Endometrial Cancer in Postmenopausal Women Using Estradiol–Progestin Therapy

Susanna Jaakkola, MD, Heli Lyytinen, MD, Eero Pukkala, PhD, and Olavi Ylikorkala, MD

OBJECTIVE: To estimate the risk of endometrial cancer in all Finnish postmenopausal women using various forms of estradiol–progestin therapy.

METHODS: All Finnish women (aged more than 50 years) who had used estradiol–progestin therapy in 1994–2006 for at least 6 months (n=224,015) were identified from the national medical Reimbursement Registry and linked to the Finnish Cancer Registry. A total of 1,364 type I and 38 type II endometrial cancers were recorded by the end of 2006. The incidence of endometrial cancer in estradiol–progestin therapy users was compared with that in the general population in this cohort study.

RESULTS: The use of a continuous estradiol–progestin therapy regimen for 3 years or more was associated with a 76% reduction of the risk for type 1 cancer (95% confidence interval [CI] 6–60%). In contrast, the use of a sequential estradiol–progestin therapy regimen for at least 5 years was accompanied with a 69% elevation (95% CI 43–96%) if the progestin was added monthly, and with a significantly higher, 276% risk elevation (95% CI 190–379%) if progestin was added at 3-month intervals. Sequential regimens containing norethisterone acetate, medroxyprogesterone acetate or dydrogesterone administered orally showed no significant differences in the endometrial safety. Oral and transdermal norethisterone acetate were associated with similar risk elevations. Women using a monthly sequential estradiol–progestin regimen tended to be diagnosed with endometrial cancer in an earlier stage than the background population.

CONCLUSION: Use of a continuous rather than a sequential estradiol–progestin regimen decreases the risk of endometrial cancer, whereas the route of administration or type of progestin does not differ in terms of endometrial cancer risk.

(Obstet Gynecol 2009;114:1197–1204)

LEVEL OF EVIDENCE: II

Well-known risk factors of endometrial cancer are nulliparity, obesity, endogenous hyperestrogenism, hereditary nonpolyposis colon cancer syndrome, history of breast cancer, tamoxifen use, unopposed estrogen use, and inadequate progestin addition to estrogen.[1] A large international variation in incidence rates of endometrial cancer indicates that many of those risk factors may be modifiable.[2]

It is known that approximately 80% of the endometrial cancers are preceded with endometrial hyperplasia.[3] These type I tumors are mostly low-grade adenocarcinomas with a fairly good prognosis.[4] In contrast, type II tumors, such as serous papillary carcinomas, clear cell adenocarcinomas or squamous carcinomas, originate from polyps or other nonhyperplastic endometrial lesions. They are more malignant and usually diagnosed at a more advanced stage than type I tumors.[5] Except for advanced age, no other confirmed risk factors exist for type II tumors, although estrogen may also be involved.[6–8]

Previous data uniformly show that unopposed estrogen therapies or an inadequate progestin complement to estrogen is accompanied by an elevation in the risk for endometrial cancer.[9] In these studies, progestins as part of hormone therapy (HT) have mainly been given orally, and the role of long-term use of transdermal progestin in endometrial protection is open.[10] Moreover, various progestins used in commercial combined HT preparations show large differences in their capacity to bind progesterone and other receptors,[11] and therefore differences in endo-

From the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki; Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki; and Tempere School of Public Health, University of Tempere, Tempere, Finland.

Supported by the grants from Research Council of Helsinki University Central Hospital and from Finnish Cancer Research Foundation.

Presented at the Eigth European Congress on Menopause, London, United Kingdom, May 16–18, 2009.

Corresponding author: Olavi Ylikorkala, MD, Professor, Helsinki University Central Hospital, Department of Obstetrics and Gynecology, P.O. Box 140, FI-00029 HUS, Finland; e-mail: olavi.ylikorkala@hus.fi.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/09

metrial safety between various progestins as part of HT are possible. There are no long-term follow-up data on this issue so far.[12]

Due to the large national differences in the use and content of HT,[13] its effect on endometrial cancer burden should ideally be studied in each country separately.[14] The objective of our study was to estimate the risk of endometrial cancer in all Finnish postmenopausal women using various forms of estradiol–progestin therapy.

