Low-potency oestrogen and risk of endometrial cancer: a case-control study

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Summary

Background Urogenital symptoms are common among postmenopausal women. Such symptoms may be alleviated by low-potency oestrogen formulations administered orally or vaginally. Although low-potency oestrogen formulations are assumed to have few, if any, adverse effects on the endometrium, risk of endometrial neoplasia has not been quantified.

Methods In a nationwide population-based case-control study in Sweden of endometrial cancer among postmenopausal women, we obtained detailed information on hormone replacement from 789 cases of endometrial cancer and 3368 population controls. In a histopathological review, 80 cases were reclassified as having endometrial atypical hyperplasia. Odds ratios and 95% CI were calculated with unconditional logistic regression.

Findings After multivariate adjustment, oral use of oestriol 1–2 mg daily increased the relative risk of endometrial cancer and endometrial atypical hyperplasia: the odds ratios for at least 5 years of use compared with never use were 3·0 (95% CI 2·0–4·4) and 8·3 (4·0–17·4), respectively. The association was stronger for well-differentiated cancers and those with limited invasion. The excess relative risk was lost rapidly after cessation of treatment. Only weak associations were observed between vaginal application of low-potency oestrogen formulations and relative risk of endometrial neoplasia.

Interpretation Oral, but not vaginal, treatment with low-potency oestrogen formulations increases the relative risk of endometrial neoplasia. Thus close surveillance of patients is needed, and addition of a progestagen should be considered.

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Introduction

Early symptoms of oestrogen deficiency after the menopause are mainly systemic, dominated by vasomotor instability (eg, hot flushes and night sweats).[1] Among older postmenopausal women, local symptoms due to atrophy of the vaginal and urethral epithelium may predominate.[2] Although medium-potency oestrogens, mainly oestradiol and conjugated oestrogen, clearly alleviate these symptoms,[1,2] benefits may be achieved by the use of low-potency oestrogen formulations administered orally (oestriol) or intravaginal (oestriol, dienoestrol, or oestradiol in very low doses).[3–6] Therefore, prescription of such formulations is common in several countries, particularly in Europe.

Is treatment with low-potency oestrogen formulations based on good scientific evidence? An excess risk of endometrial cancer after use of the more potent oestrogens is well established, although this increase in risk may be reduced or prevented by addition of progestagens.[7] By contrast, the risk of endometrial cancer among users of low-potency oestrogen formulations has never been adequately quantified in epidemiological studies. If, as is generally assumed,[4,6,8–11] such compounds provide symptomatic relief without adverse endometrial effects, more widespread use might be justified. We addressed these issues because low-potency oestrogen formulations have been used estensively in Sweden and we had access to detailed information on hormone replacement within a large nationwide epidemiological study on endometrial cancer.

Participants and methods

Participants

This population-based case-control study was carried out among women aged 50–74 years, born in Sweden and resident there between Jan 1, 1994, and Dec 31, 1995. We restricted our study to postmenopausal women who had not undergone hysterectomy or had a previous diagnosis of endometrial or breast cancer. Women eligible as cases had newly diagnosed and histopathologically confirmed endometrial cancer during the study period. They were identified through the six regional cancer registries covering all of Sweden. Women were contacted through their physicians.

Control women were randomly selected during the whole study period from a continuously updated population register, which includes the national registration number, name, date of birth, address, and place of birth for all residents of Sweden. Most of the controls (2633) were also participants in a coordinated, concomitant breast-cancer case-control study; the remaining (735) controls were separately sampled for this study after completion of the breast-cancer study. The study bases for the breast-cancer and endometrial-cancer studies were similar, the only difference being the exclusion of women who had undergone hysterectomy.

Controls were matched by frequency to the expected age distribution of breast-cancer and endometrial-cancer cases (age was adjusted for in all analyses). All participants and technical staff were unaware of the aims of the study. The local ethics committee approved the design of the study.

Participation rates were 75% (789 of 1055 eligible) among cases and 80% (3368 of 4216 eligible) of controls. Non-participation was due to refusal in 171 (16%) cases and 811 (19%) controls, and to death or poor health in 37 (1%) controls. The patients' physicians refused permission to contact an additional 95 (9%) cases.

