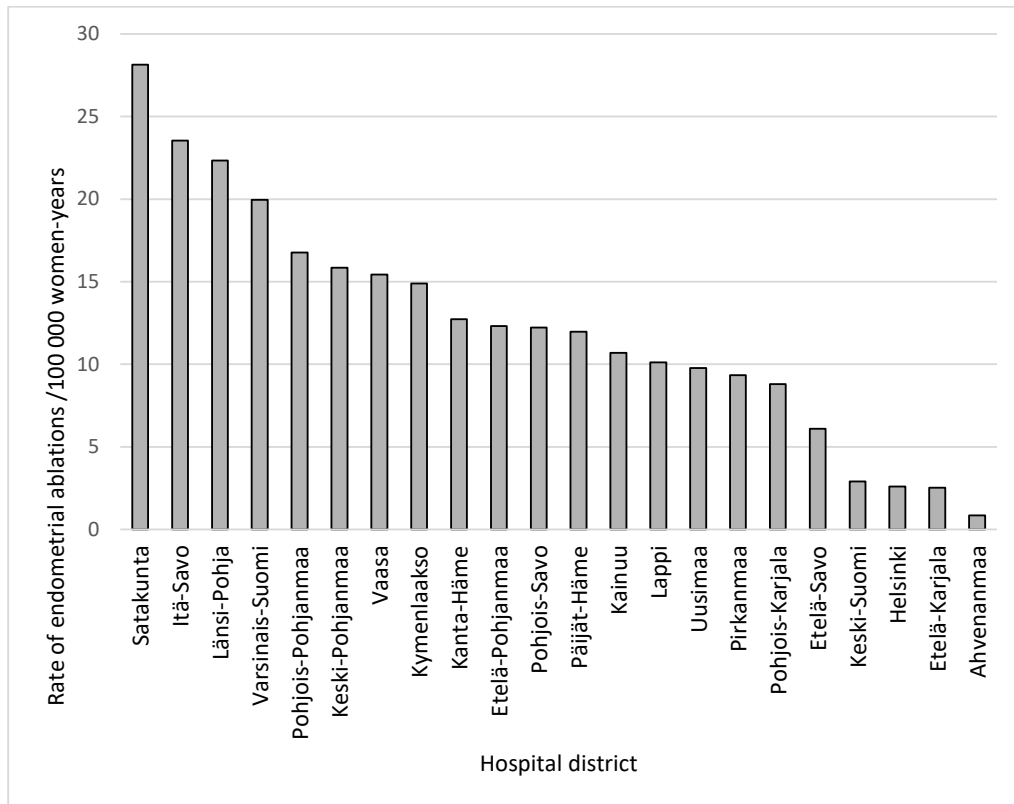
Endometrial cancer and other cancers (Study IV)

During the study period 1997–2014 with 39 892 women-years of follow-up, a total of 154 cancers were diagnosed among the study cohort of 5484 endometrial ablation treated women in Finland (Table 12). The SIRs for all cancers were stable during the whole follow-up period (Table 13).

Table 12. *Observed and expected number of cancer cases and standardized incidence ratios (SIRs), with 95% confidence interval (CI), among Finnish women treated with endometrial ablation at ages 30–49 years. Follow-up 1997–2014.*

| Age (years)	n	Women-years	OBS	EXP	SIR	95% CI
30–34	329	558	0	0.5	0.00	0.00–7.44
35–39	1 286	3 389	2	4.8	0.42	0.05–1.50
40–44	2 151	9 408	27	21.5	1.26	0.83–1.83
45–49	1 718	13 613	53	52.8	1.00	0.75–1.31
50–54	0	9 086	42	51.1	0.82	0.59–1.11
over 55	0	3 839	30	29.2	1.03	0.69–1.47
Total	5 484	39 892	154	160.0	0.96	0.82–1.13

EXP = expected, OBS = observed.

Table 13. *Diagnosed cancer cases and standardized incidence ratios (SIRs), with 95% confidence interval (CI), among women treated with endometrial ablation during 1997–2014 at ages 30–49 years in Finland.*

Time since endometrial ablation	Cancer cases	SIR	95% CI
0–0.99 years	13	0.94	0.50–1.61
1–4.99 years	54	1.00	0.75–1.31
5 years and over	87	0.94	0.76–1.16
Entire follow-up	154	0.96	0.82–1.13

Of all diagnosed cancers among the endometrial ablation treated women, 3 were endometrial cancers. The SIR for endometrial cancer among endometrial ablation treated women was 0.56 (95% CI 0.12–1.64; 5.3 expected cases). Of the endometrial cancers, 2 cases were local and one was of unknown location. The SIR for ovarian cancer was 0.59 (95% CI 0.12–1.72; 3 observed compared with 5.1 expected cases), and for cervical cancer 0.78 (95% CI 0.10–2.83; 2 observed compared with 2.6 expected cases) (Figure 13).

