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A Nationwide Study on Breast Cancer Risk in Postmenopausal Women Using Hormone Therapy in Finland

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Academic Dissertation

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To my family

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LIST OF ORIGINAL PUBLICATIONS

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

I Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. Obstet Gynecol 2006;108:1354-60.

II Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestagen therapy. Obstet Gynecol 2009; 113:65-73.

III Lyytinen H, Dyba T, Ylikorkala O, Pukkala E. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: Intrauterine system carries a risk as well. Int J Cancer (published on line: Jul 8 2009).

IV Lyytinen H, Dyba T, Pukkala E, Ylikorkala O. Do the dose or route of administration of progestagen as a part of hormone therapy play a role in risk of breast cancer: Nation-wide comparative data on norethisterone acetate in Finland (tentatively approved by Int J Cancer).

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ABBREVIATIONS

BRCA1/2	breast cancer gene 1/2
BMD	bone mineral density
BMI	body mass index
CEE	conjugated equine estrogens
CI	confidence interval
EPT	estrogen-progestagen therapy
ER	estrogen receptor
ET	estrogen-only therapy
HDL	high density lipoprotein
HR	hazard ratio
HT	postmenopausal hormone therapy
LNG	levonorgestrel
LNG-IUS	levonorgestrel releasing intrauterine system
MPA	medroxyprogesterone acetate
NETA	norethisterone acetate
OR	odds ratio
RR	relative risk
SIR	standardized incidence ratio
WHI	Women's health initiative

ABSTRACT

Since national differences exist in genes, environment, diet and life habits and also in the use of postmenopausal hormone therapy (HT), the associations between different hormone therapies and the risk for breast cancer were studied among Finnish postmenopausal women.

All Finnish women over 50 years of age who used HT were identified from the national medical reimbursement register, established in 1994, and followed up for breast cancer incidence (n= 8,382 cases) until 2005 with the aid of the Finnish Cancer Registry. The risk for breast cancer in HT users was compared to that in the general female population of the same age.

Among women using oral or transdermal estradiol alone (ET) (n = 110,984) during the study period 1994-2002 the standardized incidence ratio (SIR) for breast cancer in users for < 5 years was 0.93 (95% confidence interval (CI) 0.80–1.04), and in users for ≥ 5 years 1.44 (1.29–1.59). This therapy was associated with similar rises in ductal and lobular types of breast cancer. Both localized stage (1.45; 1.26–1.66) and cancers spread to regional nodes (1.35; 1.09–1.65) were associated with the use of systemic ET. Oral estriol or vaginal estrogens were not accompanied with a risk for breast cancer.

The use of estrogen-progestagen therapy (EPT) in the study period 1994-2005 (n= 221,551) was accompanied with an increased incidence of breast cancer (1.31;1.20-1.42) among women using oral or transdermal EPT for 3-5 years, and the incidence increased along with the increasing duration of exposure (≥10 years, 2.07;1.84-2.30). Continuous EPT entailed a significantly higher (2.44; 2.17-2.72) breast cancer incidence compared to sequential EPT (1.78; 1.64-1.90) after 5 years of use. The use of norethisterone acetate (NETA) as a supplement to estradiol was accompanied with a higher incidence of breast cancer after 5 years of use (2.03; 1.88-2.18) than that of medroxyprogesterone acetate (MPA) (1.64; 1.49-1.79). The SIR for the lobular type of breast cancer was increased within 3 years of EPT exposure (1.35; 1.18-1.53), and the incidence of the lobular type of breast cancer (2.93; 2.33-3.64) was significantly higher than that of the ductal type (1.92; 1.67-2.18) after 10 years of exposure.

To control for some confounding factors, two case control studies were performed. All Finnish women between the ages of 50-62 in 1995-2007 and diagnosed with a first invasive breast cancer (n= 9,956) were identified from the Finnish Cancer Registry, and 3 controls of similar age (n=29,868) without breast cancer were retrieved from the Finnish national population registry. Subjects were linked to the medical reimbursement register for defining the HT use.

The use of ET was not associated with an increased risk for breast cancer (1.00; 0.92-1.08). Neither was progestagen-only therapy used less than 3 years. However, the use of tibolone was associated with an elevated risk for breast cancer (1.39; 1.07-1.81). The case-control study confirmed the results of EPT regarding sequential vs. continuous use of progestagen, including progestagen released continuously by an intrauterine device; the increased risk was seen already within 3 years of use (1.65;1.32-2.07). The dose of NETA was not a determinant as regards the breast cancer risk.

Both systemic ET, and EPT are associated with an elevation in the risk for breast cancer. These risks resemble to a large extent those seen in several other countries. The use of an intrauterine system alone or as a complement to systemic estradiol is also associated with a breast cancer risk. These data emphasize the need for detailed information to women who are considering starting the use of HT.

INTRODUCTION

Breast cancer is the most common malignancy among women in Western countries, and its incidence has increased in recent decades (*Parkin et al 2001*). In Finland, more than 4000 invasive breast cancers were diagnosed in 2007, which comprises one third of all female cancers (www.cancerregistry.fi). There are many explanations for the increase in the breast cancer incidence, such as organized mammographic screening programs (*Moller et al 2005*), increased life-expectancy and changes in established risk factors such as advanced age at first pregnancy, low parity and overweight (*Hakulinen et al 1989*).

The majority of the risk factors are associated with either endogenous levels or the use of exogenous estrogens (*Yager and Davidson 2006*); for instance, breast cancer occurs 150 times more often among women than men (*Clemons and Goss 2001*). Furthermore, more than 100 years ago, it was demonstrated that bilateral oophorectomy resulted in a remission of breast cancer in premenopausal women. Early menarche, late menopause, low parity and postmenopausal obesity are characterized with a prolonged exposure to endogenous estrogens and an increased breast cancer risk. Yet, not all risk factors are linked to estrogens, and e.g. genetic mutations or radiation (*Ronckers et al 2005, Oldenburg et al 2007*) may also lead to breast cancer.

Because endogenous hyperestrogenism appears to predispose to breast cancer risk, it is no wonder that exogenous use of estrogens, alone or in combination with progestagen, is associated with an increased risk for breast cancer, as demonstrated in a pooled analysis of 51 epidemiological studies (*Collaborative Group on Hormonal Factors in Breast Cancer 1997*). Since then, numerous studies have analyzed the associations between the use of postmenopausal hormone therapy (HT) and breast cancer in different countries (*Bakken et al 2004, Collins et al 2005, Fournier et al 2008, Flesch-Janys et al 2008*).

The use of HT, mammography screening programs, genes and lifestyles vary from one country to another (*McPherson et al 2000, Clemons and Goss 2001, Key et al 2003, Oldenburg et al 2007*). Therefore, it is possible that the HT use may have a nation-specific effect on the risk for breast cancer. The present studies aimed to clarify the risk for breast cancer among Finnish postmenopausal women using different HT regimens.

Menopause

Natural menopause is defined as a spontaneus cessation of natural menstruation for 12 consecutive months at 45-55 years (mean 50-52) (*McKinlay et al 1992*). A woman enters menopause through a perimenopause period of 4-5 years, when ovarian function declines gradually. The final cause for ovarian suppression may be a genetically controlled apoptosis (e.g. *Vaskivuo and Tapanainen 2003*). At menopause, a drastic decline in circulating estrogens occurs, and this may lead to various symptoms and consequences (*Stearns et al 2002*).

Immediate symptoms

The symptoms which may occur before and/or within the first months of menopause are defined as immediate symptoms. They include vasomotor symptoms, such as hot flushes and night sweats, which are the most characteristic for menopause. Vasomotor symptoms are present in 70-80% of postmenopausal women (*Stearns et al 2002*). The reason for hot flushes is unknown, but the basis appears to be the hypoestrogenism-induced alteration in the hypothalamic thermo-regulatory centre (*Sturdee 2008*). Vasomotor symptoms almost always break the sleeping pattern and can be accompanied with dizziness and anxiety (*Kopernik and Shoham 2004*). A woman with hot flushes can also often be depressive. Immediate symptoms are the leading cause to initiate HT use in clinical practice.

Long term consequences

Advancing age per se is certainly associated with a number of health risks. However, there are some specific conditions which start to appear in the postmenopause.

Genital atrophy

After the onset of menopause, the vaginal epithelium becomes atrophic, and the pH rises. Atrophy itself, or in association with inflammatory changes, can cause vaginal dryness, itching, discomfort and dyspareunia (*Castelo-Branco et al 2005*). Similar changes can occur in the urethral and/or bladder epithelium, which may predispose to urinary incontinence, dysuria and infections (*Cardozo et al 1998*). All these conditions become more common in postmenopausal women not using any estrogen therapy.

Osteoporosis

Both bone-forming osteoblasts and bone-resorpting osteoclasts have alfa and beta estrogen receptors (*Bord et al 2001*), indicating that bone is a target for estrogen. Bone mass, bone mineral density (BMD) and bone strength are highest around 25-35 years of age and remain stable until the menopause, when bone loss begins (*Kleerekoper and Gold 2008*). This is a result of hypoestrogenism, which induces bone resorption not compensated by adequate bone formation. Other hypoestrogenic conditions, such as premature ovarian failure, ovariectomy and anorexia also predispose to osteoporosis (*American College of Obstetricians and Gynecologists Women's Health Care 2004*). Bone loss can be 1-2% annually after menopause, being highest during the first 5-7 years (*Kanis and Melton 1994*). Osteoporosis is defined by The World Health Organization criteria

as a BMD that is at least a 2.5 standard deviation below the average value for young, healthy women (T-score < -2.5). In Finland, it is estimated that approximately 400 000 people have osteoporosis and 30,000-40,000 osteoporotic fractures are diagnosed annually (*The Finnish Current Care Guidelines, Finnish Medical Society Duodecim*, www.kaypahoito.fi). According to a population based study in Eastern Finland, up to 7% of women aged 47-56 years are osteoporotic and every third woman of the same age osteopenic (T-score between -1- -2.5). (*Tuppurainen M 1995*). It can be generalized that 40% of women over 50 years will experience a bone fracture during the rest of her lifetime, although a majority of fractures occur in women over 75 years (*Kopernik and Sholam 2004*). The high risk for osteoporosis after menopause is one important cause in clinical practice to initiate HT to preserve the bone.

Cardiovascular diseases

Before menopause, a woman's risk to have a cardiovascular disease is considerably smaller as compared to men (*Kopernik and Sholam 2004*), but this risk increases rather soon after menopause; the prevalence of cardiovascular diseases being equal among men and women by the age of 70 (*Lobo 2007*). Furthermore, epidemiological studies have shown that premature menopause, either natural or artificial, increases the risk of cardiovascular disease, compared to menstruating women of the same age (*Atsma et al 2006, Lokkegaard et al 2006*). The causes of these phenomena are unknown, but the decline in estrogen levels after menopause is the most common explanation (*Barret-Connor 1997*). After menopause with declining estrogen levels, high-density lipoprotein cholesterol levels gradually decrease, and this decrease is greatest during the first year after menopause. With advancing age, triglycerides, systolic and diastolic pressure, weight and the levels of low-density lipoprotein cholesterol increases, together with increasing insulin resistance (*Turgeon 2006, Collins et al 2007*); these factors are important in developing cardiovascular diseases. There are several mechanisms by which estrogen may protect against the risk for cardiovascular diseases. Estrogen alters serum lipid concentrations by increasing high-density lipoprotein and decreasing low-density lipoprotein cholesterol levels. It increases the production of vasoactive molecules, such as nitric oxide and prostacyclin, which are important factors in vasodilatation. Furthermore, estrogen increases insulin sensitivity, all of which in turn reduce the risk of vascular disorders (*Lobo 2008*).

Cognition and dementia

The brain is one of the target organs of estrogen. Estrogen enhances synaptic plasticity, neurite growth, hippocampal neurogenesis, and long-term potentiation, which is a process involved in the formation of episodic memories (*Henderson 2008*). During the menopause, many women report a worsening of the memory. This might be a secondary phenomenon to hot flushes and broken sleep, because there is no evidence that estrogen deficiency among postmenopausal women is a direct cause of cognitive decline (*Alhola et al 2006, Herlitz et al 2007, Henderson 2008, Lethaby et al 2008*).

Dementia can be caused by multiple factors, of which Alzheimer's disease is the most common. Alzheimer's disease is more common among postmenopausal women than in men of the same age (*Burns and Iliffe 2009*). This may hint at a role of hypoestrogenism as a cause of Alzheimer's disease, but no such conclusive evidence exists so far.

Hormone therapy

Estrogen-replacement therapy has been used for more than 60 years (*Warren 2004, Stefanick 2005*). In the US, conjugated equine estrogens (CEE), which are obtained exclusively from pregnant mares' urine, have been used for substitution, while in Europe the predominant estrogen has been 17beta-estradiol. The most common progestagen in the US is medroxyprogesterone acetate (MPA), but in Europe a large variety of different progestagens are available. In Scandinavia and the UK, norethisterone acetate (NETA) and levonorgestrel (LNG) are preferred, while MPA is used to a lesser extent. In Central and Southern Europe, micronized progesterone and dydrogesterone are predominant (*Campagnoli et al 2005*). Moreover, there are some alternatives to the traditional HT such as tibolone, testosterone, phytoestrogens and selective estrogen-receptor modulators (SERM).