PATIENTS AND METHODS

This study has been approved by Helsinki University Hospital Ethical Board (Number 298/E9/06). All women aged more than 50 years who had used estradiol–progestin regimens from 1994 to 2006 (n=254,555) were extracted from the national Reimbursement Registry of the Social Insurance Institution (Fig. 1). We classified as estradiol–progestin therapy users women who had used estradiol–progestin therapy for more than 6 months, and thus, the women using estradiol–progestin therapy for less than 6 months were excluded (n=30,540). We did not regard tibolone as an estradiol–progestin regimen, and therefore, women exposed to tibolone were excluded. We also excluded the women with a levonorgestrel releasing intrauterine device because in this analysis the time of extraction remained unclear. Since we do not have data on the pre-registry use before 1994, we assumed that we have complete estradiol–progestin therapy history only for those who started their first estradiol–progestin regimen in 1995 or later, and analyses related to short-term use (less than 5 years) were restricted to this subcohort called fresh starters later in this article (n=121,036).

The final study cohort (n=224,015) was followed through a record linkage with the population-based nationwide Finnish Cancer Registry to the diagnosis of endometrial cancer, hysterectomy, immigration, death, or to the closing date of follow-up (December 31, 2006). The dates of hysterectomies (n=23,371) were obtained from the Hospital Inpatient Register of the Social Welfare and Health Care, which has data on hysterectomies in Finland since 1986. The coverage of the registry is almost 100%.[15] The rate of hysterectomy was 14% (n=14,044) among the older group who were users at registry opening and 8% (n=9,327) among fresh starters with a complete estradiol–progestin therapy history.

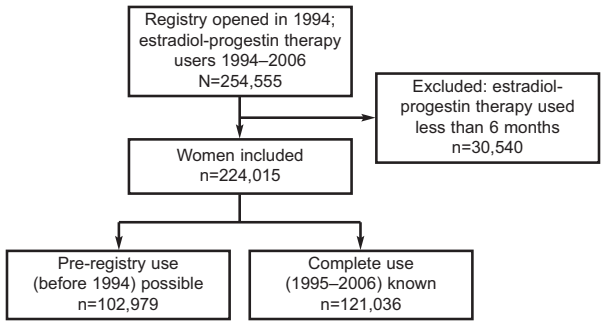

Fig. 1. Selection of the study cohort of women using estradiol–progestin therapy in Finland 1994–2006.

Jaakkola. Estradiol–Progestin for Endometrial Cancer. Obstet Gynecol 2009.

The only estrogen component in fixed commercial estradiol–progestin therapy preparations in Finland is estradiol, which is given at daily doses of 1 or 2 mg orally, 50 or 80 micrograms in patches, or 0.5 to 1.5 mg in gel transdermally. In this study, the regimen was considered oral or transdermal according to the mode of progestin administration; estradiol could be given either orally or transdermally. Some women comprised an individual estradiol–progestin regimen by taking progestin orally for 10–14 days at 1- to 3-month intervals as a complement to continuous estradiol. An estradiol–progestin regimen was defined as sequential if the daily estradiol was complemented with 10 to14 days of progestin once a month (monthly regimen) or at 3-month intervals (long cycle). The estradiol–progestin regimen was defined as continuous, if both estradiol and progestin were given concomitantly.

For comparing individual progestins, the users of norethistoterone acetate, medroxyprogesterone acetate or dydrogesterone as parts of oral estradiol–progestin therapy provided big enough subgroups for statistical analysis. The use of estradiol–progestin regimens for less than 5 years was classified according to the first estradiol–progestin therapy used. For estradiol–progestin therapy use exceeding 5 years, analyses were based on categories when the first and the 5- or 10-year regimen delivered the same progestin. Users, who switched from one progestin to the other, from sequential to continuous progestin use, or visa versa, were analyzed separately as a mixed-use group. According to Finnish national guidelines, estradiol-only therapy is not allowed in women who have not had a hysterectomy. Women using norethistoterone acetate containing sequential estradiol–progestin therapy formed big enough subgroups (number of users for less than 5 years was 5,409 and for 5 years or more 2,380) for meaningful statistical comparison between oral and transdermal route of administration.