Figure 13. Standardized incidence ratios (SIRs), with 95% confidence interval (CI), among women treated with endometrial ablation during 1997–2014 at ages 30–49 years in Finland, by type of cancer. Follow-up 1997–2014.
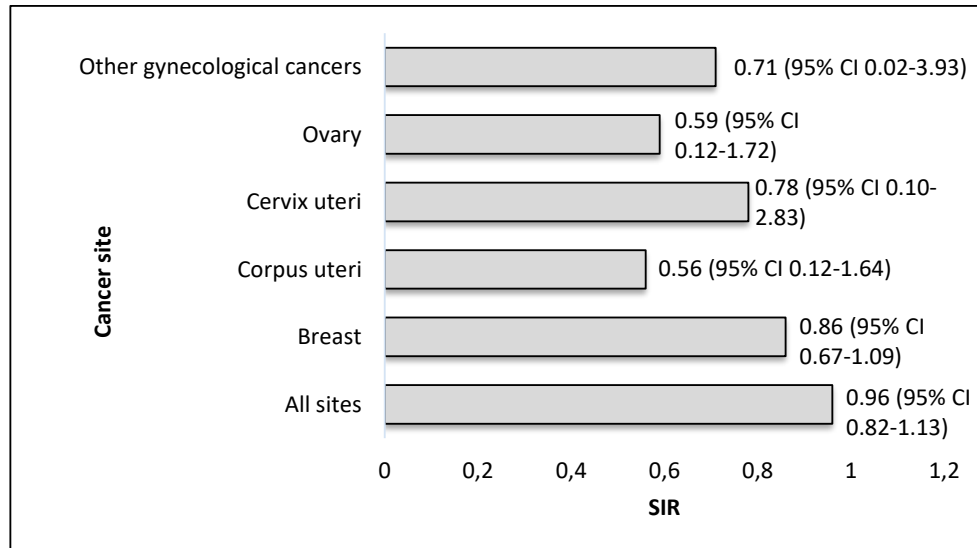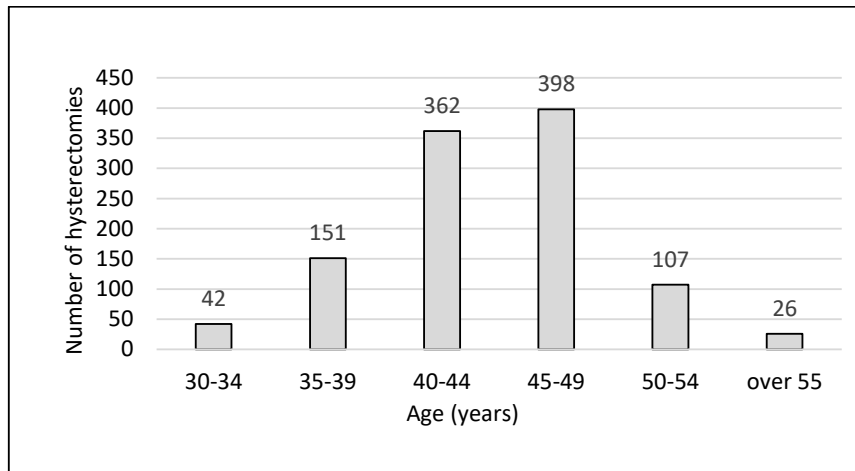

Among the endometrial ablation treated women, a total of 67 breast cancers were diagnosed during the follow-up (SIR 0.86, 95% CI 0.67–1.09; 77.9 expected cases), which was comparable with that of the general population (Figure 13).

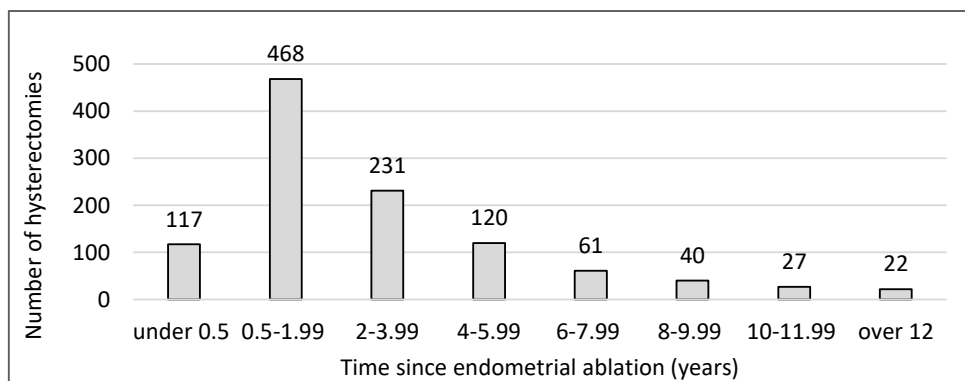## Hysterectomy after endometrial ablation (Study IV)

A total of 1086 women (19.8%) underwent hysterectomy in the endometrial ablation cohort during the follow-up (mean 7.3 years, maximum 18 years). Most hysterectomies were among those 45–49 years old (Figure 14). The mean age at hysterectomy was 44.7 ± 5.2 years in the endometrial ablation cohort and 44.4 ± 5.7 years in the controls.

Figure 14. Hysterectomies by age group among endometrial ablation treated Finnish women. Follow-up 1997–2014.


Most hysterectomies were performed during the first few years after endometrial ablation (Figure 15). Compared with the controls, endometrial ablation treated women had a 3.6-fold risk of hysterectomy (HR 3.63, 95% CI 3.32–3.96).

Figure 15. Time interval from endometrial ablation to hysterectomy. Follow-up 1997–2014.

The most frequent indications for hysterectomy after endometrial ablation were HMB (47.8%), leiomyomas (18.9%), and other not specified indications (14.0%) (Figure 16).