Estrogen-only therapy

Estrogen-only therapy (ET) comprises systemic and vaginal use of estrogens, although in medical writing the term of ET is reserved to the systemic use of estrogen. According to the Finnish guidelines, only hysterectomized women can use systemic ET, because the long term ET is accompanied with a risk for endometrial cancer (*Stefanick 2005*). Estradiol is the only potent systemic estrogen available in Finland. There are many modalities to use systemic estradiol which is by far the most effective therapy for alleviating menopausal symptoms alone, or together with progestagen. Estradiol is also available vaginally (Table 1). Estradiol is oxidized reversibly to estrone and both estradiol and estrone are converted to estriol in the liver (*Coelingh Bennink 2004*). The significance of estriol as HT is limited, due to its poor estrogenic effect. However, vaginal use of estriol can alleviate vaginal atrophy.

Table 1. **Estrogens available for the use of postmenopausal women in Finland**

Administration	Dose
Oral	
Estradiol	1.0mg, 2.0mg
Estriol	1.0mg, 2.0mg
Transdermal	
Patch	25-100µg
Gel	0.5mg, 1mg, 0.6mg/g, 1mg/g
Vaginal	
Estradiol	
Tablet	25µg
Ring	7.5µg/24h
Estriol	
Suppository	0.5mg
Creme	1.0mg/g, 0.1mg/g

Estrogen-progestagen therapy

A progestagen component, as a complement to estrogen, is needed only in nonhysterectomized women. Progestagen protects the endometrium against hyperplasia and malignant transformation (*Manson 2001*), which ET use can cause. Progestagen can be administered either sequentially, in addition to estrogen, for 10-14 days each month or continuously when both estrogen and progestagen are given every day. In a long cycle sequential regimen, progestagen is administered every three months for 14 days. Both oral and transdermal EPT preparations are available in fixed commercial preparations. In clinical practice, women often combine estrogen and progestagen individually. In Finland several regimens with different doses and administrations are available (Table 2).

Table 2. **Type and dose of progestagens in fixed commercial estrogen-progestagen therapy**

Sequential progestagen	**Dose (mg)**	**Continuous progestagen**	**Dose (mg)**
Oral		Oral	
Norethisterone acetate	1	Norethisterone acetate	0.5, 0.7, 1
Medroxyprogesterone acetate	10, 20	Medroxyprogesterone acetate	2.5, 5
Levonorgestrel	0.25	Dydrogesterone	5
Dydrogesterone	10, 20	Drospirenone	2
Trimegestone	0.5		
Transdermal		Transdermal	
Norethisterone acetate	0.17, 0.25	Norethisterone acetate	0.17, 0.25
Levonorgestrel	0.01, 0.02		
Type and dose of progestagens in individually formed EPT			
Oral		Intrauterine administration	
Dydrogesterone	10-20	Levonorgestrel	0.02
Progesterone	100-300		
Norethisterone	2.5-5		
Medroxyprogesterone acetate	5, 10		
Megestrol acetate	10		

Progestagens

Progestagens can be divided to natural progesterone and synthetic progestagens. Progesterone is the most specific and binds exclusively to a progesterone receptor. Dydrogesterone is closest to progesterone. It is retroprogesterone, a stereoisomer of progesterone and binds almost exclusively to progestagen receptors, thus having only effects mediated by progesterone receptors (*Shindler et al 2003*). Synthetic progestagens can be further divided to 17alfa-hydroxyprogesterone derivates (MPA, megestol acetate) and 19-norprogesterone derivates (trimegestone), 19-nortestosterone derivates (norethisterone/acetate, lynestrenol, levonorgestrel) and spironolactone derivates (drospirenone) (table 3). They show some variation in biological activities, which is also dependent on the tissue concentrations of a given progestagen.

Table 3. **Biological activities of progestagens used in hormone therapy**

	pro-gestogenic	anti-gonado-tropic	anti-estrogenic	estrogenic	androgenic	anti-androgenic	gluco-corticoid	anti-mineralo-corticoid
Progesterone	+	+	+	-	-	±	+	+
Dydrogesterone	+	-	+	-	-	±	-	±
Progesterone derivates								
MPA[1]	+	+	+	-	±	-	+	-
Megestrol acetate	+	+	+	-	±	+	+	-
Trimegestone	+	+	+	-	-	±	-	±
Testosterone derivates								
Norethisteronea cetate	+	+	+	+	+	-	-	-
Levonorgestrel	+	+	+	-	+	-	-	-
Lynesterol	+	+	+	+	+	-	-	-
Spironolactone derivates								
Drospirenone	+	+	+	-	-	+	-	+

(Adapted from Schindler 2003) + effective; (+-) weakly effective; (-) not effective. [1]Medroxyprogesterone acetate. Data are based mainly on animal experiments.

Tibolone

Tibolone is a synthetic steroid, the pharmacological and clinical profile of which is different from those of estrogens and progestagens. Tibolone taken orally is metabolized in the liver and intestine into active metabolites, two of which binds estrogen receptors and one which binds to progesterone and androgen receptors. Thus, tibolone has estrogenic, progestagenic and androgenic properties (*Kloosterboer 2001, Notelovitz et al 2007*). Tibolone use does not cause withdrawal bleedings.

Selective estrogen receptor modulators, phytoestrogens, testosterone

The selective estrogen receptor modulator (SERM) was originally defined as a compound that binds with high affinity to the estrogen receptor (ER), without significant binding activity to any other nuclear receptor. Later, SERMs were defined as a class of synthetic compounds which bind to the ER and produce agonistic activity in some tissues while being an estrogen antagonist in others (*Riggs et al 2003*). However, each SERM may have a unique clinical response which is not applicable to another SERM (*Shelly et al 2008*). Antiestrogenic effects of SERMs have been successfully used as adjuvant therapy (tamoxifen, toremifene) in the prevention of the recurrence of ER positive breast cancer. Raloxifene, another widely used SERM, is effective for the prevention of osteoporosis. Ospemifene, being now in phase III clinical trials, is well tolerated, does not cause or worsen hot flushes, and has an estrogenic effect on vaginal epithelium (*Rutanen et al 2003*). Ospemifene is comparable to raloxifene as regards effects on bone turnover and therefore, it may also be a potential drug for the prevention and treatment of osteoporosis in postmenopausal women.

Plant extracts that exhibit estrogenic activities, are called phytoestrogens (*Murkies et al 1998*). Phytoestrogens are classified into three main classes: isoflavones, lignans, and coumestans. They have estrogen-like structure, which enables them to bind ERs, although they are not steroids. In alleviating menopausal symptoms, phytoestrogens are not proven to be effective (*see e.g. Nikander et al 2003*).

Postmenopause is often characterized with low sexual desire (*Sarrel et al 1998, Leiblum et al 2006*). This does not respond well to ET and/or EPT, which has led to the use of testosterone in women with low libido, because female sexual desire is in part androgen dependent (*Somboonporn et al 2005*). The European Agency for the Evaluation of Medical Products recently approved a testosterone patch as a therapy for hypoactive sexual desire.

Effects of hormone therapy

Although hormones used as the components of HT mimic natural hormones, and certainly give some benefits, it is understandable that they are also associated with desired and undesired effects; no medical agent is completely safe, because a risk of side-effects always exists (Table 4).

Table 4. **Benefits, controversial effects and risks of long-term hormone therapy (references, see the text)**		
Benefits	**Controversial effects**	**Risks**
Alleviation of vasomotor symptoms	Dementia	Venous tromboembolism (oral therapy)
Strengthening of urogenital epithelium	Coronary artery disease	Stroke
Prevention of osteoporosis		Endometrial cancer (ET^2, sequential EPT)
Protection against colon cancer		Breast cancer
Protection against endometrial cancer (continuous EPT[1])		
[1]Estrogen-progestagen therapy, [2]estrogen-only therapy.		

Benefits

Improvement of vasomotor symptoms and urogenital atrophy

Estrogen most effectively alleviates vasomotor symptoms already within a few days use (*Notelowitz et al 2000, MacLennan 2001, and Stearns et al 2002*), and this relief is dependent on the estrogen dose (*Notelowitz et al 2000, Ettinger 2005, 2007*). Because mood and sleep disturbances are strongly associated with vasomotor symptoms, relieving these symptoms improves the quality of life (Table 4.) (*Welton et al 2008*). Estrogen therapy is also effective against urogenital atrophy. Both vaginal and systemic estrogen therapies are effective in this regard (*Cardozo et al 1998*).

Prevention of osteoporosis

Estrogen reduces the activity of osteoclasts and increases their apoptosis, thus decreasing the postmenopausal bone loss (*Manolagas 2000*). A meta-analysis of 22 trials on hormone therapy and fractures demonstrated an overall 27% reduction in nonvertebral fractures (*Torgerson and Bell-Syer 2001*). The risk for vertebral fractures was 34% lower, and the risk for nonvertebral fractures was 13% lower among HT users compared to nonusers (*Wells et al 2002*). The Women's Health Initiative (WHI) trial was the first randomized clinical trial which showed a significant reduction of hip (hazard ratio (HR) 0.61;0.41-0.91) and vertebral fractures (HR 0.62; 0.42-0.93), with estrogen use among women without risk factors for osteoporosis (*Anderson et al 2004*). Because the BMD is the best single predictor of fracture risk in postmenopausal women, it has been used to evaluate the efficacy of drugs used for the treatment of osteoporosis. The bone strengthening effect of HT is established both in the spine and hip after 2 years of treatment (*Wells et al 2002*).

Protection against colon cancer

Meta-analyses have shown a reduction of 33-34% in colon cancer in users of HT (*Nanda et al 1999, Grodstein et al 1999*). The mechanism behind the protective effect of HT is not fully understood, although several theories have been suggested (*Newcomb et al 2008*). The Women's Health Initiative reported a reduction of colorectal cancers by 37% among EPT users after a mean of 5.2

years of use, although the colon cancer of EPT users was diagnosed at a more advanced stage than that in the placebo group (*Rossouw et al 2002*). The reduction of the risk for colon cancer was not seen among ET users in another arm of the same study (*Anderson et al 2004*), although contradicting data on ET exist (*Newcomb et al 1995, Johnson et al 2009*).

Controversial effects

Alzheimer's disease and dementia

Estrogen may have neurotrophic and neuroprotective properties (*Inestrosa et al 1998, Turgeon et al 2006*). This is supported by observational studies showing a 39-50% decline in the risk for Alzheimer's disease among women using HT (*Turgeon et al 2006*). However, the only large randomized controlled trial could not confirm this result; on the contrary, the use of HT increased this risk. In this study, HT users were 65-79 years at the initiation of HT (*Shumaker et al 2003, 2004*), which is not a typical age to start the use of HT. It is suggested that there can be a critical period when HT is still protective against dementia (*Henderson 2008*). Moreover, dementia in the randomized trial was mostly due to vascular reasons and not due to Alzheimer's disease (*Shumaker et al 2004*).

Coronary artery disease

Observational studies have shown a significantly decreased risk for myocardial infarction among current HT users (*Barrett-Connor and Grady 1998, Grodstein et al 2000*). Yet, this effect was not seen in randomized controlled trials. In contrast, HT appeared to elevate the risk of myocardial infarction both in primary (*Rossouw et al 2002, Anderson et al 2004*) and secondary prevention trials (*Grady et al 2002*). Recent meta-analysis concluded that HT reduces the risk of cardiac events among younger postmenopausal women, while among older postmenopausal women the risk increases during the first year of use, but decreases after 2 years of use (*Salpeter et al 2006*). Estrogen therapy initiated in women at 50 to 59 years of age may reduce plaque formation in the coronary arteries and then be protective against the risk of myocardial infarction in younger postmenopausal women (*Mikkola and Clarkson 2002, Mikkola and Ylikorkala 2005, Manson et al 2007*). In this regard, hot flushes may be an important determinant, because they are associated with beneficial changes in endothelial function (see e.g. *Tuomikoski et al 2009*).

Risks

Venous tromboembolism

The impact of estrogen on fibrinolysis and coagulation is complex. Estrogen reduces the fibrinogen concentration in plasma, activates fibrinolysis and thus, it increases the risk of venous tromboembolism (*Grodstein et al 1996, Braunstein et al 2002*). The association between HT use and venous tromboembolism is well demonstrated (*Sare et al 2008, Canonico et al 2008*), and it increases the risk of tromboembolism 2-fold (*Rossouw et al 2002, Anderson et al 2004, Sare et al 2008, Canonino et al 2008*); the risk of venous tromboembolism being highest during the first year of use (*Miller et al 2002*). There is some evidence that EPT would increase the risk more than ET alone (*Sare et al 2008*), and this effect may be progestagen-specific (*Canonico et al 2007*). Recent studies have demonstrated a lower risk for the transdermal administration of estrogen compared to an oral one, or no risk at all (*Scarabin et al 2003, Canonico et al 2007*).