Data collection

Data were obtained through a mailed questionnaire requesting detailed information on use of replacement hormones, including brand, dose, and date of first and last use for each treatment episode. Recall was aided by a picture chart of all brands commercially available in Sweden during 1950–95. The questionnaire also covered reproductive and medical history, anthropometry, and lifestyle (eg, smoking, drinking, and dietary habits). The mean time from diagnosis to questionnaire response was 8·4 months (SD 4·6).

Age at menopause was defined as the age of the last menstrual period or age at bilateral oophorectomy, if at least 1 year before data collection (if later, women were classified as premenopausal and excluded). Women with menses resulting from hormone replacement therapy or with missing information (44 cases and 206 controls) were classified as postmenopausal if they had reached the 90th percentile of age at natural menopause of study participants (current smokers 55 years for cases and controls; non-smokers 56 years for cases and 55 years for controls); if they had not reached this age (one case and 51 controls) they were classified as having unknown menopausal status and were excluded from the analysis. Women classified as postmenopausal in this way were assigned an age at menopause according to their current smoking status and mean age at natural menopause in our data.

Among participating controls, 491 (15%) did not return the mailed questionnaire but agreed to a telephone interview that included all relevant items in the mailed questionnaire. All cases who had given consent to participate in the study returned the mailed questionnaire. About 50% of all cases and controls were contacted by telephone for essential completion of missing information in their mailed questionnaire (mainly details of hormone use).

Histopathological classification

The original histopathological specimens from the cases (reported as endometrial cancer to the cancer registry) were retrieved from all 35 departments of pathology in Sweden. The specimens were reviewed by one pathologist (AL) who, unaware of hormone use and other exposures, reclassified them as endometrial adenocarcinoma, seropapillary carcinoma, clear-cell carcinoma, adenoacanthoma, adenosquamous carcinoma, anaplastic carcinoma, malignant mixed mullerian tumours, or endometrial atypical hyperplasia (slight, moderate, or severe), defined as adenomatous hyperplasia with slight, moderate, or severely pronounced atypia. Endometrioid adenocarcinoma was further classified as well (grade 1), moderately (grade 2), or poorly (grade 3) differentiated.

Slides of the uterine body (from hysterectomy) were available for 542 (76%) cases. Myometrial invasion was classified as none, less than 50%, at least 50% of the myometrial thickness, or through the serosa.

Among cases included, the carcinoma diagnosis was confirmed in 709, whereas 80 were reclassified as having atypical hyperplasia without evidence of invasion; these two groups were analysed separately. 13 women with anaplastic and six with malignant mixed mullerian tumours, four with cancer diagnoses other than endometrial cancer, and five whose histopathological slides were missing were excluded from the analysis.

Data analysis

We classified all reported treatment episodes by duration and recency. Low-potency oestrogen formulations were oral oestriol in doses of 1–2 mg (daily) or vaginal dienoestrol 0·5 mg, oestriol 0·5 mg, or oestradiol 25 μg (daily applications during the initial 2–3 weeks of treatment, followed by applications twice weekly), used without addition of progestagens. Medium-potency oestrogens were mainly oestradiol and conjugated oestrogens; treatment episodes were classified as without added progestagens or as combined oestrogen-progestagen therapy (oestrogens combined cyclically or continuously with a progestagen). The fourth category was progestagens without concomitant use of oestrogen.

We calculated all exposure after an index date, defined in cases as 6 months before the date of diagnosis, and in controls as 6 months before the date of questionnaire arrival minus the mean time from diagnosis to questionnaire arrival for the cases.

We calculated odds ratios as measures of relative risk, using unconditional logistic-regression models estimated by the maximum-likelihood method. SAS version 6.12 was used. Women who had never used oral or vaginal low-potency oestrogen formulations were compared with women who had ever used them. Women who had used these formulations were subdivided by duration of use (up to 5 years and at least 5 years, and for each year of use) and recency of use, defined as the time elapsed between cessation of treatment and index date (less than 1 year and at least 1 year, and for each year after cessation of treatment). We estimated odds ratios in age-adjusted models, and subsequently in multivariate models. In the multivariate models we included covariates previously described as associated with risk of endometrial cancer that did change estimates of relative risk in our data. These covariates were age (as a continuous variable), use of other hormone-replacement regimens (medium-potency oestrogens without added progestagens, combined oestrogen-progestagen therapy, and progestagens without oestrogens), smoking (ever or never smoked regularly), parity (nulliparous, one to three children, four or more children), age at last birth (nulliparous, <27 years, 27–29 years, 30–33 years, ⩾34 years), age at menopause (<45 years, 45–49 years, 50–51 years, 52–54 years, >54 years), body-mass index (according to quartiles of the distribution among controls), and use of oral contraceptives (never or ever). We also analysed the effect of exclusive use of oral or vaginal low-potency oestrogen formulations (ie, we excluded from the dataset women who had used any other kind of hormone-replacement therapy). In the anlysis of exclusive use we included in the logistic-regression models all covariates described above (except for hormone-replacement variables). We calculated tests for trend according to duration of use of low-potency oestrogen formulations by the introduction of semi-continuous variables obtained by assigning consecutive integers to values of the categorised duration variables.