Figure 16. Indication of postablation hysterectomy in the endometrial ablation group. Follow-up 1997–2014.
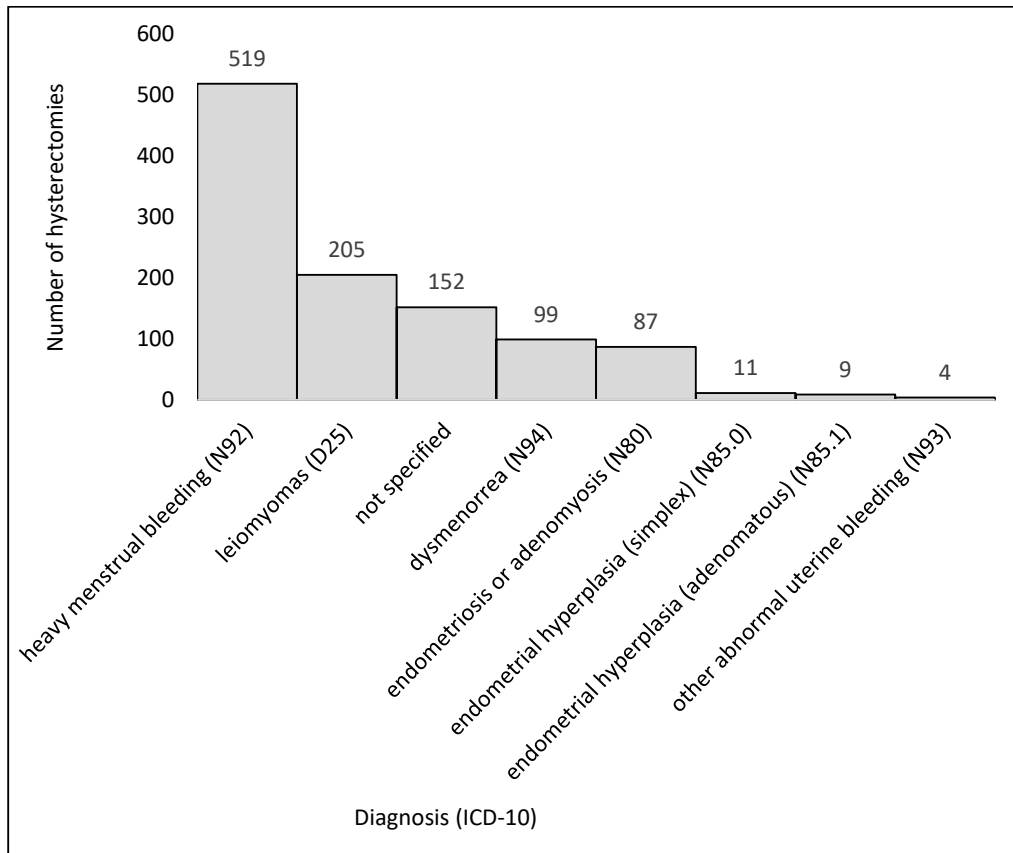
Risk factors for postablation hysterectomy

Risk of postablation hysterectomy was highest among women with leiomyoma diagnosis at endometrial ablation (HR 1.78, 95% CI 1.03–3.10), or who were younger than 35 years at the time of endometrial ablation (HR 1.44, 95% CI 1.15–1.81). In addition, the risk of hysterectomy was significantly increased among women with at least two prior cesarean deliveries (HR 1.27, 95% CI 1.04–1.55), or with a history of sterilization (HR 1.15, 95% 1.01–1.32) (Table 14).

Table 14. *Predictors for hysterectomy after endometrial ablation.*

Variable	Adjusted HR (95% CI)[1]
Age at index date, years	
30–34	1.44 (1.15–1.81)**
35–39	1.15 (0.99–1.34)
40–44	1
45–49	0.90 (0.77–1.05)
Number of deliveries before index date	
0	1
1	1.06 (0.77–1.46)
2	0.82 (0.62–1.10)
≥ 3	0.91 (0.68–1.20)
Number of cesarean sections before index date	
0	1
1	1.09 (0.91–1.32)
≥ 2	1.27 (1.04–1.55)*
History of tubal sterilization before index date	
No	1
Yes	1.15 (1.01–1.32)*
Indication of endometrial ablation	
Heavy menstrual bleeding	1
Leiomyomas	1.78 (1.03–3.10)*
Endometriosis/Adenomyosis	1.44 (0.64–3.24)
Endometrial hyperplasia	1.35 (0.64–2.85)
Other abnormal uterine bleeding	0.66 (0.30–1.47)
Dysmenorrhea	1.06 (0.47–2.37)
Other	0.83 (0.71–0.98)*
Follow-up time, years since index date	
0–0.99	4.44 (3.67–5.36)***
1–4.99	2.43 (2.03–2.91)
5–9.99	1
10–14.99	0.68 (0.48–0.98)*
≥ 15	1.14 (0.58–2.23)

Index date, the date of endometrial ablation and the beginning of the follow-up.
CI = confidence interval, HR = hazard ratio.

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

[1] Adjusted for age at endometrial ablation, parity, number of cesarean sections, sterilization, and follow-up time.

Discussion

Intrauterine treatment for HMB in the form of LNG-IUS or endometrial ablation has been extensively used for the last two decades but its effect on women's later cancer risk has been only poorly studied. The finding of the crucial role of progestins in the carcinogenesis of the female reproductive organs, especially of the breast and uterus, has raised questions about the effect of long-term hormonal treatments used during fertile years.