Stroke

The increased risk of stroke among ET (HR 1.39; 1.10-1.77, mean follow-up 6.8 years) (*Anderson et al 2004*) and EPT (1.41; 1.07-1.85, mean follow-up 5.2 years) (*Rossouw et al 2002*) users was one of the reasons which led to an early termination of the WHI randomized controlled trials. A previous large observational study (Nurses' health study) had reported a slightly elevated risk for stroke (relative risk (RR) 1.35; 1.08-1.68) among ET/EPT users with the dose of ≥ 0.625 mg CEE. However, the lower dose was not associated with an increased risk for stroke (*Grodstein et al 2000*). A meta-analysis of observational studies, including the Nurses' health study, showed an increased stroke incidence among ever users of HT (*Miller et al 2002*), but the Heart and Estrogen/progestagen Replacement Study, a randomized controlled trial on the effect of EPT on coronary heart disease, reported no increase in strokes (*Grady et al 2002*). The recent analysis of the Nurses' health study evaluated the risk for stroke among younger and older women using HT, but the risk appeared not to be related to the age at the initiation of HT (*Grodstein et al 2008*).

Endometrial cancer

A prolonged use of estrogen predisposes to the hyperplasia and malignant transformation of the endometrium (*Smith et al 1975*). A one year use of unopposed estrogen is accompanied with a 1.4-fold risk for endometrial cancer, and in 10 years of use the risk increases 9.5-fold. The risk of estrogen can be eliminated by adding progestagen to estrogen, either sequentially or continuously (*Manson et al 2001*). The continuous EPT regimen is associated with an even smaller risk of endometrial cancer than in women not using HT (*Weiderpass et al 1999*, *Wells et al 2002*). The risk reduction of endometrial cancer was also seen in a Finnish study after 3 years of use (standardized incidence ratio (SIR) 0.24; 95% CI 0.06-0.60). However, the use of a sequential EPT regimen for 5 years was accompanied with a modest risk elevation (1.69; 1.43-1.96) (*Jaakkola et al 2009*, accepted for publication).

Breast cancer

Approximately every 10th woman in Finland will have breast cancer during her life-time, and almost every woman has at least one friend or relative affected by this disease. Therefore, it is no surprise that breast cancer is the leading cause for cancer fear, despite the considerably improved prognosis of this disease.

Diagnostics and screening

The diagnosis of breast lesions includes palpation, imaging the breast by mammography or ultrasound and histological or cytological examination by fine needle aspiration or thick needle biopsies (*Hermansen et al 1987*). The most common imaging method of breasts is the mammography. Population-based screenings were started in Finland in 1987. All women between 50-62 years are invited to screenings (in some communities up to age of 69) every second year. The coverage of the screenings in Finland is 95-100% (*Dean and Pamilo 1999, Sarkeala et al 2008*), and 90% of the invited women take part in these screenings.

Incidence

Breast cancer is the most common cancer among women comprising one fifth of all cancers worldwide (*Bray et al 2004, Colditz et al 2006*). The incidence has been increasing in recent decades (Figure 1) (*Engholm et al 2009*), and in 2007, 4160 new breast cancer cases were diagnosed in Finland, comprising 31% of all female cancer cases. Breast cancer is more common in large urban areas (Figure 2) and has been more common among women with higher socioeconomic status (www.cancerregistry.fi).

Figure 1**. Number of women diagnosed with breast cancer in ages 45-85+ during 1953-2007 in Finland (Engholm et al 2009)**

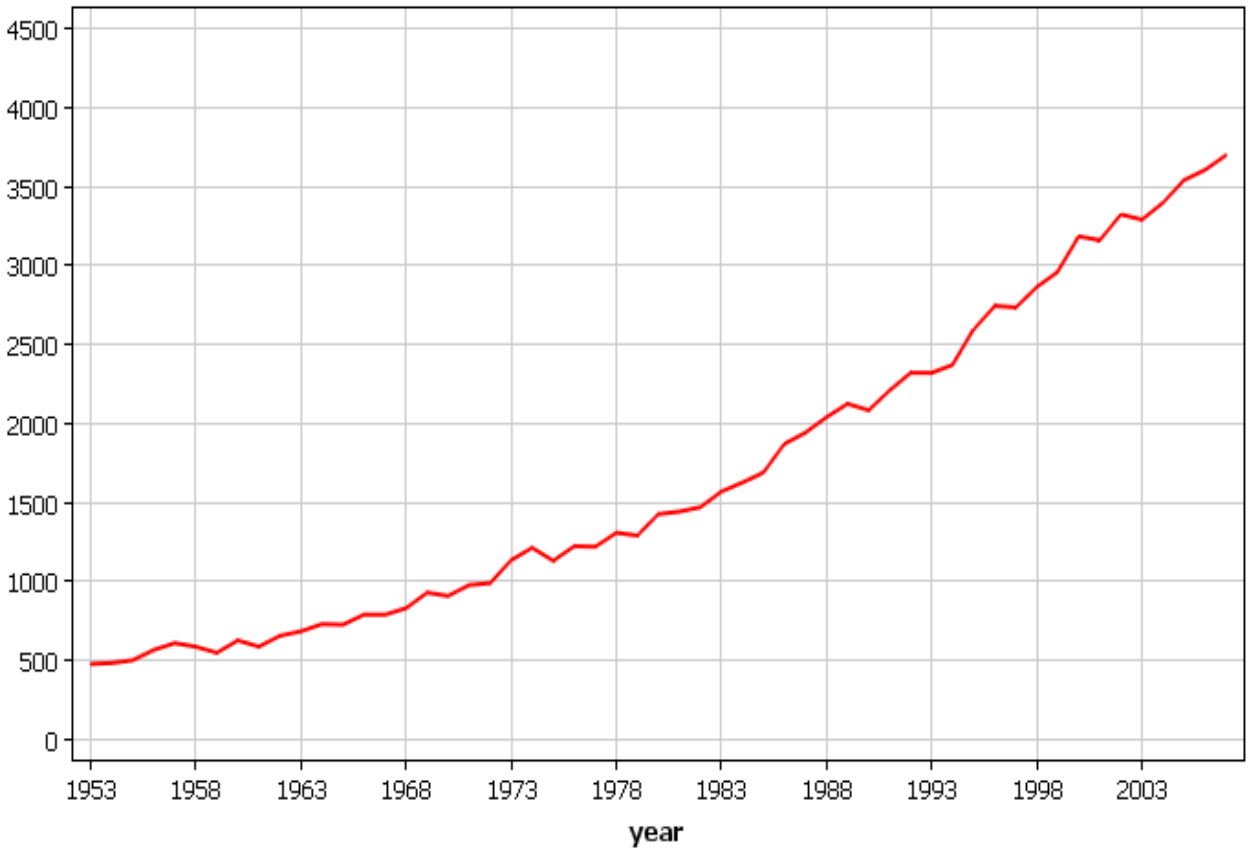
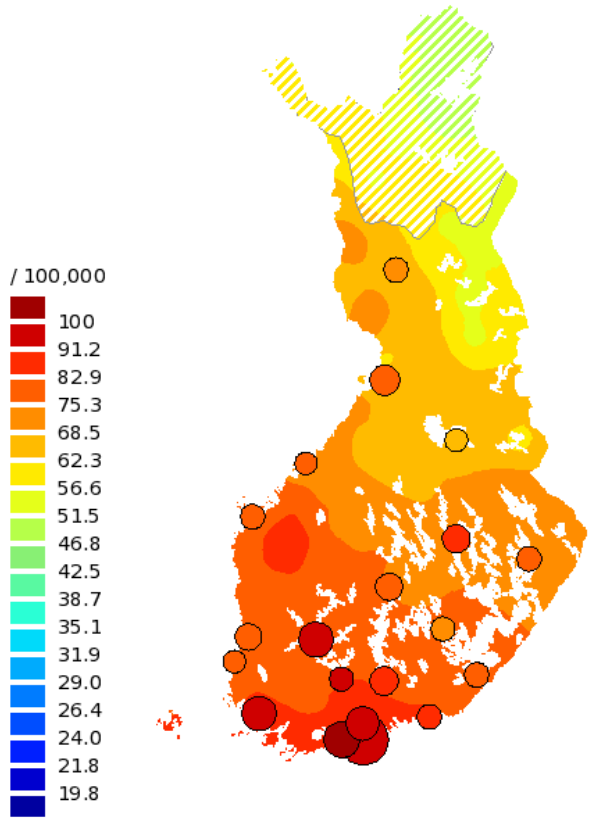


Figure 2. **Incidence of breast cancer in Finland in 1997-2006 (www.cancerregistry.fi)**



Survival and mortality

In recent decades, the mortality for breast cancer has been decreasing (*Hermon and Beral 1996, Boyle and Ferlay 2005)*. In Finland the mortality was 14.4 per 100,000 in 2007, and the relative 5-year survival rate in 2003-2005 was 89% (www.cancerregistry.fi). It has been calculated that the screening reduces the breast cancer mortality by 22% (*Sarkeala et al 2008*).

Risk factors

Breast cancer is a multifactoral disease, which is affected by reproductive, hormonal and genetic factors. Lifestyle and environmental features are also involved. (Table 4).

Table 4. **Some risk factors for breast cancer**		
Factor	Risk group[1]	Relative risk (RR)
Sex	Female	150
Age	≥ 50	> 6.5
Age at menarche	Menarche before age 12	1.5-3.0
Age at menopause	Menopause after age 54	2.0
Age at first birth	First child after 30	1.9-3.5
Parity	Nulliparous	1.4
Benign breast disease	Proliferative lesion with atypia Proliferative lesion without atypia	3.5-5 1.5-2.0
Family history of breast cancer	Breast cancer in first degree relative	> 2.0
Height	> 175 cm	1.5
Weight	Postmenopausal BMI[2] > 35	2.0
Alcohol use	2 drinks/day	1.2
Exposure to ionising radiation	Abnormal exposure in young females after age 10	3.0
Modified from McPherson 2000, Clemons and Goss 2001, Singletary 2003. [1]Relative risk compared with the low-risk population. [2] Body mass index.		

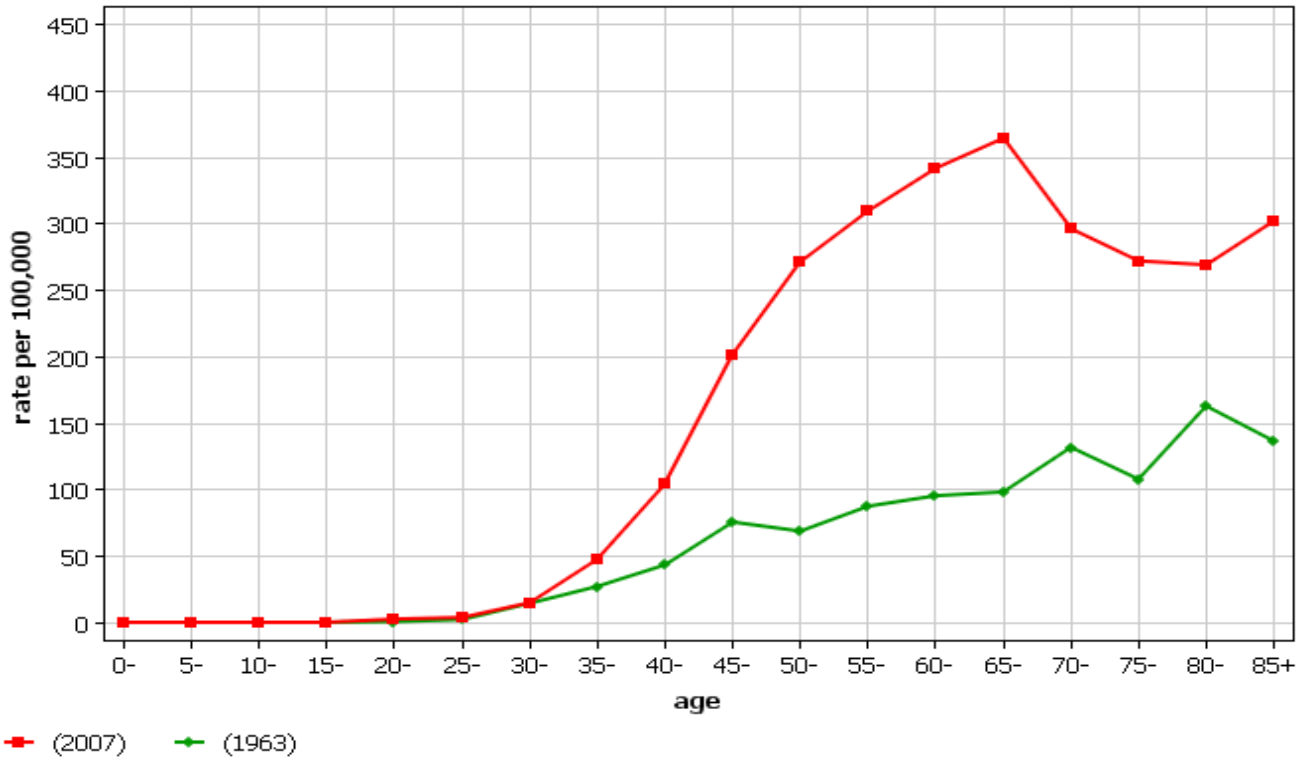
Gender

Female gender is a strong risk factor for breast cancer. Women have a 150-fold higher breast cancer risk than men (*Clemons and Goss 2001*, *Engholm et al 2009*). This is evidently due to female sex hormones. Conditions which lead to high estrogen levels in men are also associated with male breast cancer (*Weiss 2005*).