The personal identity codes of the estradiol–progestin therapy users were linked to the Finnish

Cancer Registry, which receives notifications from all cancer cases from hospitals and pathology laboratories in Finland. The coverage of this registry is nearly 100%.[16] Endometrial cancers were classified as type I (endometrioid adenocarcinoma) and type II tumors. Type II includes papillary (serous) carcinoma, clear cell carcinoma, epidermoid carcinoma, and carcinoma, which cannot be classified into the former categories. In situ tumors were excluded from our analysis. The Cancer Registry also includes data on the clinical stage of the cancer at the time of diagnosis, and it was classified as restricted inside of the uterus or advanced stage, the latter including cancers that had spread to regional lymph nodes or beyond.

The expected numbers of endometrial cancer cases were calculated by multiplying the number of woman-years in each 5-year age group by the corresponding endometrial cancer incidence among all Finnish women during the same period of observation.

The standardized incidence ratios for endometrial cancer were calculated by dividing the number of observed cases by the number expected. Ninety-five percent confidence intervals (95% CIs) for standardized incidence ratioss were based on the assumption that the number of observed cases represents a Poisson distribution.[17]

RESULTS

The 224,015 estradiol–progestin therapy users were followed for a total 1.6 million women-years, and altogether, 1,402 cases of endometrial cancers were encountered (Table 1). The majority of the endometrial cancers (97%) were type I, and the rest (3%) were type II cancer (Table 1). Women who used their first estradiol–progestin therapy regimen in 1995 or later contributed 41% of all accumulated woman-years and 21% of all endometrial cancers (Table 1, lower portion).

For estradiol–progestin regimens among fresh starters, a sequential estradiol–progestin therapy was more common (54%) than a continuous one (23%), and oral estradiol–progestin therapy (86%) was favored over transdermal (7%) (Table 2). Of the different progestins, norethistoterone acetate was the most popular; it was present in 44% of oral and in 91% of transdermal estradiol–progestin regimens. Medroxyprogesterone acetate (27% of all users) and dydrogesterone (12% of all users) were available only for oral use. The rest of the progestins (10% of all users) as parts of estradiol–progestin therapy were levonorgestrel, megestroleacetate progesterone, lynesterol, trimegestone, and drospirenone (Table 2). In continu-

Table 1. Number of Women Using Estradiol-Progestin Therapy, Women-Years at Risk, and Numbers of Endometrial Cancers of Type I or Type II Diagnosed up to December, 31, 2006, by Age*

			Endometrial Cancer		
Age (y)	n	Woman-Years	Type I	Type II	Total
All estradiol–progestin therapy users 1994–2006					
50–54	142,148	376,707	106	6	112
55–59	46,906	528,661	263	4	267
60–64	20,358	353,478	385	8	393
65–69	9,076	200,737	309	9	318
70–74	3,707	88,280	186	5	191
75–79	1,356	31,825	94	5	99
80–84	374	9,223	18	–	18
85 and older	90	2,291	3	1	4
Total	224,015	1,591,201	1,364	38	1,402
Users with completely known estradiol–progestin therapy 1995–2006					
50–54	92,792	241,105	61	3	64
55–59	18,653	260,756	99	3	102
60–64	5,260	91,064	83	3	86
65–69	2,452	32,621	28	1	29
70–74	1,155	14,862	10	–	10
75–79	510	6,698	8	–	8
80–84	159	2,444	1	–	1
85 and older	55	784	–	–	
Total	121,036	650,334	290	10	300

* Number of all women (N) counted by age at the beginning of the follow-up; women-years counted by age at the follow-up; cancer cases counted by the age at diagnosis.