Breast cancer is the most frequent female cancer, and its incidence has been increasing in many countries (Ferlay et al. 2012). It has been estimated that up to one in eight women will be diagnosed with breast cancer during their lifetime, and 25% of them will be under 50 years of age at the time of diagnosis (Ferlay et al. 2012, Rojas and Stuckey 2016) (www.cancer.fi). Due to the emerging role of LNG-IUS as a primary treatment for HMB even at young ages, the effect of long-term use of levonorgestrel on the risk of endometrial cancer or breast cancer is of major interest. On the other hand, due to the increasing prevalence of obesity already at young ages, decreasing parity, and the resulting increase in the incidence of endometrial cancer also in the premenopausal population (Arnold et al. 2015, Kamal et al. 2016), the possible protective effect of intrauterine levonorgestrel has to be elucidated.

Due to the possible negative effects of hormonal treatments on cancer risks (Bassuk and Manson 2015), many women desire non-hormonal options for the treatment of HMB. The newer non-hysteroscopic endometrial ablation techniques, which are safe and easy to perform in an outpatient setting and are as effective for HMB as LNG-IUS, have become more popular than before in many countries (Reid 2007, Wortman et al. 2015). However, the effect of the destruction of the endometrium by endometrial ablation on later cancer risk, especially on endometrial or breast cancer risk, is not well known and needs to be assessed.

We conducted four national studies to evaluate the risk of cancer, especially of endometrial and breast cancer, among women using LNG-IUS for HMB or

treated with endometrial ablation during their reproductive years. The national nature of the studies was important in particular for examining the effect of LNG-IUS use on cancer risk as LNG-IUSs considered globally have been on the market for the longest time in Finland, and the prevalence of LNG-IUS use is very high in Finland (Lindh et al. 2017). Ideally, the possible risk evaluations on LNG-IUS use and cancer risk should be studied in each country, as the prescription policies, genetic landscapes due to ethnic backgrounds, and lifestyle factors among women may vary between regions.

All studies of this thesis were register studies based on Finnish law-based health-care registers. The register-based studies were well suited to test the hypotheses on cancer risks. Also, conducting a prospective randomized controlled study would not be a realistic option, as it would take decades to provide information on cancer risks, would be difficult to conduct, be expensive, and even be unethical to expose young women to a hormonal method with contraceptive properties for a long time. With the data of the Finnish health registers, we were able to study the impact of LNG-IUS use on cancer risks in the largest patient series so far reported.

With the first three cohort studies, we were able to test our primary hypotheses of decreased risk of endometrial and ovarian cancers among LNG-IUS users. When the unexpected finding of an increased risk of breast cancer among LNG-IUS users was found in the first study, and also the second study supported the previous findings, we decided to conduct a study among women with HMB but treated non-hormonally with endometrial ablation and assess their risk of breast cancer and other cancers, especially endometrial cancer.

LNG-IUS and breast cancer risk
We observed that risk of breast cancer among women treated with LNG-IUS for HMB was increased by 19% compared with the background population. This was a novel and unexpected finding. In absolute numbers, this means 2–4 excess cases of breast cancer per 1 000 LNG-IUS users followed for 10 years. Previously published studies had not observed an increase in the risk of premenopausal breast cancer among LNG-IUS users (Backman et al. 2005,

Dinger et al. 2011). Moreover, neither did a recent case-control study observe elevated risk of breast cancer among premenopausal women with prior LNG-IUS use (Heikkinen et al. 2016a). However, in the first published study on the topic (Backman et al. 2005), the follow-up was only 10 years, which is probably too short to detect differences in cancer incidence. Also, the comparisons of cancer incidence in that study were unusual, as the breast cancer incidence of the LNG-IUS users during the whole study period was compared with the breast cancer incidence of the background population for a single year (Backman et al. 2005). Two later studies (Dinger et al. 2011, Heikkinen et al. 2016a) were case-control studies, which carry significant limitations especially due to recall, misclassification, and selection biases. Women who are diagnosed with cancer might be more prone than healthy controls to report any use of hormonal preparations, and also misclassify the preparations they have used. Also, some of the breast cancer patients may have already died due to the most aggressive diseases, and were thus missed from the analysis.

In our study, a significant increase in breast cancer incidence among LNG-IUS users was observed during the first years of follow-up among women aged 50–54 years, but after 5 years, the risk was significantly elevated also in the younger age groups. The increased risk of breast cancer was most evident – 40% higher than in the general population – among women with two or more LNG-IUS purchases. In absolute numbers, this means approximately an excess of 7 breast cancers among 1 000 women with a history of two or more LNG-IUS purchases and followed for 10 years. The risk of both most common histological subtypes of breast cancer – ductal and lobular – was increased among LNG-IUS users. Moreover, the risk of lobular subtype, generally considered to be associated with the use of exogenous hormones, was 73% higher among LNG-IUS users than among other women. This means one extra case of lobular breast cancer among 1 000 LNG-IUS users followed for 10 years. In LNG-IUS users, during the first years of follow-up, the risk of localized breast cancer was higher than in the general population, but after 5 years of follow-up, the risk of non-localized breast cancer was also increased.