Advanced age

Breast cancer incidence increases rapidly after age of 40, but after the age of 65 the incidence decreases (Figure 3). Mammographic screening program from 1987 in Finland has been accompanied with an increased incidence of breast cancer among women aged 50-59 as demonstrated in figure 3 (*Engholm et al 2009*).

Figure 3. **Incidence of breast cancer in 1963 and 2007 in Finland, by age. The organised mammography screening of breast cancer was started in 1987 (Engholm et al 2009)**



Age at menarche and menopause

Women experiencing menarche before 12 years have a 50% higher risk for breast compared to women having menarche when older than 14 years (*Clemons and Goss 2001*). Likewise, the delayed menopause is associated with a risk elevation of 3% for each delayed year (*Cuzick 2003*). Both early menarche and late menopause increase the length of lifetime exposure to endogenous female sex hormones which hints at the importance of these hormones in the development of breast cancer.

Age at first birth and parity

Full-term pregnancy has a protective effect against breast cancer risk. During pregnancy, both estrogen and progestagen cause proliferation and differentiation of the ductal and lobular-alveolar epithelium, which ultimately reduces the risk for malignant transformation of the breast tissue (*Russo et al 1982*). Human breast tissue also contains receptors for human chorionic gonadotropin and luteinizing hormones. Human chorionic gonadotropin and pregnancy may affect the expression of certain genes and growth factors which inhibit cell proliferation. Human chorionic gonadotropin may be the most important protective factor (*Russo and Russo 2000*). The earlier the first full-term pregnancy has occurred, the lower the risk (*Ramon 1996 et al, Hinkula et al 2001*). Women older than 30 at first delivery have a 2- 3.5 –fold higher risk for breast cancer, compared to women whose first delivery was before 21(*Ramon et al 1996, Hinkula et al 2001*). The risk of breast cancer

decreases by approximately 10% per birth (*Ewertz et al 1990, Hinkula et al 2001*). Even if the first birth is at age 30 or later, multiparity (5 deliveries) has a protective effect against breast cancer (*Hinkula et al 2001*).

Benign breast disease

Heterogenous groups of proliferative and non-proliferative breast lesions are defined as benign breast diseases. These include benign tumors, trauma, mastalgia, mastitis, and nipple discharge (*Miltenburg and Speights 2008*). Non-proliferative lesions are not associated with breast cancer risk, but proliferative lesions, either with (3.5-5-fold) or without atypia (1.5-2-fold), are associated with an increased risk for breast cancer (*Cuzick 2003*). Proliferative diseases account for 25-30% of all benign breast diseases, of which 5-10% show proliferative lesions with cellular atypia. Both benign and malignant breast disease can present similar symptoms with a palpable mass or an abnormal screening mammogram with no clinical findings (*Miltenburg and Speights 2008*).

Family history

Approximately 30% of all breast cancer patients have relatives with breast cancer (*Lichtenstein et al 2000*). If a first-degree relative has breast cancer, the risk for breast cancer is elevated approximately 2-fold (*Collaborative Group on Hormonal Factors in Breast Cancer 2001, Oldenburg 2007*). The risk increases with the number of relatives affected and is greater for women with relatives affected at young age (*Olderburg et al 2007*). The overall lifetime breast cancer risk for women without a family history of breast cancer is 7.8%. For those who have one first degree-relative affected, the risk is 13.3%, and for those having two, the risk is 21.1% (*Collaborative Group on Hormonal Factors in Breast Cancer 2001*).

Breast cancer genes

It has been approximated that 5-10% of all breast cancers are caused by mutations in well-identified breast cancer susceptibility genes. The two most important mutations are the high-risk breast cancer genes BRCA1 and BRCA2. However, these mutations only account for a part of the genetic susceptibility of breast cancer (*Oldenburg 2007*). In a large meta-analysis, the cumulative risk for breast cancer by age 70 among BRCA1 carriers was 65%, and among BRCA2 carriers the risk for breast cancer was 46% (*Antoniou et al 2003*). In a Finnish study, the risk for breast cancer among first-degree relatives of a BRCA1 carrier was 6-12 fold, and for a BRCA2 carrier 5-11-fold (*Eerola et al 2001*).

Alcohol use

Alcohol use is associated with an increased risk for breast cancer (*Longnecker 1994, Smith-Warner et al 1998, Zhang et al 2007*). This elevation may be 9-11% with a daily consumption of one alcoholic drink (10g/d) (*Longnecker 1994, Smith-Warner 1998*), and the risk increase is linear up to 6 drinks. The mechanism of alcohol-induced elevation in breast cancer risk is unknown, but increased levels of estrogen and androgen appear important. Alcohol may also enhance the susceptibility of mammary cells to carcinogenesis and increase the metastatic potential of breast cancer cells (*Singletary and Gapstur 2001*).

Size of a woman

Obesity is associated with a risk for breast cancer. However, obesity in childhood has not proven to have an effect on the risk of breast cancer later in life (*Huang et al 1997*), but weight gain after the age of 18 or after menopause is associated with increased risk of breast cancer among postmenopausal women (*Eliassen et al 2006*). On the contrary, a higher body mass index (BMI) at 18 years is associated with a lower risk of breast cancer in premenopausal life and, in some studies in postmenopausal life as well (*Huang et al 1997*). A high BMI (>31 vs. < 21) is also associated with a 46% lower risk for breast cancer in premenopause (*Friedenreich 2001*). One explanation for the increased risk for breast cancer after menopause in obese women is the high amount of endogenous estrogens produced in adipose tissue. Furthermore, obesity increases the circulating concentrations of insulin, which may be associated with the risk for breast cancer (*Friedenreich 2001*). Tall women appear to have a higher risk for breast cancer (*Friedenreich 2001*). Childhood energy intake, the cumulative exposure to growth hormone and insulin-like growth factor-I, or the number of ductal stem cells in the mammary gland have been proposed as potential biologic mechanisms associated with an increased breast cancer risk among tall women.

Hormone therapy and breast cancer

As evidenced before, conditions characterized with endogenous hyperestrogenism are associated with an elevated risk for breast cancer. Therefore, it is expected that the exogenous use of female sex steroids may increase the risk for breast cancer. A pooled analysis of 51 epidemiological studies defined the association between breast cancer and HT (*Collaborative Group on Hormonal Factors in Breast Cancer 1997*). This finding has been confirmed later by numerous studies (see *reviews Collins et al 2005, Lee et al 2005*). However, recent reports which have focused on more precise analyses on the association between different therapies and breast cancer have produced inconclusive data. So far, only one randomized controlled trial has had enough power to evaluate the breast cancer risk with different hormone therapies. This study failed to found any association with breast cancer and estrogen-only therapy (CEE 0.625 mg/d) in 6.8 years' of use (HR 0.77, 95% CI 0.59-1.01) (*Anderson et al 2004*) but the EPT (CEE 0.625 mg/d and MPA 2.5 mg/d) was accompanied with an elevated risk for breast cancer (1.24; 95% CI 1.01-1.54) (*Rossouw et al 2002*). This result, together with the adverse effects of HT on cardiovascular events, has changed the policy of prescribing HT in the Western world.

Estrogen-only therapy

A meta-analysis of 45 studies on the use of ET revealed no association between ET and the risk of breast cancer (*Bush et al 2001*). Later on, numerous observational studies have reported either an increased risk or no impact on the risk for breast cancer associated with the use of ET (table 5). The largest cohort study so far showed that the current use of ET was accompanied by an increased risk for breast cancer (RR 1.25, 95% CI 1.10–1.41) already in 1-4 years of use (*Beral et al 2003*). In contrast, ET in a placebo-controlled study (CEE) was associated with an almost statistically significant decrease in the risk for breast cancer (HR 0.77; CI 0.59–1.01) (*Anderson et al 2004*). In a Finnish study on ET use, the mean duration of 8.2 years, was not accompanied with an increased risk for breast cancer (*Sourander et al 1998*). However, the association between ET and breast cancer may be relative to the duration of the use (Table 5).

Table 5. **Previous data on the use of estrogen-only therapy and the risk for breast cancer**

Study	Design	Type of estrogen	Duration of use	RR/HR/OR[2]
Collaborative Group on Hormonal Factors in Breast Cancer 1997	Pooled analysis of 51 studies (Median age at first use 48 years) 52,705 cases	mostly CEE[1]	< 5 years ≥ 5 years	0.99 (0.065) 1.35 (1.21-1.49)
Sourander et al 1998	cohort 7,944 97 cases	estradiol	mean duration 8.2 years	1.00 (0.47-1.90)
Magnusson et al 1999	case-control (50-74 years) 3,345/3,454	mostly estradiol	≤ 2 years > 2 ≤ 5 years > 5 ≤ 10 years 10+ years	1.72 (1.13-2.62) 1.49 (0.85-2.63) 2.18 (1.07-4.45) 2.70 (1.47-4.96)
Colditz et al 2000	cohort (50-70 years) 58,520 1,761 cases	CEE	10 years	1.23 (1.06-1.42)
Shairer et al 2000	cohort (BMI ≤ 24.4) (58+ years) 46,335	mostly CEE	< 8 years 8 < 16 years ≥ 10 years	1.00 (0.80-1.30) 1.50 (1.20-2.00) 1.60 (1.20-2.20)
Chen et al 2002	case-control (50-74 years) 705/692	CEE	≤ 3 years > 3 < 5 years ≥ 5 years	1.13 (0.64-2.01) 1.45 (0.84-2.49) 1.84 (1.04-3.27)
Kirsh et al 2002	case-control (20-74 years) 404/403	not given	1-9 years ≥ 10 years	1.00 (0.44-2.24) 1.74 (0.93-3.24)
Newcomb et al 2002	case-control (50-79 years) 5,298/5,951	mostly CEE	< 5 years ≥ 5 years	1.08 (0.92-1.27) 1.36 (1.17-1.58)
Porch et al 2002	cohort (≥ 45 years) 17 835 411 cases	not given	< 5 years ≥ 5 years	0.95 (0.64-1.40) 0.87 (0.65-1.53)
Weiss et al 2002	case-control (35-64 years) 1,870/1,953	not given	6 mo < 2 years 2 < 5years 5+ years	0.83 (0.55-1.27) 1.00 (0.67-1.50) 0.97 (0.68-1.37)
Li et al 2003a	case-control (65-79 years) 975/1,007	not given	6 months < 5 years ≥ 5 < 15 years ≥ 15 < 25 years ≥ 25 years	0.80 (0.60-1.20) 1.20 (0.80-1.70) 1.30 (0.90-1.90) 1.00 (0.70-1.40)
Olsson et al 2003	cohort 29,508 556 cases	estradiol	1-4 years > 4 years	0.77 (0.38-1.57) 0.58 (0.22-1.55)
Beral et al 2003	cohort 1,084,110 (50-64 years) 9364 cases	CEE/estradiol	1-4 years 5-9 years ≥ 10 years	1.25 (1.10-1.41) 1.32 (1.20-1.45) 1.37 (1.22-1.54)
Anderson et al 2004	RCT[3] (50-79 years) 10,739 (94 vs 124)	CEE	6.8 years	0.77 (0.59-1.01)

Bakken et al 2004	cohort (45-64 years) 67,336 624 cases	not given	< 5 years ≥ 5 years	2.50 (1.40-4.50) 1.00 (0.40-2.50)
Stahlberg et al 2004	cohort (≥ 45 years) 19,898 244 cases	estradiol	Mean duration 7.2 years	1.96 (1.16-3.35)
Fournier et al 2008	cohort (mean age at start of HT 52.4 years) 80 337 2,354 cases	mostly estradiol	Mean duration 7 years	1.29 (1.02-1.65)
Flesch-Janys et al 2008	case-control (50-74 years) 3,464/6,657	not given	< 5 years 5-<10 years 10-<15 years 15+ years	0.92 (0.80-1.07) 1.13 (0.94-1.35) 1.16 (0.95-1.43) 1.09 (0.85-1.39)
Opatrny et al 2008	case-control (50-75 years) 6,347/31,516	mostly CEE	Mean duration 2891 days	1.22 (0.74-2.00)

[1]Conjugated equine estrogens; [2]RR=relative risk, HR=hazard ratio, OR=odds ratio; [3]randomized placebo-controlled trial

Route of administration

The impact of the route of administration of estrogen for health benefits and non-malignant risks has been much studied (*see e.g. Cacciatore et al 2001, Strandberg et al 2003, Scarabin et al 2003, Canonico et al 2007*). In contrast, the data on whether the estrogen effect on breast cancer is dependent on the route of administration are sparse. The English study found no difference between oral and transdermal administration as regards to the risk for breast cancer, but the analyses were based only on the regimen which was used at the time of interview (*Beral et al 2003*). Yet, previous data may imply that the different estrogenic milieu in users of oral and transdermal estrogen might similarly affect breast cells.