Estimates of increment in relative risk per year of use of hormones included unexposed women, to whom we attributed zero as duration of treatment. Because age-adjusted results were generally similar to results from the chosen multivariate models, only the latter are presented.

Results

The characteristics of the study participants are summarised in table 1. The differences between endometrial cancer cases and controls in age at menopause, parity, age at last birth, body-mass index, use of oral contraceptives, and smoking reflected established epidemiological associations. Among the 648 cases of adenocarcinoma, 241 (37%) were classified as well differentiated, 286 (44%) as moderately differentiated, and 121 (19%) as poorly differentiated; no or little endometrial invasion was observed in 362 women (67% of those with available myometrium slides) and 180 (33%) had more than 50% tumour infiltration. Owing to small numbers, all atypical hyperplasias were analysed together, but most (44%) were classified as severe.

Use of oral oestriol was reported by a higher proportion of endometrial-cancer cases than controls (20·1% *vs*

Characteristic	Number providing information		Cases	Controls
	Cases	Controls		
Demography and anthropometry				
Age (years)	709	3368	65·4 (6·0)	64·0 (6·6)
Body-mass index (kg/m²)	709	3323	27·6 (5·3)	25·5 (4·3)
Reproductive history				
Age at menarche (years)	643	3060	13·5 (1·4)	13·6 (1·4)
Age at menopause (years)	705	3304	51·0 (4·1)	50·1 (3·9)
Parity	709	3366	1·9 (1·2)	2·1 (1·4)
Nulliparous	709	3366	104 (14·7%)	390 (11·6%)
Age at first birth (years), among parous	605	2975	24·8 (4·4)	24·6 (4·6)
Age at last birth (years), among parous	604	2973	29·5 (5·0)	30·4 (5·3)
Risk factors				
Ever-use of oral contraceptives	708	3363	157 (22·2%)	1106 (32·9%)
Ever smoked regularly	709	3367	241 (34·0%)	1428 (42·4%)
Diabetes mellitus	709	2884	83 (11·7%)	164 (5·7%)
Hypertension	700	2871	245 (35·0%)	772 (26·9%)
Use of low-potency oestrogen formulations				
Orally administered oestriol (1–2 mg daily)	707	3339	142 (20·1%)	361 (10·8%)
Vaginal application*	708	3338	104 (14·7%)	377 (11·3%)
Use of medium-potency oestrogens				
Without progestagens	687	3270	98 (14·3%)	177 (5·4%)
With progestagens	692	3275	119 (17·2%)	478 (14·6%)
Use of progestagens without oestrogens	707	3338	36 (5·1%)	107 (3·2%)

Data are mean (SD) or number (% of total providing information).
*Oestriol 0·5 mg, dienoestrol 0·5 mg, oestradiol 25 μg; daily applications during the initial 2–3 weeks of treatment, followed by applications twice weekly.

Table 1: **Characteristics of postmenopausal endometrial cancer cases and controls**

10·8%; table 1). Among women who used oral oestriol, the daily dose was 1 mg in 58% and 2 mg in 31%; 1% could not remember the dose taken. Women who had ever used oestriol had a two-fold increased relative risk of endometrial cancer compared with those who never used oral oestriol. Women exposed for less than 5 years had an odds ratio of 1·7 and those exposed for at least 5 years had an odds ratio of 3·0 ($p<0·0001$ for trend). When duration of use of oral oestriol was analysed as a continuous variable, relative risk increased by 8% per year ($p<0·0001$; table 2).

Most women had recent exposure. Women who stopped exposure more than 1 year before the index date (6 months before diagnosis) had no discernible increase in relative risk compared with those who had never used oestriol (table 2). Because of small numbers, no stratified analyses were done for duration within recency categories.