Altough it is possible that the mechanism explaining increased risk of breast cancer among LNG-IUS users is other than levonorgestrel per se, a causal effect of levonorgestrel on breast cancer promotion cannot be excluded. Several plausible biological mechanisms behind the possible adverse effect of levonorgestrel in the mammary tissue exist. Levonorgestrel is released continuously from the LNG-IUS, and continuous progestin administration has been associated with a higher risk of breast cancer compared with cyclical administration of progestin in studies among postmenopausal women (Lyytinen et al. 2009). Levonorgestrel may also have a proliferative effect on breast cells. It has been reported that the mitotic activity in breast cells obtained from women using levonorgestrel-containing contraceptive pills was significantly higher during the first week of the menstrual cycle than in women with a natural cycle (Garcia y Narvaiza et al. 2008). Additionally, levonorgestrel is the most potent progestin used in hormonal preparations (Dorflinger 1985), which could explain possible actions even in low systemic concentrations.

LNG-IUS and endometrial cancer risk

Our study was the first to show that LNG-IUS use during fertile years is associated with a decreased risk of endometrial cancer. Among the LNG-IUS users, after one purchase of LNG-IUS, the risk of endometrial adenocarcinoma was 54% lower than that of the general population. In absolute numbers, 3–6 cases of endometrial adenocarcinoma are prevented among 10 000 women using LNG-IUS and followed for 10 years. The protective association of LNG-IUS use against endometrial cancer was even stronger after two or more purchases of LNG-IUS, potentially reflecting the effect of long-term use of LNG-IUS. The incidence of endometrial adenocarcinoma among women with two or more purchases of LNG-IUS was 75% lower than in the general population. This means that approximately 8 cases of endometrial adenocarcinomas are prevented per 10 000 women with two or more LNG-IUSs and followed for 10 years. Our finding is in line with a study on postmenopausal women using LNG-IUS (Jaakkola et al. 2011). The risk of endometrial cancer has been reported to be decreased among copper IUD

users (Felix et al. 2015), and our results indicate that the risk is significantly lower with the hormonal intrauterine system.

In our study among fertile-aged women, virtually all endometrial cancers were endometrial adenocarcinomas possibly due to the young age distribution of our study population. During the past decade, endometrial cancer classification has changed, and it has been established that endometrial cancer is a heterogeneous group of tumors with distinct morphological, genetic, and risk characteristics with different prognoses (Murali et al. 2014). The effect of LNG-IUS use on the risk of specific endometrial cancer molecular subtypes with different mutational landscapes should be separately studied.

LNG-IUS use and risk of ovarian cancer or primary fallopian tube carcinoma

LNG-IUS use in relation to ovarian cancer was analyzed overall and separately according to tumor histology. The total risk of invasive ovarian cancer among LNG-IUS users was decreased by 41% compared with that of the general population of similar age. In absolute numbers, this means that 3–6 cases of invasive ovarian cancer are prevented among 10 000 LNG-IUS users followed for 10 years. The decrease in ovarian cancer risk was observed in the first years after the LNG-IUS purchase, and it was maintained during the whole follow-up. The risk of borderline ovarian tumors, precursors for invasive cancers, was also significantly lower among LNG-IUS users than among the other women. No previous studies exist on the effect of LNG-IUS use on ovarian cancer risk among premenopausal women, but a neutral effect was observed in a study among postmenopausal women with ET combined with LNG-IUS (Koskela-Niska et al. 2013b). However, the number of cases in that study was probably too sparse to detect significant associations.

In terms of histological subtypes, the risk decrease was largest for mucinous ovarian cancers among LNG-IUS users. The risk was decreased by 51% for mucinous invasive ovarian cancer compared with the general population. Also, the incidence of borderline ovarian tumors among LNG-IUS users was lower than in other women, yet it reached statistical significance only after 10 years

of follow-up. Before our studies, no previous reports existed on the effect of LNG-IUS on the risk of mucinous ovarian tumors.

Mucinous ovarian cancer is a distinct subtype of ovarian cancer, as it is suggested to originate from cells of gastrointestinal origin (Kelemen and Kobel 2011). Also, the risk factors for mucinous ovarian cancer differ from the other ovarian cancers (Kelemen and Kobel 2011). COCs have not been reported to provide protection from mucinous ovarian tumors (Schuler et al. 2013, Fortner et al. 2015), which may be reflected by the lower PR expression of mucinous tumors compared with the other ovarian cancers (Diep et al. 2015). Among postmenopausal women, the effect of HT on mucinous ovarian cancer risk is inconsistent (Yang et al. 2012, Koskela-Niska et al. 2013a, Collaborative Group on Epidemiological Studies of Ovarian Cancer et al. 2015, Fortner et al. 2015). Thus, our finding of a protective association of LNG-IUS use with mucinous ovarian cancer can be mediated by other mechanisms than the direct effect of levonorgestrel.

The risk of ovarian endometrioid carcinoma was almost halved among LNG-IUS users compared with the general population. Plausible biological mechanisms explaining the protective effect of LNG-IUS exist. Endometrioid ovarian cancer seems to originate from endometriotic cells and abundantly expresses PRs (Diep et al. 2013, Nezhat et al. 2015). LNG-IUS use significantly decreases menstrual bleeding and thus minimizes retrograde transportation of blood including endometriotic cells, growth factors, as well as inflammatory or carcinogenic factors into the fallopian tubes (Cramer and Xu 1995, Lethaby et al. 2015). Additionally, LNG-IUS is an efficient treatment for endometriosis, a risk factor for endometrioid ovarian cancer (Dunselman et al. 2014, Nezhat et al. 2015). Also, it can be hypothesized that the protective effect of LNG-IUS may be mediated via a direct progestin effect. The decreased ovulation theory probably does not explain the effect of LNG-IUS on ovarian cancer risk as LNG-IUS does not have any significant effect on ovarian function, or suppress ovulations (Nilsson et al. 1984).