Table 2. Number of Women Starting Estradiol–Progestin Therapy During 1995–2006 and Women-Years at Risk by Type of Therapy (N=121,036)

Estradiol–Progestin Therapy	n	Women-Years	%
Mode of regimen			
Sequential	66,129	377,429	54
Monthly	63,356	357,109	52
Long cycle (3-mo intervals)	2,773	20,320	2
Continuous	27,467	132,311	23
Other/mixed continuous	21,891	113,748	18
Route of administration			
Oral	103,590	559,695	86
Transdermal	9,110	53,656	7
Progestin			
Norethisterone acetate	53,683	291,712	44
Medroxyprogesterone acetate	32,964	205,303	27
Dydrogesterone	14,282	54,171	12
Other	11,771	62,165	10
Unclassified	8,336	36,983	7

ous estradiol–progestin regimens, norethistoterone acetate was the most common progestin (69%), followed by medroxyprogesterone acetate (11%) and dydrogesterone (4%). The long-cycle estradiol–progestin regimen contained almost exclusively medroxyprogesterone acetate.

In the total cohort, there was a risk elevation of 54% for type I cancer and 23% for type II cancer (Table 3). The standardized incidence ratios were slightly higher for cancers restricted to the uterus than for cancers spread outside of the uterus in endometrial cancer types I or II (Table 3).

The use of sequential estradiol–progestin therapy was associated with a significant risk rise (69%, 95% CI 43–96%) of type I endometrial cancer after 5 years of use and a rise of 156% (95% CI 28–358%) after 10 years (Table 4). The use of a long-cycle estradiol–progestin regimen tended to be accompanied with a higher risk for the same exposure times (3.8- and 6.6-fold risks, respectively; Table 4). The mixed use of estradiol–progestin therapy was also associated with 2.3- to 2.5-fold risks for endometrial cancer from 5 exposure years onward (Table 4).

In contrast, the use of continuous estradiol–progestin therapy was associated with a significantly reduced risk for endometrial cancer already from 3 to 5 years of use; the risk reduction was 76% (95% CI 6–60%; Table 4). The continuation of estradiol–progestin therapy for more than 5 years did not further reduce the risk (Table 4).

The use of estradiol–progestin therapy containing norethistoterone acetate for more than 5 years was accompanied by a 75% (95% CI 32–126%) risk elevation if given orally and 143% (95% CI 42–289%) risk elevation if given transdermally (Table 5); these risks did not differ significantly from each other. Sequential monthly regimens (less than 5 years) containing norethistoterone acetate, medroxyprogesterone acetate, or dydrogesterone were not associated with significant risk elevations (Table 5).

The use of estradiol–progestin therapy was accompanied by comparable risk elevations for localized and advanced-stage endometrial type I cancer (Table 6). The use of a monthly estradiol–progestin regimen favored the cancer restricted inside the uterus, which was also most reduced in women using continuous estradiol–progestin regimens (Table 6).

DISCUSSION

Taken as a whole, the use of estradiol–progestin therapy for at least 6 months was associated with a 54% elevation in the risk of endometrial cancer in the Finnish postmenopausal female population. However, only monthly and long-cycle sequential estradiol–progestin regimen use for more than 5 years were associated with significant elevation (69% and 276%, respectively) in the risk of endometrial cancer, whereas the use of continuous estradiol–progestin

Table 3. Number of Endometrial-Cancer Cases and Standardized Incidence Ratios Among Women Aged More Than 50 Years Using Estradiol–Progestin Therapy for at Least 6 Months During 1994–2006 by Type and Stage of Endometrial Cancer (N=224,015)

	Observed	Expected	SIR	95% CI
Type I endometrial cancer	1,364	887	1.54	1.46–1.62
Restricted to inside of uterus	1,195	769	1.55	1.47–1.64
Spread outside of uterus	169	118	1.43	1.22–1.65
Type II endometrial cancer	38	31	1.23	0.87–1.69
Restricted to inside of uterus	21	16	1.32	0.87–1.69
Spread outside of uterus	17	15	1.14	0.66–1.82
Total	1,402	917	1.53	1.45–1.61

SIR, standardized incidence ratios; CI, confidence interval.