Exclusive use of orally administered oestriol, without previous or subsequent use of any other hormone-replacement formulations, was observed among 77 (9·6%) cases and 226 (6·3%) controls. The odds ratio (multivariate analysis) for those who had used only oral oestriol compared with those who did not use any treatment was 2·1 (95% CI 1·6–2·9) and the increment in relative risk per year of use was 1·09 (1·05–1·13); these estimates were similar to those shown in table 2, which included women with mixed exposures.

In a further subgroup analysis by histological grade, the association with oral oestriol use was much stronger for well-differentiated (grade 1) than for less-differentiated (grades 2 and 3) cancers; after at least 5 years of use, relative risks were increased about five-fold and two-fold, respectively. Similarly, the excess relative risk after oral oestriol was higher for tumours with no or limited infiltration than for tumours with 50% or more infiltration (table 3).

Among the 80 cases who were reclassified after histopathological review as having atypical hyperplasias rather than invasive cancer, 27 (34%) had used oral oestriol. In a multivariate analysis, the odds ratio for use was 3·7, with an eight-fold increase in relative risk after at least 5 years of use. The increment in relative risk per year of use was 12% ($p<0·0001$). As for invasive cancer, the excess relative risk for atypical hyperplasia was lost soon after cessation of treatment (table 2).

Use of vaginally administered low-potency oestrogen formulations was reported by 14·7% of cases and 11·3% of controls (table 1). After multivariate adjustment, the odds ratio associated with ever use was 1·2 and the increment per year of use was 2% ($p=0·15$; table 4). Exclusive use of vaginal low-potency oestrogen formulations was reported by 56 (6·9%) cases and 241 (6·8%) controls, yielding an odds ratio for ever use of 1·4 (1·0–2·0). We found no evidence of a differential effect of vaginal use of low-potency oestrogen formulations on tumour grade or myometrial invasiveness (data not shown). We also examined the 15 women who had their tumour reclassified as atypical hyperplasia, and who had used vaginal low-potency oestrogen formulations (table 4).

49% of vaginal treatment episodes consisted of oestriol (0·5 mg), 44% dienoestrol (0·5 mg), and 7% oestradiol (25 μg). Because of the possibility that vaginal use of oestriol and dienoestriol could have different effects on the endometrium, we also analysed use of these hormones separately. (There were not enough women who used vaginal oestradiol to allow a meaningful analysis in that subgroup.) In the multivariate analysis, use of vaginal oestriol (used by 49 cases and 195

Category	Endometrial cancer			Endometrial atypical hyperplasia		
	Cases	Controls	Odds ratio (95% CI)	Cases	Controls	Odds ratio (95% CI)*
Never use	534	2792	1·0	497	2792	1·0
Ever use	137	336	2·0 (1·6–2·6)	24	336	3·7 (2·1–6·5)
Duration						
<5 years	86	247	1·7 (1·3–2·3)	10	247	2·2 (1·0–4·6)
⩾5 years	51	89	3·0 (2·0–4·4)	14	89	8·3 (4·0–17·4)
Increment per year of use	. .	. .	1·08 (1·05–1·12)	. .	. .	1·12 (1·07–1·18)
Recency of use						
<1 year	116	248	2·4 (1·8–3·0)	20	248	4·7 (2·6–8·5)
⩾1 year	21	88	1·2 (0·7–2·0)	4	88	1·3 (0·3–4·9)
Decrease per year after cessation	. .	. .	0·92 (0·87–0·98)	. .	. .	0·83 (0·68–1·01)

From the 709 cases and 3368 controls enrolled in the study, women with missing values for any covariate were excluded from the analyses.
*Adjusted for age, parity, age at menopause, body-mass index, use of oral contraceptives, age at last birth, smoking, duration of use of oestrogens without progestagens, oestrogens with progestagens, progestagens without oestrogens, and vaginal low-potency oestrogen formulations (oestriol 0·5 mg, dienoestrol 0·5 mg, oestradiol 25 μg).