The risk of clear cell carcinoma, which is also suggested to be of endometrial origin, was non-significantly decreased among LNG-IUS users. However, due

to the rarity of clear cell carcinomas and the low number of cases in our study, robust conclusions cannot be made.

The risk of the most common ovarian cancer, serous carcinoma, was 25% lower among LNG-IUS users than in the background population. A limitation of our study was that we were not able to distinguish serous ovarian carcinomas according to the new classification (Prat and FIGO Committee on Gynecologic Oncology 2014, Kurman et al. 2014) into high-grade and low-grade categories but analyzed all serous ovarian carcinomas as one group. High-grade serous ovarian cancer originates from the distal fallopian tubes and is the most lethal ovarian cancer (Kurman and Shih 2010, Crum et al. 2012). Low-grade serous ovarian cancer subtype has more indolent character, and expresses higher levels of PRs compared with high-grade serous subtype (Kurman and Shih 2010, Diep et al. 2015). Due to the heterogeneous character of high-grade and low-grade serous ovarian cancers, more separate studies on the effect of LNG-IUS use for the serous ovarian cancer subtypes are needed.

The incidence of PFTC among LNG-IUS users was comparable with that of the general population. No other reports have been published on LNG-IUS use at reproductive ages and later PFTC risk. Among postmenopausal women with long-term estrogen treatment combined with LNG-IUS use for more than 5 years, an increased risk of PFTC has been reported (Koskela-Niska et al. 2015). However, due to the rarity of PFTC, more studies with larger cohorts are needed.

LNG-IUS use and risks of other cancers
The risk of pancreatic cancer among LNG-IUS users was only one-half of that in the background population. The incidence of pancreatic cancer is markedly lower among women than among men (www.cancerregistry.fi) (Ilic and Ilic 2016). Female hormone exposure may play a role in this, but more likely explanations may be related to the confirmed risk factors for pancreatic cancer, most importantly smoking. The women in our LNG-IUS cohort also had significantly lower lung cancer incidence than the background population, suggesting that LNG-IUS users smoke less than the other Finnish women. This

should also be taken into account when interpreting the SIRs of the other smoking-related cancers among the LNG-IUS users.

In our study, the risk of cervical cancers, including squamous cell cancers and adenocarcinomas of the cervix, did not differ between LNG-IUS users and the general population. Persistent high-risk HPV infection is the cause of cervical cancer, but only one previous report on the role of LNG-IUS as a potential cofactor exists. In that small observational study, LNG-IUS use was not associated with precancerous cervical atypia (Lessard et al. 2008). Non-hormonal IUD use has been reported to be associated with a halved risk of cervical cancer (Castellsague et al. 2011). Our results are in line with these previous studies.

Endometrial ablation and cancer risk
In the study on endometrial ablation treated Finnish women, we found that the total cancer risk of these women was similar to that of the background population.

The risk of breast cancer among women treated with endometrial ablation was not increased and was comparable with that of other Finnish women. This is in line with the only previous study assessing breast cancer incidence after endometrial ablation (Cooper et al. 2011). A similar incidence of breast cancer to that of other women suggests that HMB per se is not a risk factor for breast cancer. This finding should be taken into account when interpreting the results of breast cancer risk among women using LNG-IUS for HMB.

We found that the risk of endometrial cancer was not altered after endometrial ablation. This is a reassuring finding as traditionally premenopausal AUB has been considered to be associated with an increased risk of endometrial cancer (Soliman et al. 2005). Moreover, according to a recent systematic review (Pennant et al. 2017), premenopausal AUB is not associated with increased prevalence of endometrial cancer (1.31%, 95% CI 0.96–1.80), and the prevalence of endometrial cancer was even lower among women with HMB (0.11%, 95% CI 0.04–0.32) (Pennant et al. 2017). In our study, the proportion

of women diagnosed with endometrial cancer after endometrial ablation was 0.05%, which is even lower (Pennant et al. 2017), and is similar to that of a large Scottish study (Cooper et al. 2011). This suggests that women suffering from HMB are not at an increased risk of endometrial cancer.

In our study, the majority of endometrial ablation treated women were parous, which is a protective factor against breast cancer and endometrial cancer. If the endometrial ablation treated women had more pregnancies than the background population, the risk estimates for breast cancer and endometrial cancer would be too low.

The risk of ovarian cancer or cervical cancer after endometrial ablation was not increased in our study. Only one previous report on the incidence of these cancers after endometrial ablation exists (Cooper et al. 2011), and our results are in line with that study. However, based on the small numbers of observed ovarian and cervical cancers in our study, robust conclusions cannot be made.

Hysterectomy after endometrial ablation

In our study, most women (80%) treated with endometrial ablation did not need a later hysterectomy, which is comparable with the results from other studies based on second-generation endometrial ablations. In our study, the most common indication for postablation hysterectomy in half of the cases was HMB, and the second most common cause was leiomyomas in every fifth case. The risk of hysterectomy was highest during the first 2 years, but remained higher than that of other women during the whole follow-up. Compared with the other women of similar age, women treated with endometrial ablation had an almost 4-fold risk of hysterectomy. The significantly elevated risk of hysterectomy during the first couple of years after endometrial ablation has also been observed in other studies (Cooper et al. 2011, Shavell et al. 2012).