Table 4. Number of Type I Endometrial Cancer Cases and Standardized Incidence Ratios Among Women Aged More Than 50 Years Using Various Forms of Estradiol–Progestin Therapy During 1994–2006 by Mode of Regimen and Duration of Use

Mode/Duration	n	Observed	Expected	SIR	95% CI
Sequential (monthly)					
6 mo to less than 3 y*	27,698	79	75	1.05	0.83–1.31
3 y to less than 5 y*	16,330	44	38	1.17	0.85–1.57
5 y or more†	25,582	152	90	1.69	1.43–1.96
10 y or more†	2,176	11	4	2.56	1.28–4.58
Long cycle (3-mo intervals)					
6 mo to less than 3 y*	1,085	6	6	1.03	0.38–2.26
3 y to less than 5 y*	666	3	3	1.03	0.21–3.01
5 y or more†	3,500	65	17	3.76	2.90–4.79
10 y or more†	356	4	1	6.64	1.81–16.99
Continuous					
6 mo to less than 3 y*	15,559	33	46	0.72	0.49–1.05
3 y to less than 5 y*	6,278	4	17	0.24	0.06–0.60
5 y or more†	10,759	12	33	0.36	0.19–0.62
10 y or more†	1,807	1	3	0.32	0.01–1.77
Mixed use‡					
6 mo to less than 3 y*	7,660	21	23	0.92	0.57–1.41
3 y to less than 5 y*	5,577	16	15	1.09	0.63–1.78
5 y or more†	57,431	421	180	2.34	2.12–2.57
10 y or more†	15,832	70	29	2.45	1.91–3.09

SIR, standardized incidence ratios; CI, confidence interval.
* Classified according to the first estradiol–progestin used.
† Classified according to the progestin used first and at 5 or at 10 years (unknown pre-register use possible).
‡ Switching mode of progestin use.

therapy showed a protective efficacy (approximately 70%) against endometrial cancer. Transdermal sequential estradiol–progestin therapy did not differ from oral therapy, and norethistoterone acetate, medroxyprogesterone acetate, and dydrogesterone did not differ from each other in endometrial safety.

We compared the incidence of endometrial cancer in estradiol–progestin therapy users with that in the entire same-aged female population, also including those using any type of postmenopausal hormone therapy. About 11% of postmenopausal women use estradiol–progestin therapy for more than 5 years.[18] Such a small proportion of women with a partly elevated and partly decreased risk for endometrial cancer in the reference background population should not markedly alter the risk estimates and

Table 5. Number of Type I Endometrial Cancer Cases and Standardized Incidence Ratios Among Women Aged More Than 50 Years Using Different Progestins and Mode of Administration in Sequential Estradiol–Progestin Therapy During 1994–2006

	6 Months to Less Than 5 Years*					5 Years or More†				
Administration	n	Observed	Expected	SIR	95% CI	n	Observed	Expected	SIR	95% CI
Oral										
Norethisterone acetate	17,118	29	34	0.84	0.56–1.20	8,508	56	32	1.75	1.32–2.26
Medroxyprogesterone acetate	15,747	53	48	1.10	0.83–1.44	7,006	35	26	1.33	0.93–1.84
Dydrogesterone	7,702	12	9	1.33	0.69–2.33	591	2	1	4.81	0.58–17.4
Other/mixed‡	4,993	16	13	1.19	0.68–1.93	7,097	42	24	1.74	1.25–2.34
Sequential (all)	45,560	110	104	1.06	0.87–1.26	23,202	135	83	1.63	1.36–1.91
Transdermal										
Norethisterone acetate	5,409	19	16	1.21	0.73–1.89	2,380	17	7	2.43	1.42–3.89

SIR, standardized incidence ratios; CI, confidence interval.
* Classified according to the type of progestin that was used first and at 5 years (no preregister use).
† According to the type of progestin that was used first and at 5 years (unknown preregister use possible).
‡ Includes progestin other than mentioned above or mixed use.

Table 6. Numbers of Type I Endometrial Cancer Cases and Standardized Incidence Ratios Among Women Aged More Than 50 Years Using Sequential Estradiol–Progestin Therapy During 1994–2006 by Mode of Regimen of Therapy and Stage of Cancer