Dose

A longer exposure to estrogen appears to be limited to the higher risk for breast cancer, as discussed above. Therefore, it may be plausible that also the dose of estrogen is a determinant, although in a pooled analysis of 51 epidemiological studies no differences between various doses of CEE were determined (*Collaborative Group on Hormonal Factors in Breast Cancer 1997*). Furthermore, in a large cohort study of 58 520 nurses (*Colditz et al 2000*), no dose-dependence was found, whereas in another study, a trend toward higher relative risks with higher doses of CEE was seen (*Porch et al 2002*). The study in the UK failed to show any dependence between the doses of estradiol and CEE and the risk for breast cancer (*Beral et al 2003*).

Estrogen-progestagen therapy

It is generally accepted that postmenopausal EPT is accompanied with a higher risk of breast cancer than estrogen alone (Table 6). This risk elevation is primarily attributed to the progestagen

component of EPT; the first data published on this association was already in the late 80s (*Bergkvist et al 1989*). Later, particularly that therapy with CEE for a mean 6.8 years was not associated with an increased risk of breast cancer (*Anderson et al 2004, Collins et al 2005*), but CEE given together with progestagen, was associated with an increased risk of breast cancer in 5.2 years (*Rossouw et al 2002*), confirmed this association.

Mode of administration and duration of use

It can be concluded from the above that progestagen as a complement to estrogen appears to be an established risk factor. The mode of progestagen administration may also be a significant determinant. Abundant data have shown that sequential administration appears safer than continuous use (*Magnusson et al 1999, Weiss et al 2002, Newcomb et al 2002, Jernström et al 2003, Olsson et al 2003 Stahlberg et al 2004, Flesch-Janys et al 2008*), although data are not uniform in this regard (*Ross et al 2000, Beral et al 2003, Li et al 2003a, Opatrny et al 2008*). Additionally, there is no clear-cut duration of exposure after which the risk for breast cancer increases significantly. In less than 5 years of use, a slightly increased risk associated with either sequential or continuous progestagen use is seen (*Magnusson et al 1999, Ross et al 2000, Chen et al 2002, Bakken et al 2004*) (table 6).

Type of progestagen

Progestagens can act as a proliferative or as an antiproliferative agent in the breast, depending on the dose, type of progestagen, and duration of exposure. Progestagens can bind with various steroid receptors with different affinity and exert different effects on breast cell proliferation, to modify estrogen metabolizing enzymes, cell cycle, growth factors and oncogenes (*Pasqualini et al 1998*). Several in vitro studies have shown differences between progestagens towards normal breast cells and breast cancer cells (*Seeger and Mueck 2008*). Progestagens may also induce proliferation in breast tissue through paracrine mechanisms, i.e. in the circumstances which cannot be modelled in the culture cell lines (*Lange 2008*). Therefore, discordant opinions exist on the effects of various progestagens on breast cancer risk.

Medroxyprogesterone acetate has been primarily used in US studies, and the increased breast cancer risk associated with MPA containing EPT was confirmed in the WHI trial (*Rossouw et al 2002*). In Scandinavia, norethisterone acetate (NETA) and levonorgestrel (LNG) are the most common progestagens, and in Scandinavian studies, the risk for breast cancer has been reported to be slightly higher compared to the US studies (*Lee et al 2005*). This may imply that NETA and LNG could carry a higher risk than MPA. It has been speculated that MPA, being a 17alfa-hydroxyprogesterone derivate, affects breasts more physiologically than NETA, which is a derivate of 19-nortestosterone (*Campagnoli et al 2005*). However, a large cohort study from the UK reported no marked differences between MPA, NETA and levonorgestrel (*Beral et al 2003*). In France, where the most used progestagens are dydrogesterone and progesterone, no increased risk of breast cancer was seen among users of these progestagens combined with estrogen (*Fournier et al 2008*). It should also be noted that the preferred estrogen component in the USA is CEE, in contrast to Scandinavian countries where estradiol is a leading commercial estrogen. Therefore, it may not be justified to compare only different progestagens and the risk for breast cancer between various countries if the estrogen component of EPT is not the same.

Table 6. **Previous data on estrogen-progestagen therapy (EPT) and risk for breast cancer**

Study	Design	Mode of regimen	Duration of use	RR/HR/OR[1]
Magnusson et al 1999	case-control (50-74 years) 3,345/3,454	EPTsequential	≤ 2 years > 2 ≤ 5 years > 5 ≤ 10 years 10+ years	1.58 (1.01-2.46) 1.34 (0.71-2.54) 1.89 (0.88-4.09) 2.45 (0.82-7.30)
		EPTcontinuous	≤ 2 years > 2 ≤ 5 years > 5 ≤ 10 years 10+ years	0.93 (0.63-1.36) 1.26 (0.76-2.09) 2.89 (1.66-5.00) 5.36 (1.47-19.56)
Ross et al 2000	case-control (55-72 years) 1,897/1,637	EPTsequential	≤ 5 years > 5 ≤ 10 years 10+ years EPTcontinuous	1.19 1.58 1.79 per 5 y 1.38 (1.13-1.68)
			≤ 5 years > 5 ≤ 10 years 10+ years	0.88 1.28 1.23 per 5 y 1.09 ns (0.88-1.35)
Chen et al 2002	case-control (50-74 years) 705/692	EPTsequential	≤ 1 years > 1 < 3 years ≥ 3	1.37 (0.85-2.20) 1.00 (0.59-1.71) 1.62 (1.03-2.55)
		EPTcontinuous	≤ 6 months 7-19 months ≥ 20 months	0.85 (0.36-2.03) 1.32 (0.60-2.89) 1.85 (1.03-2.55)
Newcomb et al 2002	case-control (50-79 years) 5,298/5,951	EPT	<5 years ≥ 5 years	1.32 (1.02-1.70) 1.50 (1.09-2.06)
		EPTsequential EPTcontinuous		0.96 (0.70-1.31) 1.54 (1.15-2.07)
Olsson et al 2003	cohort 29,508 556 cases	EPTsequential	1-4 years > 4 years	1.18 (0.62-2.23) 1.44 (0.67-3.08)
		EPTcontinuous	1-4 years > 4 years	2.01 (1.14-3.55) 3.13 (1.70-5.75)
Weiss et al 2002	case-control (35-64 years) 1,870/1,953	EPTsequential	< 2 years 2-<5 years 5+ years	0.72 (0.42-1.24) 1.44 (0.79-2.61) 1.18 (0.70-1.98)
		EPTcontinuous	< 2 years 2-<5 years 5+ years	1.11 (0.71-1.75) 1.38 (0.86-2.22) 1.77 (1.04-3.01)
Li et al 2003a	case-control (65-79 years) 975/1,007	EPTsequential	6 months < 5 years ≥ 5 < 15 years ≥ 15 years	1.50 (0.80-2.80) 1.70 (1.00-3.00) 2.90 (1.30-6.60)
		EPTcontinuous	6 months < 5 years ≥ 5 < 15 years ≥ 15 years	1.30 (0.90-2.00) 2.00 (1.30-3.00) 1.80 (1.00-3.30)

Beral et al 2003	cohort (50-64 years) 1,084,110 9,364 cases	EPTsequential EPTcontinuous	< 5 years ≥ 5 years < 5 years ≥ 5 years	1.77 (1.59-1.97) 2.12 (1.95-2.30) 1.57 (1.37-1.79) 2.40 (2.15-2.67)
Chlebowski et al 2003	RCT[2] (50-79 years) 16,608 199 vs 150 cases	EPTcontinuous	5.2 years	1.24 (1.01-1.54)
Bakken et al 2004	cohort (45-64 years) 67,336 624 cases	EPTsequential EPTcontinuous	< 5 years ≥ 5 years < 5 years ≥ 5 years	1.70 (1.00-2.80) 2.20 (1.30-3.80) 2.60 (1.90-3.70) 3.20 (2.20-4.60)
Jernström et al 2004	cohort (50-64 years) 6,586 101 cases	EPTcontinuous	≤ 2 years > 2 ≤ 4 years > 4 years	3.00 (1.30-7.00) 1.50 (0.45-5.30) 3.20 (1.40-7.20)
Stahlberg et al 2004	cohort (≥ 45 years) 19,898 244 cases	EPTsequential EPTcontinuous	< 5 years 5-9 years 10+ years < 5 years 5-9 years 10+ years	1.58 (0.79-3.17) 2.47 (1.23-4.95) 2.18 (1.09-4.33) 1.96 (0.72-5.36) 4.96 (2.16-11.39) 6.78 (3.41-13.48)
Ewertz et al 2005	cohort (40-67 years) 78,380 1462 cases	EPTsequential	current use	1.52 (1.21-1.93)
Opatrny et al 2008	case-control (50-75 years) 6,347/31,516	EPTsequential EPTcontinuous	Mean duration 2681 days	1.33 (1.21-1.46) 1.29 (1.07-1.56)
Flesch-Janys et al 2008	case-control (50-74 years) 3,464/6,657	EPTsequential EPTcontinuous	< 5 years 5-<10 years 10-<15 years 15+ years < 5 years 5-<10 years 10-<15 years 15+ years	1.03 (0.87-1.22) 1.30 (1.10-1.54) 1.39 (1.13-1.69) 1.37 (1.04-1.80) 1.11 (0.96-1.28) 1.88 (1.59-2.23) 2.04 (1.66-2.50) 1.91 (1.46-2.49)

[1] RR=relative risk, HR=hazard ratio, OR=odds ratio; [2] randomized placebo-controlled trial

Route of administration

Oral EPT has been in use much longer than transdermal EPT. Therefore, most data on the risk of breast cancer in HT users have been accumulated from its oral use. Progestagen for endometrial protection can be administered by intrauterine system and such a use of levonorgestrel was not associated with increased risk of breast cancer among women aged 35-54, but these women were not treated with estrogen (*Backman et al 2005*).

Tibolone

Tibolone is a synthetic steroid which is metabolized to estrogenic, progestagenic and androgenic compounds (*Vos et al 2002*). Tibolone alleviates climacteric symptoms and protects against osteoporosis (*Notelovitz 2007*). The association between tibolone and breast cancer is controversial. In epidemiological studies, tibolone (2.5mg/d) is either accompanied with an increased risk for breast cancer (*Beral et al 2003, Stahlberg et al 2004*) or has no effect (*Opatrny et al 2008*). In contrast, a randomized trial on osteoporotic elderly women demonstrated that a smaller dose of tibolone (1.25mg/d) led to a significantly reduced risk for breast cancer (*Cummings et al 2008*). However, in a recent big placebo controlled trial in women with a history of breast cancer, the use of tibolone (2.5mg/d) was associated with a 48% increase in the risk of new cancer or recurrence within 4 years of use (*Kenemans et al 2009*). It has been hoped that the vascular effects of tibolone could be enhanced in combination with phytoestrogens, but the tibolone+soya combination proved to have rather minimal vascular benefits over the sole tibolone (*see e.g. Jernman 2008*); no such data exist as regards the effects of tibolone on breast.

Selective estrogen receptor modulator, testosterone, phytoestrogens

Tamoxifen is currently considered the gold standard for adjuvant therapy in the treatment of hormone sensitive breast cancer (*Shelly et al 2008*). Raloxifene also reduces the risk for new invasive breast cancer (*Shelly et al 2008*). Overall, SERMs act as opposites to estrogen or have a neutral effect in the breast. For the adjuvant treatment of hormone sensitive postmenopausal breast cancer, aromatase inhibitors appear to be more effective than tamoxifen, and they will replace the SERMs.

The data on the association of breast cancer and testosterone are limited. In a recent study, the use of testosterone for more than 5 years was not associated with an increased risk for breast cancer (*van Staa and Sprafka 2009*). It has even been suggested that testosterone could counteract breast cell proliferation induced by EPT (*Hofling et al 2007*).

Despite the weak estrogenic effects of phytoestrogens, epidemiological studies suggest that the incidence of breast cancer is lower in countries where the intake of phytoestrogens is high, implying that these compounds may reduce the breast cancer risk (*Adlercreutz 2003*). However, short-term intervention studies suggest a possible stimulatory effect on breast tissue, raising concerns of possible adverse effects in breast cancer patients. Presently, no clear evidence exists as regards the guidelines for the clinical use of phytoestrogens in healthy women or in women with a history of breast cancer (*Rice and Whitehead 2008*).

