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Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition

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Epidemiology

Menopausal hormone therapy (MHT) is characterized by use of different constituents, regimens and routes of administration. We investigated the association between the use of different types of MHT and breast cancer risk in the EPIC cohort study. The analysis is based on data from 133,744 postmenopausal women. Approximately 133,744 postmenopausal women contributed to this analysis. Information on MHT was derived from country-specific self-administered questionnaires with a single baseline assessment. Incident breast cancers were identified through population cancer registries or by active follow-up (mean: 8.6 yr). Overall relative risks (RR) and 95% confidence interval (CI) were derived from country-specific Cox proportional hazard models estimates. A total of 4312 primary breast cancers were diagnosed during 1,153,747 person-years of follow-up. Compared with MHT never users, breast cancer risk was higher among current users of estrogen only (RR: 1.42, 95% CI 1.23–1.64) and higher still among current users of combined MHT (RR: 1.77, 95% CI 1.40–2.24; $p = 0.02$ for combined *vs*. estrogen-only). Continuous combined regimens conferred a 43% (95% CI: 19–72%) greater risk compared with

Key words: breast cancer, HRT, epidemiology, cohort studies, menopause, estrogens, progestins, dosage

Abbreviations: MHT: menopausal hormone therapy; CEE: conjugated equine estrogen; EPIC: European Prospective Investigation into Cancer and Nutrition; ICD-10: International Classification of Diseases, 10th revision; RR: relative risk; CI: confidence interval; SD: standard deviation; NETA: norethisterone acetate

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sequential regimens. There was no significant difference between progesterone and testosterone derivatives in sequential regimens. There was no significant variation in risk linked to the estrogenic component of MHT, neither for oral *vs.* cutaneous administration nor for estradiol compounds *vs.* conjugated equine estrogens. Estrogen-only and combined MHT uses were associated with increased breast cancer risk. Continuous combined preparations were associated with the highest risk. Further studies are needed to disentangle the effects of the regimen and the progestin component.

There is considerable epidemiologic evidence that menopausal exposure to exogenous sex steroid hormones plays an important role in the development of breast cancer in women[1] and combined estrogen-progestin hormonal therapy has been classified as carcinogenic to humans (Group 1).[2,3]

Worldwide, use of menopausal hormone therapy (MHT) tremendously increased in the 1980 and 1990s. The publishing of the first report of the Women's Health Initiative in 2002,[4] showing an increased risk of breast cancer, coronary heart disease and stroke in postmenopausal North American women using MHT [conjugated equine estrogen (CEE) and medroxyprogesterone acetate], led to a dramatic decline in sales.[5–9] The incidence of breast cancer subsequently fell in many countries,[10–14] suggesting a causal association. However, there are still ~10 million MHT users worldwide,[2] and the possible public health consequences, therefore, remain considerable.

It has been suggested that breast cancer risk increases with increasing duration of use[15–17] and that users of combined estrogen-progestin MHT have a higher risk than estrogen-only users.[18,19] In particular, elevated risks have been associated with current use of fixed combinations with a continuous supply of a testosterone-related progestin and long duration of use.[20–23] Results from the French E3N-EPIC cohort suggested that estrogen-progesterone and estrogen-dydrogesterone are less harmful combinations of MHT regarding breast cancer,[24] and a German case-control study suggested that the differences in risk between continuous and sequential therapies was largely due to the progestinic dose.[25]

Further investigation is, therefore, needed to identify which MHT preparations are associated with the least risk with regard to subsequent breast cancer risk. We investigated the relation between use of MHT and the risk of breast cancer according to different hormones, regimens and routes of administration using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Material and Methods

The EPIC-cohort is a multicentre prospective cohort with 23 contributing centres in 10 European countries [Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Great Britain (Cambridge, Oxford), Greece, Italy (Florence, Varese, Ragusa, Turin, Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), Sweden (Malmø, Umeå) and The Netherlands (Bilthoven, Utrecht)], covering more than half a million participants. The cohort was designed to investigate the relation between nutritional, lifestyle and environmental factors and cancer. Participants were mainly recruited from the general population with some exceptions: the cohorts of Norway, Utrecht, France and Naples include women only. Turin, Ragusa and Spain recruited mostly blood donors, France recruited mostly teachers, Oxford recruited a high proportion of health-conscious individuals, and Utrecht and Florence recruited women attending mammographic screening programs. For a complete description of the cohort and data collection, see Ref. [26]. The study was approved by the International Agency for Research on Cancer ethical committee and by the local ethical committees at the participating centres.