Mode of Regimen	Observed	Expected	SIR	95% CI
Sequential				
Restricted to inside of uterus	140	78	1.79	1.51–2.10
Spread outside of uterus	12	12	1.00	0.52–1.75
Long cycle				
Restricted to inside of uterus	54	15	3.65	2.74–4.76
Spread outside of uterus	11	2	4.45	2.22–7.96
Continuous				
Restricted to inside of uterus	9	29	0.31	0.15–0.60
Spread outside of uterus	3	5	0.63	0.13–1.85
Mixed use				
Restricted to inside of uterus	376	156	2.41	2.18–2.66
Spread outside of uterus	45	24	1.88	1.37–2.51
Any use				
Restricted to inside of uterus	579	277	2.09	1.92–2.26
Spread outside of uterus	71	43	1.65	1.29–2.07

SIR, standardized incidence ratios; CI, confidence interval.

certainly should not invalidate the conclusions. It is acknowledged that our present study cannot control important confounding factors, such as parity, weight, or the use of oral contraceptives,[1] but lack of major differences between HT users and nonusers in these factors in Finland[19,20] is reassuring.

The purchases of estradiol–progestin therapy could be accurately traced from the national medical Reimbursement Registry from 1994 onward, but one can argue if the users actually used estradiol–progestin regimens. Because only a minor portion of the estradiol–progestin therapy price is reimbursed, it is apparent that women, spending their own money for estradiol–progestin regimens really used them. The whole history of modes, route of administrations, and exposure times of estradiol–progestin therapy were known only for women entering the registry as fresh starters at 1995, but even this group was big (n=121,036) for meaningful subgroup analyses.

It was vital that we could discontinue the follow-up of estradiol–progestin therapy users at hysterectomies.[21] The coverage of the Finnish Cancer Registry is almost 100%,[16] but it was conspicuous that only 3% of endometrial cancers were classified as type II cancer. The lower proportion of this cancer in our study than in some other studies[4,6] may also derive, at least in part, from national differences in the histological criteria of type II endometrial cancer.

Previous studies on the effect of sequential estradiol–progestin therapy have reported both elevations[22–26] and no effect[27–30] in the risk of endometrial cancer. In these studies, various progestins for 10–14 days have been added to conjugated equine estrogens, or estradiol, primarily each month. Our data show that monthly estradiol–progestin therapy was associated with significant risk elevations after 5 years (69%) and especially after 10 years (156%) of exposure. The opinions on the optimal duration of the monthly progestin phase in estradiol–progestin therapy are not uniform,[31] but based on our data, the progestin phases of 10–14 days each month, or for 14 days at 3 month-intervals, fail in endometrial protection. The highest risk for endometrial cancer in long-cycle estradiol–progestin therapy users in our study is in line with previous data.[32,33]

Previous studies rather uniformly indicate that the use of continuous estradiol–progestin therapy is protective against endometrial cancer.[34] The protection was 29% in a British study after 3.4 years exposure,[29] and 20% in the Women's Initiative Study after 5.6 years exposure.[35] In our study, the use of continuous estradiol–progestin therapy was associated with a marked risk reduction (approximately 76%) of endometrial cancer. The total accumulated doses of progestins in sequential and continuous estradiol–progestin regimens do not necessarily show drastic differences. Yet the sequential estradiol–progestin therapy increases, and continuous estradiol–progestin therapy reduces the risk of endometrial cancer. Thus, some estradiol-induced endometrial proliferations may fail to be eliminated with a subsequent progestin phase, and they may proceed to cancer. This may imply that, for truly effective protection, progestin must be present in the endometrium daily. The use of continuous combined estradiol–progestin therapy may eliminate some premalignant endometrial changes.[36] This may further be substantiated by our findings that the risk of endometrial cancer already started to reduce during the first 3 years of continuous estradiol–progestin therapy use.

Oral and transdermal estradiol and progestins undergo different enterohepatic metabolism, and the hormonal milieu is thus different between oral and transdermal users of estradiol–progestin therapy.[11,37] Therefore, the endometrial effects of oral and trans-

dermal regimens may not be uniform.[10] We could compare norethistoterone acetate containing sequential regimens, given orally or transdermally; they showed a similar endometrial cancer risk.