Levonorgestrel releasing intrauterine system with estrogen

The levonorgestrel releasing intrauterine system (LNG-IUS) was designed for contraception (*Nilsson et al 1981*). It can also be used for endometrial protection in postmenopausal estrogen users and it was introduced as part of the EPT in the early 90s (*Andersson et al 1992*). Due to the small release of LNG (20µg/d), LNG-IUS as a complement to estrogen has been assumed to be safe for breasts (*Sitruk-Ware 2007*). This hypothesis is supported by data on fertile age women in whom the risk for breast cancer was not increased with the use of LNG-IUS (*Backman et al 2005*). However, no data existed on the relation between LNG-IUS+estrogen and breast cancer among postmenopausal women at the time of planning of the present study.

Histology of breast cancer

The most common histologic type of breast cancer is ductal (70-80% of all breast cancer types) followed by the lobular type of cancer (5-10% of all types) (www.cancerregistry.fi). Cancer can also be ductal-lobular, tubular, medullary and mucinous, and these classes only amount to a minority of all breast cancers (*Reeves et al 2006*). For an unknown reason, the rate of lobular cancer has increased more than that of ductal cancer in recent years (*Verkooijen et al 2003, Li et al 2003b*). Ductal cancer is more easily detected in a mammogram, but the prognosis for the lobular type of breast cancer is better than that for ductal cancer (*Verkooijen et al 2003, Li et al 2000,2008*). It is a general consensus that the use of HT favours the occurrence of lobular, ductal-lobular and tubular types of breast cancer (*Collins et al 2005, Reeves et al 2006, Borgquist et al 2007, Li et al 2008, Fournier et al 2008*).

It has been hypothesized that EPT could act as a promoter of foci of lobular carcinoma that would remain small or perhaps clinically undetectable in the absence of EPT exposure (*Li et al 2008*). This theory is supported by the studies which reveal an increased risk for breast cancer in a rather short duration of exposure (*Magnusson et al 1999, Beral et al 2003, Bakken et al 2004, Jernström et al 2004, Li et al 2008*). It has been calculated that it can take approximately 7-10 years before a cancerous DNA change leads to clinically diagnosed breast cancer (*Speroff 2008*). Therefore, the disappearance of the risk elevation for breast cancer within 5 years after the cessation of EPT use may also support the speculation that HT would not initiate a new cancer (*Collaborative Group on Hormonal Factors in Breast Cancer 1997, Collins et al 2005*).

Other characteristics of breast cancer

Many observational studies have reported that the breast cancers in HT users are smaller (*Holli et al 1998, Magnusson et al 1999, Delgado and Lopez 2001, Cheek et al 2002, Sacchini et al 2002, Daling et al 2003, Schuetz et al 2007*) and of a lower histological grade (*Holli et al 1998, Magnusson et al 1999, Delgado and Lopez 2001, Sacchini et al 2002, Daling et al 2003, Borgquist et al 2007, Schuetz et al 2007*), but data are not conclusive in this regard (*Chlebowski et al 2003, Kerlikowski et al 2003, Stahlberg et al 2004*). Furthermore, breast cancer among HT users is more often local (*Manjer et al 2001, Delgado and Lopez 2001, Cheek et al 2002*), although contradicting data also exist in this regard (*Chlebowski et al 2003, Kerlikowske et al 2003*). A randomized controlled trial found no difference in tumour receptor status among EPT users compared to nonusers (*Chlebowski et al 2003*), while various observational studies have found the association between ER+ tumours and EPT (*Delgado and Lopez 2001, Daling et al 2002, Kerlikowske et al 2003, Chen et al 2004, Hwang et al 2005, Fournier et al 2008*). The association is less evident between ET and ER+ (*Chen et al 2004*) tumours.

Women with a history of breast cancer

The use of HT has been considered to be contraindicated among women diagnosed with breast cancer. However, the survival rate for breast cancer has been improved, and numbers of survivors with climacteric symptoms are willing to consider HT. A Finnish study reported no increased risk among breast cancer survivors using HT for short durations (mean 2.5 years) (*Metsä-Heikkilä 2001*). Later a meta-analysis of 8 observational studies also revealed no increased risk of recurrence among HT users after treatment of breast cancer (*Col et al 2005*). However, a randomized study comparing HT for menopausal symptoms with management without HT among breast cancer survivors was discontinued early (median 4 years), due to the increased risk of new breast cancer following HT (HR 2.4; 1.3-4.2) (*Holmberg et al 2008*).

AIMS OF THE STUDY

Due to the national differences in the pattern of HT use and background factors contributing to the risk for breast cancer, the impact of HT use for breast cancer should be studied in each country where HT is being used. The purpose of this study was to evaluate the impact of the common HT regimens used in Finland on the risk for breast cancer.

The specific aims were to analyse the impact of doses, routes of administration of progestagens and estrogens, and various progestagens as regards the risk for breast cancer. Consequently, the following studies were performed:

1. Estrogen-only therapy and the risk for breast cancer (cohort study) (I)
2. Estrogen-progestagen therapy and the risk for breast cancer (cohort study) (II)
3. Hormone therapy including intrauterine system and tibolone and the risk for breast cancer (case-control study) (III)
4. Dose and route of norethisterone acetate (as a part of HT) as a determinant of breast cancer risk (case-control study) (IV)

SUBJECTS AND METHODS

All studies were register-based (Table 7), and the use of different registers in each study are described below.

Postmenopausal hormone therapy is currently reimbursed for 42% of the price.

The Finnish Population Information System contains basic information about Finnish citizens and foreign residents in Finland. Personal data recorded in the system includes name, personal identity code, address, citizenship and native language, family relations and date of birth and death (if applicable).

Table 7. **Registers used in the present study**

Register	Complete data available	Used in following studies during the given period	
Medical reimbursement register (The social insurance institution of Finland)	all reimbursable hormone therapy regimens since 1994	Study I Study II Study III Study IV	1994-2001 1994-2005 1994-2007 1994-2007
Finnish Cancer Registry	1953	Study I Study II Study III Study IV	1994-2001 1994-2005 1995-2007 1995-2007
Finnish Population Register Centre	1969	Study III Study IV	1995-2007 1995-2007

Study population in cohort studies

The study cohort of ET users consisted of all women over 50 years (n=110,984) who had purchased for at least 6 months any type of estrogen-only regimen in 1994–2001, the first purchase being at the age of 50 or later (table 8). These women were identified from the medical reimbursement register of the Social Insurance Institution of Finland. The women who had bought regimens for less than 6 months use were excluded, because this group could include women who had only bought estrogens, but not used them. Only 387 women had bought CEE, and thus, these women were not included in the analysis. Our final cohort consisted of women using estradiol and estriol-based regimens.

The cohort of EPT users consisted of all women over 50 (n=221,551) who had bought EPT regimens in 1994-2005 for at least 6 months with the first purchase being at the age of 50 or later (Table 8).

The follow-up for breast cancer among HT users was done through the Finnish Cancer Registry using personal identifiers as the key.

Study population in case control studies

All 9,956 women in Finland diagnosed with breast cancer at 50-62 years of age during 1995-2007 were identified through the Finnish Cancer Registry (Table 8). For each case subject, three control women of the same age (+/- one month) and alive at the time of diagnosis of the respective case were randomly selected from the Finnish national population registry. Cases and controls were linked to the medical reimbursement registry providing the data on the use of HT. The subgroup analysis of NETA containing HT use was done among HT users of cases and controls. All women who were included in case control studies, turned 50 years at some point during the study period, and the exposure to HT was calculated from 50 years on.

Table 8. **Study populations**

	Cohort	Cases/ controls	Age of the subjects	Follow-up period
Study I	110,984		≥ 50	1994-2002
Study II	221,551		≥ 50	1994-2005
Study III		9,956/ 29,868	50-62	1995-2007
Study IV		885/ 1,430	50-62	1995-2007

Statistical methods

The standardized incidence ratios (SIRs) were calculated by dividing the number of observed cases by the numbers expected. Ninety-five per cent confidence intervals (95% CIs) for the SIRs were based on the assumption that the number of observed cases represents a Poisson distribution. The expected numbers of breast cancer cases were calculated by multiplying the number of person-years in each 5-year age group by the corresponding breast cancer incidence among all Finnish women during the same period of observation (ww.cancerregistry.fi).

The follow-up for all HT users started in 1994 and ended for ET users at the end of 2002 or at death and for EPT users at the end of 2005 or at death.

Odds ratios (OR) and 95% CIs were used as measures of relative risk in the case control studies. These were computed from logistic regression models estimated by a conditional maximum likelihood method. The age of a woman, the age at first birth, parity, and health care district served as confounders and were adjusted in the final models. The two-tailed test was used for comparison of proportions.

Ethics and permissions

The ethics committee of the Department of Obstetrics and Gynecology, Department of Othorhinolaryngology, Department of Neurology and Neurosurgery, HUCS, The National Institute for Health and Welfare (former STAKES) and the Social Insurance Institution of Finland have given permissions for this study.

RESULTS

Detailed results are given in the original publications, and therefore only the main results are presented here.

Estradiol-only therapy and the risk for breast cancer (study I)

Altogether, 2171 cases with breast cancer were reported to the Finnish Cancer Registry during the follow-up. The use of systemic estradiol was associated with an increased incidence of breast cancer after 5 years of exposure (Table 9). Oral estriol or vaginal use of estrogen were not accompanied with any increased incidence of breast cancer (Table 9).

The elevated incidence of breast cancer associated with ET use increased with the increasing daily dose of oral estradiol, and the incidence was significantly elevated with the highest mean daily dose of estradiol (≥ 1.9 mg/day) in users of ≥ 5 years. However, the trend by dose was not statistically significant (p-trend = 0.27).

The use of patches of all doses for ≥ 5 years was accompanied by an elevated incidence for breast cancer. Most of the gel users had used > 0.9 mg/day (90%, n=867) ≥ 5 years, and the SIR was 1.52 (0.73–2.78). Transdermal use of ET for ≥ 5 years at any dose was associated with an increased incidence of breast cancer, which was comparable to that of oral ET.

The incidence of lobular type of breast cancer among ET users ≥ 5 years (1.58; 1.22-2.01) did not differ from that of ductal cancer (1.36; 1.19-1.53). The use of ET for ≥ 5 years was associated with an increased incidence of both localized cancer and cancer spread to regional nodes. The SIR for carcinoma *in situ* was 2.43 (1.66–3.42) among ET users for ≥ 5 years.

Table 9. **Standardized incidence ratios (SIR) of breast cancers among women (N) using oral or transdermal estradiol, oral estriol and vaginal estrogens by duration of use**[1]

Duration	N	Obs	Exp	SIR	95 % CI
Estradiol					
≥ 6 months < 5 years[2]	28 380	340	363	0.93	0.80-1.04
≥ 6 months < 5 years[3]	29 445	1166	895	1.30	1.23-1.38
≥ 5 years	26 904	345	239	1.44	1.29-1.59
Estriol					
≥ 6 months < 5 years[2]	2857	34	35	0.98	0.68-1.37
≥ 6 months < 5 years[3]	3717	88	82	1.07	0.86-1.32
≥ 5 years	1367	16	11	1.41	0.80-2.28
Vaginal estrogens					
≥ 6months < 5 years[2]	7 303	43	64	0.67	0.48-0.90
≥ 6 months < 5 years[3]	10 879	138	130	1.06	0.89-1.25
≥ 5 years	132	1	0.71	1.41	0.04-7.86

[1]Use in ages over 50 years during 1994-2001, observed (Obs) and expected (Exp) number of breast cases up to 31 December 2002, and standardized incidence ratios (SIR) with their 95 % confidence intervals (CI).

[2]Only users from 1995-2001(with completely known exposure history) were included.

[3]Users from 1994 (with possible preregister use) were included.

Estrogen-progestagen therapy and the risk for breast cancer (study II)

Altogether 6211 EPT users became diagnosed with breast cancer during the study period. The use of EPT for at least 3 years was associated with an increased incidence of all breast cancer types combined (1.31; 1.20-1.42) (Table 10). The SIR increased with increasing exposure to EPT, being 2.07 (1.84-2.30) after 10 years of use (Table 10).

The sequential and continuous use of progestagen as a complement to estradiol were accompanied with elevated risks for breast cancer from 3 years of exposure onwards. The use of progestagen continuously was associated with a higher risk elevation than the sequential use of progestagen after 5 years. Oral and transdermal EPT regimens showed comparable risk elevations. The risk was also elevated in EPT users with inaccurate exposure data (Table 11).

Table 10**. Standardized incidence ratios (SIR) of invasive breast cancer in women with the use of estradiol-progestagen therapy**[1]

Exposure	**N**	**Obs**	**Exp**	**SIR**	**95% CI**
≥ 6 months < 3 years	50 033	1024	976	1.05	0.97-1.11
≥ 3 years < 5 years	30 583	547	418	1.31	1.20-1.42
≥ 5 years < 10 years	32 466	472	273	1.72	1.58-1.89
≥ 10 years	23 131	299	146	2.07	1.84-2.30

[1]Use in women over 50 years during 1994-2005, observed (Obs) and expected (Exp) number of breast cancer cases up to the end of December 2005, and standardized incidence ratios (SIR) with their 95% confidence intervals (CI) at the end of the follow-up.