The risk of postablation hysterectomy was highest among those women with leiomyomas as the main indication at endometrial ablation. The role of leiomyomas as a risk factor for failure of endometrial ablation is inconsistent. Leiomyomas have been a significant risk factor for hysterectomy in some studies (Bansi-Matharu et al. 2013, Wishall et al. 2014) but not in others

(Longinotti et al. 2008, El-Nashar et al. 2009, Shavell et al. 2012). However, the role of leiomyomas as a risk factor is difficult to interpret, as most studies have not reported the sizes or locations of the leiomyomas. In our study, age younger than 35 years at ablation was also a significant risk factor, which is also observed in several other studies (Longinotti et al. 2008, El-Nashar et al. 2009, Shavell et al. 2012, Bansi-Matharu et al. 2013). Additionally, women with two or more prior cesarean sections before endometrial ablation were at significant risk of later hysterectomy, which is reported in some studies (Shavell et al. 2012, Wishall et al. 2014). Also, a prior sterilization before endometrial ablation was a risk factor for postablation hysterectomy in our study. Results from the other studies on sterilization as a risk factor are inconclusive (El-Nashar et al. 2009, Shavell et al. 2012, Wishall et al. 2014). Moreover, this finding should be interpreted carefully, as the majority of women treated with endometrial ablation were sterilized in our study. This reflects the policy of high recommendation of sterilization before endometrial ablation in Finland.

Endometrial ablations in Finland

According to our findings, there are significant variations in the incidence of endometrial ablations by different hospital districts in Finland. This was an unexpected finding and may reflect variations in clinical practices in the management of patients with HMB. As newer non-hysteroscopic endometrial ablations have shown to be similarly effective for HMB compared with LNG-IUS, have a good safety profile, and most endometrial ablation treated women seem to avoid later hysterectomy, a new evidence-based national guideline for the treatment of HMB is needed.

Study strengths and limitations

It is important to understand the strengths and limitations of observational register-based studies before drawing conclusions. Our study had many strengths. We had a large number of subjects due to the population-based

study setting. We also had detailed and complete information on LNG-IUS reimbursements since 1994 from the Medical Reimbursement Register as well as information on endometrial ablations from the Hospital Discharge Register, which reduces selection bias. However, selection bias cannot be excluded, as LNG-IUSs were used for HMB and these women might represent a special population with different intrinsic risk factors (i.e., anovulation, hyperestrogenism) to the general population. We also had a long follow-up in the studies, which is mandatory in epidemiological cancer research as cancer development from precursors to detectable invasive tumors takes years. With the high-quality register data from our national law-based registers, we had virtually no losses to follow-up. We also had complete information on surgical operations from the Hospital Discharge Register, cancer diagnoses from the Finnish Cancer Registry, and information on emigration and deaths from the Population Register Centre. This makes recall bias impossible.

There are also many limitations in this type of study based on registers, and thus the results should be interpreted with caution. Register-based studies are observational in nature and can only give information on the associations between risk factors and cancers. In a cohort study setting, the control of all potential confounding factors (e.g., age at menarche, use of other exogenous hormones, lifestyle factors, family history of cancer) is difficult, and confirmation of causality must usually be confirmed by other study settings.

In the LNG-IUS studies (Studies I–III) we could not verify that the LNG-IUS insertion truly happened, but it is likely, as the LNG-IUSs in the study population were prescribed for the treatment of HMB, women had to cover the costs of the LNG-IUS purchase from their own pocket, and only a minor portion of the price was reimbursed. Repeat purchases are also likely to reduce this potential bias. Neither did we have data on the duration of LNG-IUS use after insertion. However, most women continue LNG-IUS therapy long-term after insertion, as the continuation rate at 48 months has been reported to be over 70% in women aged over 29 years (Diedrich et al. 2015). Whether the effect of LNG-IUS use disappears as time elapses from the discontinuation of use, is unknown. In COC users, the excess risk of breast cancer has been reported to disappear after 10 years of cessation of COC (CGHFBC 1996,

Bassuk and Manson 2015), but the protective effect on the endometrium and ovaries remains for decades (Schlesselman 1997, Collaborative Group on Epidemiological Studies of Ovarian Cancer 2008, Havrilesky et al. 2013).

We did not have information on COC use or parity in the LNG-IUS studies. Use of COCs may modify the risk of cancers such as breast, endometrial, and ovarian cancer. LNG-IUS users might be more commonly parous and the increase in parity is associated with a decreased risk of breast, endometrial, and ovarian cancer. If that was the case, the risk estimates for these cancers would be too low. We did not have data on performed mammographies among the LNG-IUS users. In Finland, organized mammography screening is not offered for women under 50 years. However, according to a recent study (Heikkinen et al. 2016b), approximately two-thirds of women have had mammographies before the organized screening. Whether LNG-IUS users are overrepresented in those women with opportunistic mammographies, is unknown. However, our finding that SIRs for ductal carcinoma in situ (DCIS) lesions, most of which are detected by mammography, were lower than for invasive breast cancers, suggested that the frequency of mammographies among LNG-IUS users is comparable with that of other women. A surveillance bias could not be totally excluded, as breast tenderness is common among LNG-IUS users (Leminen et al. 2012) and may lead to more frequent clinical breast examinations. Regarding the assessment of ovarian cancer risk, a surveillance bias is also possible. LNG-IUS users often have transient ovarian cysts (Lethaby et al. 2015), which also may result in more frequent and closer monitoring of these women in health care. In such cases, more borderline tumors and invasive ovarian cancers might be diagnosed.