Progestins bind differently to their own and other steroid receptors, and significant variations exist in the potency of progestins to control endometrial bleedings.[11] We present here evidence that the most commonly used progestins–norethistoterone acetate, medroxyprogesterone acetate and dydrogesterone–show no difference in endometrial safety. Endometrium and breast tissue may differ in this regard; norethistoterone acetate as part of estradiol–progestin therapy was associated with a higher risk of breast cancer than some other progestins.[18,38]

Endometrial cancer in monthly sequential estradiol–progestin therapy users tended to be detected in a localized phase slightly more often than in the reference population, and this is in line with previous data.[39] Such a difference was not seen for long-cycle or continuous estradiol–progestin therapy users. This phenomenon may be related to the different age pattern of estradiol–progestin therapy users; women using sequential monthly estradiol–progestin regimen are usually younger than those wishing to avoid bleedings or to have them seldom. It is possible that endometrial pathology in estradiol–progestin therapy users expresses itself with earlier bleeding in the "younger" sequential users with a still reactive endometrium. The extra bleedings lead to diagnostic tests, such as endometrial ultrasonography and biopsy. In Finland, endometrial biopsies are taken only for medical indication and not routinely in symptomless women (eg, before the initiation of estradiol–progestin therapy).

Type I cancer deriving from the reactive endometrium dominated in our series, but also the type II cancer showed a clear increasing trend in estradiol–progestin therapy users (23% rise). This is in line with data in recent studies on obese women[6,8] but in contrast with the prevailing opinion.[40,41]

To sum up, continuous estradiol–progestin therapy is protective against endometrial cancer, whereas the use of sequential estradiol–progestin therapy is accompanied with significant risk elevation for endometrial cancer. Various progestins or routes of administration do not differ in this regard. In absolute terms, the use of estradiol–progestin therapy by 1,000 women for 10 years would mean eight extra cases of endometrial cancer if the estradiol–progestin regimen was monthly sequential, but three to four fewer cases if the estradiol–progestin regimen was continuous. All this information should be balanced with knowledge of the progestin-associated subjective side effects and late effects on the risk of other diseases (eg, breast cancer and cardiovascular disease) related to the use of estradiol–progestin therapy.

REFERENCES

1. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005;366:491–505.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
3. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: A synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:1531–43.
4. Prat J. Prognostic parameters of endometrial carcinoma. Hum Pathol 2004;35:649–62.
5. Brown L. Pathology of uterine malignancies. Clin Oncol (R Coll Radiol) 2008;20:433–47.
6. Bjorge T, Engeland A, Tretli S, Weiderpass E. Body size in relation to cancer of the uterine corpus in 1 million Norwegian women. Int J Cancer 2007;120:378–83.
7. Weiss JM, Saltzman BS, Doherty JA, Voigt LF, Chen C, Beresford SA, et al. Risk factors for the incidence of endometrial cancer according to the aggressiveness of disease. Am J Epidemiol 2006;164:56–62.
8. McCullough ML, Patel AV, Patel R, Rodriguez C, Feigelson HS, Bandera EV, et al. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev 2008;17:73–9.
9. Lethaby A, Suckling J, Barlow D, Farquhar CM, Jepson RG, Roberts H. Hormone replacement therapy in postmenopausal women: Endometrial hyperplasia and irregular bleeding. The Cochrane Database of Systematic Reviews, Issue 3. Art No.: CD000402.
10. Stanczyk FZ. Percutaneus administration of progesterone: blood levels and endometrial protection. Menopause 2005;2: 232–7.
11. Stanczyk FZ. All progestins are not created equal. Steroids 2003;68:879–90.
12. Davis SR, Dinatale I, Rivera-Woll L, Davison S. Postmenopausal hormone therapy: From monkey glands to transdermal patches. J Endocrinol 2005;185:207–22.
13. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. IARC Monogr Eval Carcinog Risks Hum 2007;91:1–528.
14. Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, et al. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. Lancet Oncol 2005;6:552–3.
15. Keskimaki I, Aro S, Teperi J. Regional variation in surgical procedure rates in Finland. Scand J Soc Med 1994;22:132–8.
16. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncol 1994;33:365–9.
17. Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. Philadelphia (PA): Lippincott-Raven Publishers; 1998. p 264.
18. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estradiol-progestogen therapy. Obstet Gynecol 2009;113:65–73.
19. Pukkala E, Weiderpass E. Time trends in socio-economic differences in incidence rates of cancers of the breast and

female genital organs (Finland, 1971–1995). Int J Cancer 1999;81:56–61.