Table 11. **Standardized incidence ratios (SIR) of invasive breast cancer (N) among women using estrogen+progestagen therapy in 1994-2005 according to the mode of regimen, and duration of the use**[1]

	Sequential		**Continuous**	
Exposure	N	SIR (95% CI)	N	SIR (95% CI)
≥ 6 months < 3 years[2]	781	1.04 (0.97-1.11)	253	1.24 (1.12-1.37)
≥ 3 years < 5 years[2]	385	1.09 (0.96-1.23)	105	1.42 (1.16-1.71)
≥ 5 years[3]	738	1.78 (1.64-1.90)	294	2.48 (2.09-2.91)
≥ 10 years[4]	27	2.27 (1.50-3.30)	21	5.12 (0.62-18.48)

[1]Use in ages over 50 during 1994-2005, observed (Obs) and expected (Exp) number of breast cancer cases up to 31 December 2005, and standardized incidence ratios (SIR) with their 95% confidence intervals (CI) at the end of the follow-up.
[2]Classification according to first use.
[3]Used the same mode of administration for 5 years.
[4]Used the same mode of administration for 10 years.

The use of EPT containing NETA was accompanied with a significantly higher risk for breast cancer than the use of MPA after 5 years of use (Table 12). Exposure to other progestagens, including dydrogestrone, showed no statistically significant increase in the risk for breast cancer in less than 5 years of use (1.22; 0.83-1.72). The mixed use of progestagens for 5 years or more (NETA and MPA switchers included) was accompanied with an elevated risk for breast cancer.

Table 12. **Standardized incidence ratios (SIR) of invasive breast cancer among women (N) using estrogen+progestagen therapy in 1994-2005 grouped according to the progestagen, and duration of use**[1]

	N	Obs	Exp	SIR	95% CI
Progestin type and duration					
> 6 mo < 3 years[2]					
NETA	22368	439	424	1.04	0.94-1.14
MPA	13438	336	324	1.04	0.93-1.15
≥ 3 years < 5 years[2]					
NETA	12211	266	169	1.34	1.17-1.51
MPA	8648	166	130	1.27	1.09-1.48
≥ 5years[3]					
NETA	24093	670	330	2.03	1.88-2.18
MPA	19299	454	277	1.64	1.49-1.79
Other[4]	5804	159	77	2.07	1.76-2.04
Mixed[5]	39727	860	498	1.73	1.61-1.84
≥ 10 years[3]					
NETA	4081	67	21	3.15	2.44-4.00
MPA	2049	16	8	1.90	1.07-3.07
Other[4]	289	6	2	2.79	1.02-6.07
Mixed[5]	6492	70	30	2.33	1.82-2.94

[1]Use in ages over 50, observed (Obs) and expected (Exp) number of breast cancer cases up to the end of December 2005, and SIRs with their 95 % confidence intervals (CI) at the end of the follow-up.
[2]Classified according to the first EPT.
[3]Classified according to the progestagen used first and at 5 and at 10 years (pre-register use possible.
[4]Includes progestagens other than NETA, MPA and dydrogesterone.
[5]Switching use of progestagen.

The users of NETA formed large enough groups for a comparison between the impacts of sequential or continuous use of progestagen on the risk for breast cancer. Within the use of at least 5 years, the sequential use of NETA (1.72; 1.52-1.93) was accompanied with a significantly lower incidence of breast cancer than the continuous use (2.56; 2.25-2.88). The SIR of breast cancer increased up to 1.90 (1.04-3.18) for sequential NETA and for continuous NETA to 3.83 (2.34-5.91) after 10 years of use, but the difference was not statistically significant.

The use of EPT was accompanied with rises in the incidence of both ductal and lobular cancers, yet the risk for lobular cancer was already elevated within the first 3 years of use (SIR 1.35; 1.18-1.53). The risk was significantly higher for lobular than that for ductal cancer after 10 years of use. The use of EPT was accompanied with comparable risk rises in both localized cancer and cancer spread to regional nodes.

Hormone therapy including levonorgestrel releasing intrauterine system and tibolone and the risk for breast cancer (study III)

In the case control study, parity, age at first birth, and place of residence, were significant determinants of breast cancer, and the final model was adjusted with these variables. The risk for breast cancer was especially low (0.48; 0.36-0.64) for women with 5 children and an age of under 25 at the first birth as compared with nulliparous women. The risk for breast cancer was elevated in Tampere and Helsinki hospital areas (1.16; 1.07-1.27 and 1.16; 1.08-1.26, respectively), as compared to the reference category (Oulu).

The use of ET, or oral progestagen-only therapy was not associated with an increased risk for breast cancer (Table 13), whereas the use of EPT, LNG-IUS alone, or as a complement to estradiol, tibolone, and mixed therapy use were accompanied with an elevated risk for breast cancer (Table 13).

The continuous use of progestagen as a part of EPT was more strongly associated with an elevated risk for breast cancer than sequential use of progestagen, and this risk increased along with an increasing duration of exposure. The use of estradiol plus LNG-IUS was accompanied with a more than 2–fold elevated risk for breast cancer after 3 years of exposure.

The use of sequential NETA and MPA with estradiol was accompanied with an increased risk for breast cancer, but the risk for breast cancer in users of sequential dydrogesterone with estradiol did not reach the significance in any duration category.

Continuous NETA with estradiol was associated with an increased risk for breast cancer in all exposure categories, and the risk increased with an increasing duration of use. Continuous estradiol+MPA use was associated with an increased risk for breast cancer after 5 years of use.

Table 13. **Relative risk of invasive breast cancer among postmenopausal women using hormone therapy (HT)**[1]

	Cases	Controls	OR	95% CI	p-value
No user[2]	5473	17956	1.00	(reference)	
Estradiol-only therapy	991	3300	1.01	0.93–1.09	0.88
Progestagen-only therapy	138	476	0.97	0.80–1.17	0.73
LNG-IUS[3]	329	708	1.53	1.33–1.75	0.001
Estradiol-progestagen therapy	1731	4243	1.36	1.27–1.46	0.001
Estradiol plus LNG-IUS	287	473	2.07	1.78–2.41	0.001
Mixed therapy[4]	927	2534	1.22	1.12–1.33	0.001
Tibolone[5]	80	178	1.36	1.15–1.96	0.003

[1]Adjusted with age, parity, age at first birth and health care district. OR = odds ratio; CI = confidence interval.
[2]Had bought HT never or for less than 6 months.
[3]Levonorgestrel releasing intrauterine system.
[4]Mixture of estradiol-only, progestagen-only, or estradiol-progestagen therapy.
[5]At least 6 months tibolone with other type of therapy.

Different doses and routes of administration of norethisterone acetate as a part of hormone therapy and the risk for breast cancer (study IV)

In this study, 885 cases altogether were NETA users, of which 329 had used oral sequential NETA+estradiol. The majority (85 %) of 329 cases had taken a ”high” NETA dose (1mg) sequentially as a complement to 2.0 mg of estradiol, and only 15% had used 1mg of estradiol, and therefore this group was analysed on its own regardless of the dose of estradiol. In the sequential “high” dose NETA+estradiol -group, the risk was elevated after 3 years, and increased with increasing duration of exposure being 1.89 (1.43-2.50) after 5 years of exposure. The continuous NETA+estradiol was divided into two categories; to “high” dose (1mg NETA+2mg estradiol) and “low” dose (0.5 mg NETA+1mg estradiol). The use of “low” dose NETA+estradiol was associated with an increased risk for breast cancer in less than 3 years of use (1.94; 1.39-2.70), but the use of “high” dose was not. After 3 years of use, no statistical difference between “low” and “high” dose NETA+estradiol was seen (Table 14).

Both sequential and continuous transdermal NETA, together with estradiol, were accompanied with an elevated risk for breast cancer in less than 3 years of exposure. In less than 5 years of exposure, the association was stronger for the continuous use of NETA. Transdermal sequential and the continuous administration of NETA was comparable to the oral one in the risk for breast cancer.

In the group of mixed NETA use, the duration of the exposure was a significant determinant for the risk of breast cancer. The mixed NETA group was comparable to sequential NETA+estradiol with regard to breast cancer risk.

Table 14. **Risk for breast cancer among postmenopausal women using oral sequential or continuous norethisterone acetate+estradiol by dose and duration**

Sequential NETA[1] (1mg NETA for 10-14 days/month+estradiol)	case	control	OR[2]	95% CI	p-value
< 3 years	164	441	1.21	1.01–1.46	0.04
3 < 5 yrs	87	199	1.48	1.14–1.90	0.003
≥ 5 yrs	78	146	1.89	1.43–2.50	0.001
"Low" dose continuous NETA (NETA 0.5 mg+estradiol 1 mg)					
< 3 years	57	98	1.94	1.39–2.70	0.001
3 < 5 yrs	27	39	2.45	1.49–4.02	0.001
≥ 5 yrs	6	7	3.08	1.02–9.23	0.05
"High" dose continuous NETA (NETA 1 mg+estradiol 2 mg)					
< 3 years	48	131	1.21	0.87–1.70	0.26
3 < 5 yrs	38	74	1.71	1.15–2.54	0.007
≥ 5 yrs	37	64	2.03	1.34–3.06	0.001

[1]Norethisterone acetate.
[2]Adjusted with age, parity, age at first birth and health care district, no user as reference category.

DISCUSSION

Breast cancer is a major concern among women who consider starting the use of HT or who are already using HT. Due to national differences in the use of HT (*Chlebowski et al 2003, Stahlberg et al 2004, Fournier et al 2008*), mammography screening programs, genetic background and life-style habits, the associations between HT use and breast cancer should be studied in each country where HT is being used. We conducted four studies to compare different hormone therapies as regards risks for breast cancer in Finland. The focus was on estrogen-only therapy first, because estrogen is the only hormone which alleviates menopausal symptoms. Furthermore, hysterectomy rates have been high in Finland; approximately 20% of women (*Vuorma et al 1998*) underwent a hysterectomy by age of 60 prior to our study period, and, unopposed estrogens are allowed only for hysterectomized women. In Finland, estradiol and estriol-based regimens are used, in contrast to several previous studies where CEE have been mostly used (*Li et al 2000, Newcomb et al 2002, Daling et al 2002, Daling et al 2003, Li et al 2003a, Anderson et al 2004*).

One important source of error in epidemiological studies on the risk of breast cancer in HT users is inaccurate documentation on the use of HT (*Collaborative Group on Hormonal Factors in Breast Cancer 1997, Li et al 2000, Bush et al 2001, Beral et al 2003, Newcomb et al 2002, Stahlberg et al 2004*). Recall bias is probably present in all studies based on interviews; women diagnosed with breast cancer are more likely to recall the use of HT than women without breast cancer. We retrieved the use of HT from the medical reimbursement register of the National Social Insurance Institution, which includes all the details of HT purchases since 1994. Thus, we could accurately assess the type, dose and duration of HT for the entire follow-up period, but some women certainly have used HT before the register was operational. Because HT is only partly reimbursed, women have to spend their own money for the treatment. Thus, it is very likely that the women truly used the HT preparations they had bought.

In the cohort studies we could not control confounders such as parity, age at the birth of the first child, place of residence, socioeconomic status, weight, age at menarche or age at menopause. However, socioeconomic differences among postmenopausal HT users and nonusers declined in Finland by the 1990s (*Topo et al 1999*). Therefore, it appears unlikely that there would have been major differences in the confounders between HT users and the national average in our study. In addition, the rate of BRCA1/2 mutations in unselected Finnish breast cancer patients is low (1.8%) (*Syrjakoski et al 2000*); thus, it seems unlikely that these women could have accumulated into our cohort. In case-control studies, important confounders such as age at the first birth and parity could be controlled, and the health care district was also included as a variable. Because the mean age at menopause is 50-52 years (*McKinlay et al 1992*), we only included women who were at least 50 years of age to confirm that we studied truly postmenopausal women. Although some women had used HT before the age of 50 years, such a possible use should not modify the risk for breast cancer significantly. Moreover, a late age at menopause is associated with an increased risk for breast cancer, and these women start the use of HT later (*Cuzick 2003*). Therefore, both these factors may contribute to the speculation that our risk estimates related to the short use of EPT may be slightly too high.

To get prescriptions, the HT users must visit their doctors regularly. At these appointments, breasts have most likely been palpated and examined by mammogram, if needed. This may have resulted in a breast cancer detection bias in HT users, and this might be supported by a significantly increased incidence of carcinoma *in situ* in our ET cohort. However, since 1987, organized mammogram screenings have been offered to all women between 50 and 60 years of age (in some communities up to 69 years) in Finland. The coverage of these free-of-charge screenings is 95% among 50-59

years old women, and 90% of invited women actually participate the screenings (*Sarkeala et al 2008*). This policy should reduce the impact of a possible detection bias in our cohort.