One shortcoming of this study is that the LNG-IUS users (Studies I–III) and endometrial ablation treated women (Study IV) were compared with a reference population which also included the corresponding study group (i.e., LNG-IUS users or endometrial ablation treated women) and women with previous hysterectomy or salpingo-oophorectomy. Therefore, the risk estimates are lower than they would be if the reference population had been without women who had undergone these surgical operations, without users of LNG-IUS, and without endometrial ablation treated women. However, the

diluting effect is small due to the relatively small number of LNG-IUS users and endometrial ablation treated women in the background population.

Despite the limitations, a large cohort study based on high-quality registers is a suitable way to assess cancer risks among a fertile-aged population. It would never be possible to conduct a prospective randomized study among young women with LNG-IUS at cohort size and with sufficient follow-up to evaluate the risk of malignancy.

Clinical implications

Both LNG-IUS and endometrial ablation have been shown to be equally effective on HMB as a means of reducing menstrual blood loss and regarding patient satisfaction (Marjoribanks et al. 2016). Both these treatments are superior in cost-effectiveness compared with hysterectomy. The decision of how to treat HMB depends on the woman's desire to preserve fertility, her acceptance of and suitability for hormonal or surgical treatment, and risk–benefit estimations.

The most important finding of our studies was the contrasting associations of LNG-IUS use on endometrial cancer and breast cancer risk. The leading aim of our studies was to assess the risk of endometrial cancer among LNG-IUS users. The protective effect of LNG-IUS use against endometrial cancer among premenopausal women was a novel but expected finding. Based on this finding, fertile-aged women with known risk factors for endometrial cancer (i.e., obesity, anovulatory HMB) could potentially benefit from intrauterine levonorgestrel treatment with regards to endometrial protection. However, future studies are needed to assess the molecular biological effects of intrauterine levonorgestrel. Recent data indicate that endometrial cancer is a heterogenic disease (dualistic pathway) with different mutational and hormone receptor landscapes (Murali et al. 2014) and it is possible that the effect of progestins on different subtypes of endometrial cancer may vary.

The finding of increased risk of breast cancer among fertile-aged LNG-IUS users was a novel and unexpected finding. As breast cancer is globally a vast burden and the most common female cancer, all factors increasing breast cancer risk should be thoroughly elucidated. A slight increase in breast cancer risk can have a significant impact at the population level. Previously it has been thought that the low level of levonorgestrel released from LNG-IUS into the systemic circulation may not affect the breast, and even breast cancer patients have used LNG-IUS. However, both our findings of elevated breast cancer incidence among fertile-aged women and the previous findings among postmenopausal LNG-IUS users places the long-term use of LNG-IUS under

a new light. More studies are needed, especially on different molecular subtypes (i.e., steroid hormone receptor contents, HER2 status) of breast cancers among LNG-IUS users. In addition, there is an urgent need for studies on the safety of LNG-IUS use among breast cancer survivors.

Ovarian cancer is also a heterogeneous disease, and the effect of progestins on protection from this cancer varies. Our result showing the protective association of LNG-IUS use during fertile years on the risk of epithelial ovarian cancers was novel, which necessitates future studies on the effects of levonorgestrel on ovarian carcinogenesis, especially on the most deadly type, serous high-grade ovarian cancer.

Of note is that cancer development usually takes years and many factors associated with increased cancer risk are modifiable (i.e., obesity, smoking, and excess use of alcohol). It has been estimated that 30% of breast cancers could be preventable by maintaining a healthy lifestyle (Howell et al. 2014). It is thus especially important to identify early in life those women at high risk of cancer who would benefit from the preventive efforts. Given the well-recognized increase of endometrial cancer incidence as well as the epidemic of obesity in the Western world in the last decades, even a slight decrease in endometrial cancer risk due to LNG-IUS use could have a public health importance. This finding encourages further studies on the use of LNG-IUS for the primary prevention of endometrial cancer in populations most at risk.

HMB is a common complaint and hormonal treatment with LNG-IUS for HMB is in many cases the best option. Some hormonal treatments of HMB may affect later cancer risk but it is unknown whether the effect is transient.

It is important to weigh the beneficial effects of LNG-IUS and mini-invasive surgery (endometrial ablation) for HMB against the potential risks, and decide the treatment of HMB based on these facts together with the patient.

Conclusions

On the basis of the studies included in this thesis, the following conclusions can be drawn:

1. The use of LNG-IUS for HMB is associated with a significantly decreased risk of endometrial cancer.

2. The risk of breast cancer is higher among women using LNG-IUS for HMB than in the background population.

3. Lobular breast cancer is associated most strongly with LNG-IUS use, but also the risk of the ductal subtype is elevated among LNG-IUS users.

4. The risk of all epithelial ovarian cancers is decreased among women using LNG-IUS for HMB. The risk is most decreased for mucinous, endometrioid, and serous subtypes of ovarian cancer. The risk is also decreased for borderline ovarian tumors.

5. The risk of endometrial cancer after endometrial ablation is similar to that of the background population.

6. The risk of breast cancer among women with endometrial ablation is not increased.

7. The majority (80%) of women do not need a hysterectomy after endometrial ablation.

8. The risk of postablation hysterectomy is highest during the first years after endometrial ablation. Risk factors for hysterectomy are leiomyomas, age under 35 years, and a history of prior cesarean deliveries or sterilization.

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Tuusula, August 2017

Tuuli Soini

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