Table 2: **Odds ratios of invasive endometrial cancer and endometrial atypical hyperplasia in relation to use of oral oestriol (1–2 mg)**

Category	Histological differentiation						Degree of myometrium invasion			
	Well		Moderate		Poor		0–50% of thickness		⩾50% of thickness	
	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
Never use	224/2792	1·0	275/2792	1·0	116/2792	1·0	271/2792	1·0	141/2792	1·0
Ever use	56/336	2·7 (1·9–3·8)	57/336	2·1 (1·5–3·0)	17/336	1·5 (0·9–2·6)	72/336	2·1 (1·5–2·8)	28/336	1·6 (1·0–2·5)
Duration of use										
<5 years	30/247	1·9 (1·2–3·0)	40/247	2·0 (1·4–3·0)	11/247	1·3 (0·7–2·5)	44/247	1·7 (1·1–2·4)	15/247	1.2 (0·7–2·1)
⩾5 years	26/89	5·0 (3·0–8·4)*	17/89	2·4 (1·3–4·3)*	6/89	2·1 (0·9–5·2)†	28/89	3·4 (2·1–5·5)*	13/89	2·5 (1·3–4·9)‡
Increment per year of use	. .	1·11 (1·06–1·15)		1·06 (1·02–1·11)		1·06 (1·00–1·13)		1·09 (1·05–1·13)		1·05 (1·00–1·11)

Women with missing values for any covariate were excluded from the analyses. Odds ratios adjusted for factors listed in table 2.
For trend over categories: *p<0·0001; †p=0·09; ‡p=0·009.

Table 3: **Odds ratios (OR) of endometrial cancer after menopausal use of oral oestriol, by histological grade and degree of invasion of the myometrium**

controls) entailed an odds ratio of 1·1 (0·8–1·6), and vaginal dienoestrol (used by 46 cases and 188 controls) an odds ratio of 1·0 (0·7–1·5) compared with never use of these formulations.

Discussion

We found evidence of an increased relative risk of endometrial cancer in postmenopausal women who had used oral oestriol. The relative risk increased with duration of use and was highest for well-differentiated and least invasive tumours. An even greater excess increase in relative risk was noted for endometrial atypical hyperplasia, a premalignant or early malignant lesion that may be difficult to distinguish unambiguously from invasive cancer, as shown by the histopathology review in this and previous investigations.[12] By contrast, vaginally administered low-potency oestrogen formulations were not associated with a substantial increase in relative risk for endometrial cancer or atypical hyperplasia.

Chance is unlikely to explain our findings, and there was no evidence that confounding could account for our results. Bias is a more serious concern, although the population-based design and high participation rates reduce the potential for selection bias. However, data collection through telephone interviews in 15% of the controls may have introduced information bias, although the possible enhancement of recall in these controls would, if anything, lead to an underestimation of relative risks. We believe that information bias was unlikely, since we found clear and differential patterns of relative risk with types of administration and with histopathological features of the tumour. Differential diagnostic classification in relation to hormone use can be ruled out because histopathological review was done without knowledge of hormone use. More intense surveillance among women receiving low-potency oestrogen formulations is unlikely, since oestriol has not been reported to affect the endometrial cancer risk; in Sweden, postmenopausal vaginal bleeding would lead to endometrial biopsy with short delay irrespective of such exposure. We reduced the possibility of a reverse causality association (because of treatment of symptoms) by considering only exposure at least 6 months before diagnosis.

Data from other epidemiological studies on low-potency oestrogen formulations and endometrial cancer are scarce. In a hospital-based case-control study in Finland, a 60% decrease in the relative risk of endometrial cancer was found among women who took oestriol orally; however, doses and duration of treatment were not reported.[10] In a population-based prospective cohort study in Sweden, women prescribed low-potency oestrogen formulations (oral oestriol) showed no overall increase in the risk of endometrial cancer; however, data on duration and recency of intake were not available.[13] Kelsey and colleagues[14] reported an increased risk of endometrial cancer after vaginal hormone use. However, the study had no information on formulations used or duration of therapy.