In the cohort studies, we compared the incidence of breast cancer in ET and EPT users with that in the whole age-matched population, including those using any HT. It is known that up to 40% of Finnish women around 55 years of age have used HT (*Rutanen and Ylikorkala 2004*) but according to our data, approximately 10-15% of women use such a therapy for more than 3 years. Such a proportion of moderate-risk women in the reference population dilutes the observed relative risk estimate only marginally towards unity and should not affect the conclusions (*Pukkala et al 1997*).

In our cohort study, the use of **estradiol-only therapy** for more than 5 years was accompanied with an elevated incidence for breast cancer (SIR 1.44; 1.29–1.59). However, the risk for breast cancer was not increased among ET users in the case control study. These contradicting results could be explained due to the difference in age and exposure duration among users. In the cohort study, all women 50 to 85+ years were included with some of those using ET for decades, and the use of ET before register opening could have been possible, while in the case-control study, the users were aged 50-62, when the exposure was significantly shorter. Our data are in line with other studies (*Collaborative Group on Hormonal Factors in Breast Cancer 1997, Bush et al 2001, Li et al 2003a, Colditz et al 2000, Stahlberg et al 2004, Fournier et al 2008*). The use of CEE only was not accompanied with an elevated risk for breast cancer in a randomized controlled trial (HR 0.77; CI 0.59–1.01) (*Anderson et al 2004*), while in a large cohort study in the UK; the current use of ET was associated with an elevated risk of breast cancer for the use of less than 5 years (RR 1.25; 1.10-1.41) (*Beral et al 2003*).

Due to the established adverse effects of HT, including breast cancer (*Collaborative Group on Hormonal Factors in Breast Cancer 1997, Warren 2004, Anderson et al 2004, Collins et al 2005, Conner et al 2008*), the recommendations at present are to use HT at the lowest possible doses for the shortest possible duration (*The International Menopause Society 2007, The North American Menopause Society, 2008*). However, only a few studies have compared the breast cancer risk associated with different doses of estrogen. Some studies suggest that the impact of estrogen on breast cancer risk could be dose-dependent (*Colditz et al 2000, Porch et al 2002*), while a large cohort study from the UK did not find any dose-dependence (*Beral et al 2003*). Although our data did not confirm any significant trend between increasing daily dose of estradiol and the risk of breast cancer, higher doses of oral estradiol were accompanied with a slightly higher risk of breast cancer than the lower doses, the cut-off dose level was ≥1.9 mg/d. The editorial commented, based on our data, that perhaps clinicians should prescribe low-dose estrogen-only regimens also to nonhysterectomized women and just monitor the endometrium with ultrasound and/or biopsies (*Collins 2006*). Furthermore, we did not find any association between breast cancer and vaginally used estrogens or oral estriol. Thus, these regimens can be used without a fear of increased breast cancer risk.

The use of **transdermal HT** might have some vascular benefits compared to the oral one (*Cacciatore et al 2001, Strandberg et al 2003, Scarabin et al 2003, Canonico et al 2008*). However, we did not find any differences in breast cancer risk between these routes of administrations, and the conclusion was the same for ET and EPT. This is in line with the British (*Beral et al 2003*) and French data (*Fournier et al 2005, 2008*).These data might imply that different estrogenic and progestagenic milieu in users of oral and transdermal ET or EPT might similarly affect breast cells.

It is established that the use of combined **estrogen-progestagen therapy** is associated with a higher risk elevation for breast cancer than is the sole use of estrogen (*Collins et al 2005*). Our data support this conclusion. However, an increased risk for breast cancer in our studies was seen already in 3 years of use, while the majority of the previous studies report that the first 5 years of use does not associate with a risk elevation for breast cancer (*Collaborative Group on Hormonal Factors in*

Breast Cancer 1997). Yet, some studies have also found increased risk for breast cancer already within the first 5 years of use (*Beral et al 2003, Fournier et al 2008, Flesch-Janys et al 2008*).

The **continuous EPT** showed higher risks for breast cancer than **sequential EPT** in both our studies on EPT, which is in line with previous data (*Collins et al 2005, Flesch-Janys et al 2008*), although some other studies have reported no difference in this risk between sequential and continuous EPT products (*Newcomb et al 2002, Beral et al 2003, Li et al 2003a, Opatrny et al 2008*). National differences in the use or content of various EPT preparations may be one explanation for this discrepancy. It is noteworthy that in the case control study we could control some important confounders, while in the cohort study this was not possible.

The data are sparse on the possible differences between **various progestagens** in regard to the breast cancer risk. A British study reported comparable risks for users of EPT regimens containing MPA, NETA and LNG (*Beral et al 2003*). In our cohort study, more than 5 years of use of NETA+estradiol was accompanied with a higher risk for breast cancer compared to MPA+estradiol; similar results were reported during our study from Germany (*Flesch-Janys et al 2008*). It is possible that different progestagens, together with estradiol, affect breast tissue differently (*Pasqualini et al 1998, Sitruk-Ware 2004*). The progestagen load in women using NETA containing regimens; e.g. continuous NETA products also release twice as much NETA than a sequential regimen, whereas the dose-difference is much smaller between continuous and sequential MPA products. In the case control study, we did not find any significant differences between NETA and MPA containing EPT regimens. However, these women were between 50–62 years of age and had shorter exposure of EPT. Perhaps longer exposures are needed to reveal possible differences between various progestagens. The use of EPT containing dydrogesterone was not associated with a significantly elevated risk for breast cancer in the cohort or case control study. This is in agreement with data from France (*Fournier et al 2008*). However, a relatively small sample size limits the conclusions about the breast safety of dydrogesterone in our study.

It is known that various progestagens, including **NETA**, have a dose-dependent response in the endometrium (*Stanczyk 2003, van de Weijer et al 2007*). In theory, this could be applied to breast tissue as well. We compared the modern "low" (0.5 mg+1mg) and older "high" (1mg+2mg) doses of NETA+oestradiol regimens in regard to the risk for breast cancer. However, no significant difference in breast cancer risk emerged between these two regimens. This may indicate that there is no dose-dependence between NETA (as a part of EPT) and the risk for breast cancer, at least with the doses which are available in Finland.

One important and unexpected finding in our study was the increased risk for breast cancer associated with **LNG-IUS use, either alone or in combination with estradiol,** among postmenopausal women. It is not likely, that such a low dose of LNG released by the device would cause cancerous changes in breast cells (*Raudaskoski et al 2002*). Yet LNG-IUS is one mode of continuous regimen which in general carries a higher risk than a sequential regimen (*Collins et al 2005*). Furthermore, the use of continuous LNG+estrogen in both the oral or transdermal modes of administration has shown higher risks compared to other progestagens, although the difference has not been significant (*Beral et al 2003, Flesh-Janys et al 2008*). Thus, LNG, being one of the most potent progestagens (*Stanczyk 2003*), could have an impact on the development of breast cancer, even in low doses. However, there is a chance of selection bias in our study; women characterized with an increased risk for breast cancer could have been fitted with an IUS. These characteristics may include hyperestrogenic states, such as obesity, or higher age at spontaneous menopause. Also a family risk for breast cancer may have led to the insertion of the LNG-IUS, due to the "low" release of LNG. Thus, a truly randomized prospective trial might be needed to assess the impact of LNG-IUS+estradiol on the for breast cancer.

Only a few studies have analyzed the association between **tibolone** and breast cancer, some of those reporting increased risk (*Beral et al 2003, Stahlberg et al 2004, Kenemans et al 2009*), and some have found no effect (*Opartny et al 2008*). In our study the use of tibolone was associated with an increased risk for breast cancer (2.5mg/d, OR 1.36;1.15–1.96). However, women using tibolone might have been characterized with an increased risk for breast cancer, as the users of LNG-IUS, and thus the risk could have been modified. The dose-dependence can be important; previous studies included the conventional dose of tibolone (2.5mg), while a randomized trial on osteoporotic elderly women demonstrated that a smaller dose of tibolone (1.25 mg/day) led to a significantly reduced risk for breast cancer (*Cummins et al 2008*).

It as been suggested that HT use favours the benign **character of breast cancer** (*Collaborative Group on Hormonal Factors in Breast Cancer 1997, Delgado et al 2001, Manjer et al 2001, Cheek et al 2002, Daling et al 2002*). However, we saw similar risk elevations for localized breast cancer and cancer spread to regional lymph nodes, which speaks against the benignity of breast cancer in HT users. The use of EPT, and to a lesser extent ET, increases breast density (*Greendale et al 1999, Lundstrom et al 1999, Bremnes et al 2007*), which in turn reduces the diagnostic accuracy of mammograms (*Kavanagh et al 2000*). This might explain, at least in part, the increased incidence of cancers spread to regional nodes, both in users of ET and EPT.
The use of EPT is associated more strongly with a **lobular** than with a **ductal type of breast** cancer (*Collins et al 2005, Reeves et al 2006, Rosenberg et al 2006, Li et al 2008, Flesch-Janys et al 2008*), whereas the impact of ET on the type of breast cancer is less clear (*Li et al 2008, Flesch-Janys et al 2008*). Our data show that the use of ET is associated similarly with ductal and lobular types of breast cancer in Finland, whereas the use of EPT was associated with a higher risk for lobular than that for ductal cancer. It was conspicuous that a risk elevation for lobular cancer was already significant within the first 3 years of EPT use.

Finally, I would like to consider if the use of HT could be **a cause or promoting factor for breast cancer**. Epidemiological data can seldom prove that a certain agent or factor, e.g. HT, could be the cause of cancer. Our data show associations between HT and breast cancer, but whether the use of HT would cause breast cancer is still an open question. Yet, in view of the effects of estrogens and progestagens on the breast cells (*Yager and Davidson 2006*, *Conner 2007*), such a possibility exists. Furthermore, The International Agency for Research on Cancer has classified EPT as a carcinogenic agent (*IARC 2007*) based on evidence from experimental animals and in exposed humans in which EPT acts through a relevant mechanism of carcinogenicity. However, a significant increase in the risk for breast cancer within the first 3 years of EPT use may imply that the use of EPT does not initiate the cancer, but promotes the growth of a pre-existing cancer (*Speroff 2008, Horwitz and Sartorius 2008*), because in general, it takes approximately 7 years for a malignant cell to become detectable by mammography. The increase in the risk for breast cancer rather soon after the initiation of HT suggests that HT use may lead to an earlier detection of pre-existing tumours. Yet, in practical terms, the use of ET for at least 5 years means 4 extra breast cancer cases per 1000 women and the use of EPT for 5-10 years means 6 extra cases per 1000 women.

CONCLUSIONS

On the basis of the present work, the following conclusions can be drawn:

1. Oral or transdermal estradiol for less than 5 years is not associated with an increased risk of breast cancer, but such a risk appears with the use of > 5 years. Estradiol use is associated with comparable risk rises in ductal and lobular types of breast cancer, and breast cancers at diagnosis are equally often local or spread to regional lymph nodes. Vaginal estrogens are not associated with an increased risk for breast cancer.
2. The use of EPT is accompanied with an increased risk for breast cancer within the first 3 years. The risk elevates with the exposure time and is lower for sequential than for continuous EPT regimens. Oral and transdermal EPT uses present comparable risk elevations for breast cancer. The EPT products releasing NETA are accompanied with higher elevations after 5 years of use in the risk for breast cancer than for products releasing MPA or dydrogesterone. The use of EPT is associated with risk rises in ductal and lobular cancers, and the risk for lobular cancer is already elevated within the first 3 years of use. The risk is significantly higher for lobular than that for ductal cancer after 10 years of use. The use of EPT is accompanied with comparable risk rises in both localized cancer and cancer spread to regional nodes.
3. Estradiol alone in the case control study did not associate with a risk for breast cancer. The difference between cohort and case control data in ET may derive from age differences in users. Progestagen alone does not relate to a rise in the risk for breast cancer in recently postmenopausal women. The use of EPT is associated with an elevated risk for breast cancer in less than 5 years of use, and the risk elevation is higher for continuous EPT rather than for sequential EPT use. The use of tibolone, a LNG-IUS or as a complement to estradiol, is accompanied with an elevated risk for breast cancer.
4. The dose of NETA ("low" or "high" dose) as a part of EPT is not a determinant of breast cancer. NETA together with estrogen given orally or transdermally, is accompanied with comparable risk elevations for breast cancer. A continuous mode of administration presents a stronger association with breast cancer. Thus, these data do not support a clear dose-dependence between daily doses of NETA and breast cancer risk.
5. Taken as a whole, the use of HT for 5-10 years is associated with 4-6 extra cases of breast cancer among 1000 Finnish HT users; this risk evaluation depends on the mode of HT. This unavoidable risk must be accepted by each user, and it must be considered in balance with the undisputable health benefits which also are associated with the use of HT. Each HT user should be thoroughly informed of the risks and benefits, so that she herself can make a knowledge-based decision to use or not to use HT.

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