20. Topo P, Luoto R, Hemminki E, Uutela A. Declining socioeconomic differences in the use of menopausal and postmenopausal hormone therapy in Finland. Maturitas 1999;32:141–5.
21. Luoto R, Raitanen J, Pukkala E, Anttila A. Effect of hysterectomy on incidence trends of endometrial and cervical cancer in Finland 1953–2010. Br J Cancer 2004;90:1756–9.
22. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, et al. Estrogen-progestin replacement therapy and endometrial cancer. J Natl Cancer Inst 1997;89:1110–6.
23. Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. Lancet 1997;349:458–61.
24. Weiderpass E, Adami HO, Baron JA, Magnusson C, Bergstrom R, Lindgren A, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. J Natl Cancer Inst 1999;91:1131–7.
25. Lacey JV Jr, Brinton LA, Lubin JH, Sherman ME, Schatzkin A, Schairer C. Endometrial carcinoma risks among menopausal estrogen plus progestin and unopposed estrogen users in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev 2005;14:1724–31.
26. Doherty JA, Cushing-Haugen KL, Saltzman BS, Voigt LF, Hill DA, Beresford SA, et al. Long-term use of postmenopausal estrogen and progestin hormone therapies and the risk of endometrial cancer. Am J Obstet Gynecol 2007;197:139.e1–7.
27. The writing group for the PEPI trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. JAMA 1996;275:370–5.
28. Reed SD, Voigt LF, Beresford SA, Hill DA, Doherty JA, Weiss NS. Dose of progestin in postmenopausal-combined hormone therapy and risk of endometrial cancer. Am J Obstet Gynecol 2004;191:1146–51.
29. Beral V, Bull D, Reeves G, Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the million women study. Lancet 2005;365:1543–51.
30. Lacey JV Jr, Leitzmann MF, Chang SC, Mouw T, Hollenbeck AR, Schatzkin A, et al. Endometrial cancer and menopausal hormone therapy in the national institutes of health-AARP diet and health study cohort. Cancer 2007;109:1303–11.
31. Gambacciani M, Monteleone P, Sacco A, Genazzani AR. Hormone replacement therapy and endometrial, ovarian and colorectal cancer. Baillieres Best Pract Res Clin Endocrinol Metab 2003;17:139–47.
32. Bjarnason K, Cerin A, Lindgren R, Weber T. Adverse endometrial effects during long cycle hormone replacement therapy. Scandinavian long cycle study group. Maturitas 1999;32:161–70.
33. Pukkala E, Tulenheimo-Silfvast A, Leminen A. Incidence of cancer among women using long versus monthly cycle hormonal replacement therapy, Finland 1994–1997. Cancer Causes Control 2001;12:111–5.
34. van de Weijer PH, Mattsson LA, Ylikorkala O. Benefits and risks of long-term low-dose oral continuous combined hormone therapy. Maturitas 2007;56:231–48.
35. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: The women's health initiative randomized trial. JAMA 2003;290:1739–48.
36. Wells M, Sturdee DW, Barlow DH, Ulrich LG, O'Brien K, Campbell MJ, et al. Effect on endometrium of long term treatment with continuous combined oestrogen-progestogen replacement therapy: Follow up study. BMJ 2002;325:239–43.
37. L'Hermite M, Simoncini T, Fuller S, Genazzani AR. Could transdermal estradiol + progesterone be a safer posmenopausal HRT? A review. Maturitas 2008;60:185–201.
38. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. Breast Cancer Res Treat 2008;107:103–11.
39. Weiss JM, Saltzman BS, Doherty JA, Voigt LF, Chen C, Beresford SA, et al. Risk factors for the incidence of endometrial cancer according to the aggressiveness of disease. Am J Epidemiol 2006;164:56–62.
40. Emons G, Fleckenstein G, Hinney B, Huschmand A, Heyl W. Hormonal interactions in endometrial cancer. Endocr Relat Cancer 2000;7:227–42.
41. Acharya S, Hensley ML, Montag AC, Fleming GF. Rare uterine cancers. Lancet Oncol 2005;6:961–71.