There is some evidence that oral oestriol may have systemic effects. Englund and colleagues[15] showed that more than 50% of postmenopausal women treated with oral oestriol 6 mg daily for 3 months had menstrual bleeding after addition of a progestagen. In a Swedish study, postmenopausal women referred for vaginal bleeding were examined with ultrasonographic measurement of endometrial thickness before biopsy.[16] The average endometrial thickness was greater and endometrial atypical hyperplasia was more common among users of oral oestriol and medium-potency oestrogens, than among unexposed women. A trial in Japanese postmenopausal women treated with oral oestriol 2 mg daily for 1 year showed both prevention of bone loss and alleviation of climacteric symptoms.[17]

Owing to its low affinity, oestriol binds to the oestrogen receptor in vitro for a shorter time than do medium or

Category	Endometrial cancer			Endometrial atypical hyperplasia		
	Cases	Controls	Odds ratio (95% CI)*	Cases	Controls	Odds ratio (95% CI)*
Never use	575	2776	1·0	58	2776	1·0
Ever use	94	342	1·2 (1·0–1·6)	13	342	1·5 (0·8–3·0)
Duration						
<5 years	66	242	1·2 (0·9–1·7)	6	242	1·1 (0·5–2·8)
⩾5 years	28	100	1·2 (0·8–1·9)	7	100	2·3 (0·9–5·6)
Increment per year of use	. .	. .	1·02 (0·97–1·06)	. .	. .	1·07 (1·00–1·14)

From the 709 cases and 3368 controls enrolled into the study, women with missing values for any covariate were excluded from the analyses.
*Adjusted for age, parity, age at menopause, body-mass index, use of oral contraceptives, age at last birth, smoking, duration of use of oestrogens without progestagens, oestrogens with progestagens, progestagens without oestrogen, and oral oestriol (1–2 mg).

Table 4: **Odds ratios of invasive endometrial cancer and endometrial atypical hyperplasia in relation to use of vaginal oestrogens**

high-potency oestrogens.[18,19] Oestriol administered orally is conjugated efficiently in the liver,[20] but because oestriol does not bind strongly to proteins, most of the serum oestriol is biologically active.[21] When oestriol is taken continuously, the persistently high serum concentrations can lead to long-standing proliferation of endometrial cells.[22,23]

In Heimer and Englund's study, serum concentrations of unbound oestriol 24 h after administration were similar for 1 mg oestriol administered vaginally and 10 mg taken orally; that finding suggests that vaginal absorption is more effective than oral administration.[24] However, extrapolation of those data to long-term effects is not straightforward, since oestriol is usually given in oral doses of 1 mg or 2 mg daily, and vaginal administration in a dose of 0·5 mg twice weekly. Furthermore, vaginal absorption and thereby serum concentrations decrease as the vaginal epithelium matures 1–2 weeks after the start of vaginal treatment, as shown for both vaginal oestriol and oestradiol.[3,24]

Our findings have at least two implications for medical practice. First, there is a need to monitor the endometrium during such treatment, and the addition of progestagens should be considered. Second, if the indication for treatment is atrophy only, vaginal application of low-potency oestrogen formulations is preferable. In some women there may be a rationale for use of medium-potency oestrogens or an oestrogen-progestagen regimen to gain other benefits such as a lower risk of osteoporosis and the possibility of some reduction in the risk of coronary heart disease.[25–28]

Contributors

Elisabete Weiderpass was responsible for study coordination and data processing and analysis, and drafted the paper. Hans-Olov Adami, Ingemar Persson, and John Baron suggested and designed the study and supervised data analysis. Cecilia Magnusson was responsible for recruitment and, with Nestor Correia, developed a system for classification of different medications into hormone information. Anders Lindgren reviewed histopathological slides. Reinhold Bergstrom supervised statistical analyses. All investigators contributed to the paper.

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References

1 Barrett-Connor E. Hormone replacement therapy. *BMJ* 1998; **317:** 457–61.

2 Speroff L, Glass RH, Kase NG. Menopause and postmenopausal hormone therapy. In: Clinical gynecology, endocrinology, and infertility. 5th edn. Baltimore: Williams and Wilkins, 1994: 583–650.

3 Nilsson K, Heimer G. Low-dose oestradiol in the treatment of urogenital oestrogen deficiency—a pharmacokinetic and pharmacodynamic study. *Maturitas* 1992; **15:** 121–27.

4 Heimer G, Samsioe G. Effects of vaginally delivered estrogens. *Acta Obstet Gynecol Scand Suppl* 1996; **163:** 1–2.

5 Cardozo L, Benness C, Abbott D. Low dose oestrogen prophylaxis for recurrent urinary tract infections in elderly women. *Br J Obstet Gynaecol* 1998; **105:** 403–07.

6 Genant HK, Lucas J, Weiss S, et al. Low-dose esterified estrogen therapy: effects on bone, plasma, estradiol concentrations, endometrium, and lipid levels: Estratab/Osteoporosis Study Group. *Arch Intern Med* 1997; **157:** 2609–15.

7 Grady D, Ernster V. Endometrial cancer. In: Schottenfeld D, Fraumeni J Jr, eds. Cancer epidemiology and prevention, 2nd edn. New York: Oxford University Press, 1996: 1058–89.

8 Borglin NE. Effect of oestriol on the female genital tract. *Acta Obstet Gynecol Scand* 1959; **38:** 157–71.

9 Lauritzen C, Velibese S. Clinical investigations of a long-acting oestriol (polyoestriol phosphate). *Acta Endocrinol* 1961; **38:** 73–87.

10 Salmi T. Endometrial carcinoma risk factors, with special reference to the use of estrogens. *Acta Endocrinol Suppl (Copenh)* 1980; **233:** 37–43.

11 Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. *Maturitas* 1996; **23:** 259–63.

12 Persson I, Adami H-O, Lindgren A, Nordlinder H, Petterson B, Silverberg S. Reliability of endometrial cancer diagnosis in a Swedish cancer registry—with special reference to classification bias related to exogenous estrogens. *Acta Pathol Immunol Scand* 1986; **94:** 187–94.

13 Schairer C, Adami H-O, Hoover R, Persson I. Cause specific mortality in women receiving hormone replacement therapy. *Epidemiology* 1997; **8:** 59–65.

14 Kelsey J, Livolsi V, Holford TR, et al. A case-control study of cancer of the endometrium. *Am J Epidemiol* 1982; **116:** 333–42.

15 Englund DE, Johansson DB. Endometrial effect of oral estriol treatment in postmenopausal women. *Acta Obstet Gynecol Scand* 1980; **59:** 449–51.

16 Granberg S, Ylostalo P, Wikland M, Karlsson B. Endometrial sonographic and histologic findings in women with and without hormonal replacement therapy suffering from postmenopausal bleeding. *Maturitas* 1997; **27:** 35–40.

17 Minaguchi H, Uemura T, Shirasu K, et al. Effect of estriol on bone mass loss in postmenopausal Japanese women: a multicentric prospective open study. *J Obstet Gynaecol Res* 1996; **22:** 259–65.

18 Esposito G. Estriol: a weak estrogen or a different hormone? *Gynecol Endocrinol* 1991; **5:** 131–53.

19 Botella J, Duranti E, Viader V, Duc I, Delansorne R, Paris J. Lack of estrogenic potential of progesterone- or 19-nor-progesterone-derived progestins as opposed to testosterone or 19-nor-testosterone derivatives on endometrial Ishikawa cells. *J Steroid Biochem Mol Biol* 1995; **55:** 77–84.

20 Schiff I, Tulchinsky D, Ryan KJ, Kadner S, Levitz M. Plasma estriol and its conjugates following oral and vaginal administration of estriol to postmenopausal women: correlations with gonadotropin levels. *Am J Obstet Gynecol* 1980; **15:** 1137–41.

21 Vermeulen AJ, Verdonck L. Studies on the binding of testosterone to human plasma. *Steroid* 1968; **11:** 609–35.

22 Clark JH, Paszko Z, Peck EJ Jr. Nuclear binding and retention of the receptor complex: relation to the agonist and antagonist properties of estriol. *Endocrinology* 1977; **100:** 91–96.

23 Korach K, Foz-Davies C, Baker V. Differential response to estriol and estradiol in the mouse uterus: correlation to an additional nuclear event. *Endocrinology* 1980; **106:** 1900–06.

24 Heimer GM, Englund DE. Estriol absorption after long-term vaginal treatment and gastrointestinal absorption as influenced by a meal. *Acta Obstet Gynecol Scand* 1984; **63:** 563–67.

25 Toozs-Hobson P, Cardozo L. Hormone replacement therapy for all? Universal prescription is desirable. *BMJ* 1996; **131:** 350–52.

26 Grodstein F, Stampfer MJ, Colditz GA, et al. Postmenopausal hormone therapy and mortality. *N Engl J Med* 1997; **336:** 1769–75.

27 Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coroneary heart disease in postmenopausal women. Heart and estrogen/progestin replacement study (HERS) research group. *JAMA* 1998; **280:** 605–13.

28 Petitti DB. Hormone replacement therapy and heart disease prevention: experimentation trumps observation. *JAMA* 1998; **280:** 650–52.