The Norwegian, Danish and French cohorts have already published results of MHT use and breast cancer risk using their national data,[20,23,27] which are also included in this analysis. The exposure estimates of the previous French publications were based on the integration of repeated biennial questionnaires. For the sake of comparability with the other countries that used a single baseline assessment of exposure, we included in this analysis the French MHT data from the baseline questionnaire only.

Study population

This study was based on data from 344,581 female participants after *a priori* excluding women with prevalent cancer at any site at baseline examination and those with missing nondietary questionnaire data. Cancers were identified from both self-reports and registration. Women from the Swedish (n = 26,919) and Greek (n = 15,313) cohorts were excluded because of lack of data on MHT. One Dutch centre (Bilthoven, n = 11,801) was also excluded because of missing information on some reproductive adjustment variables.

The study population was further restricted to women who were postmenopausal at baseline (n = 134,717). Menopausal status at the time of recruitment was defined according to information on ovariectomy, hysterectomy, menstruation status (still menstruating, number of menses over the past 12 months) and exogenous hormones use (oral contraceptives or MHT). Women were considered postmenopausal if they had undergone a bilateral ovariectomy or if their menses had stopped since 12 months or more (unless due to hysterectomy). Women who were still menstruating and using exogenous hormones, women for whom menopause had been obscured by a hysterectomy and women with no information on the number of menses over the past 12 months were considered postmenopausal if they were 55 yr or older.

Of the 134,717 postmenopausal women identified, we further excluded 32 who had never menstruated, 941 because they reported no information on MHT use (ever or current use), leaving a final analytic cohort of 133,744 women from 8 of the 10 participating countries.

Identification of breast cancer cases and follow-up

Incident breast cancer cases were identified through population cancer registries (Denmark, Italy, the Netherlands, Norway, Spain and United Kingdom) or by active follow-up (France and Germany). The active follow-up procedure used a combination of methods including health insurance records, cancer and pathology registries and contacts with participants and their next-of-kin. Mortality data were obtained mostly from mortality registries at the regional or national level. Women were followed up from study entry and until first cancer diagnosis (except nonmelanoma skin cancer), death and emigration or till end of the follow-up period, whichever occurred first. The follow-up period ended as follows: December 31, 2002 (Granada), December 31, 2003 (Florence, Varese, Naples, Murcia and Denmark), December 31, 2004 (Ragusa, Turin, Asturias, Navarra, Great Britain, Utrecht and Norway) and December 31, 2005 (San Sebastian). For France and Germany, the end of follow-up was considered to be the last known contact (until June 30, 2005 for France and November 30, 2006 for Germany).

We used the International Classification of Diseases, 10th revision (ICD-10). Cancers of the breast as analyzed herein were defined as C50.

Identification of MHT use

Information on hormone use was derived from country-specific questionnaire items. They covered questions on ever and current use of MHT, brand name of MHT used at recruitment, age at start and total duration of use. Based on this, it was possible to deduce the type of hormones, the route of administration and, in some centres, the regimen involved. Among past MHT users, time since last use was not available. Use of progestins was grouped into the following three classes: micronized progesterone, progesterone-derived progestins and testosterone-derived progestins according to Schindler *et al.*[28] Two regimens of estrogen plus progestin were identified: sequential (estrogen with a progestin added 10–14 d a month) and fixed continuous (estrogen plus a progestin daily).

Statistical analysis

Country-specific relative risks (RR) and their 95% confidence intervals (95% CI) for breast cancer were estimated using Cox proportional hazards models, with age as the time scale. Multivariable models included the following potential confounding variables: type of menopause (natural/artificial), body mass index (<18.5/[18.5–25]/[25–30]/30 or more kg/m^2), ever use of oral contraceptives (yes/no), number of full-term pregnancies (0/1/2/3 or more), age at first full-term pregnancy (<25/[25–30]/30 or more yr old/unknown), age at menarche (<12/[12–16]/16 or more yr old/unknown) and alcohol consumption (none/[0–15]/[15–30]/30 or more g/d/unknown). Models were further stratified by centre to control for centre effects related to different follow-up procedures and questionnaire design, and by age at recruitment (1-yr intervals) to be less sensitive against violations of the proportional hazards assumption. Sensitivity analyses investigated whether age at menopause (continuous, years), personal history of benign breast disease (yes/no), physical activity (inactive/moderately inactive/moderately active/active) and history of breast cancer in first degree relatives (yes/no), which were not included in our main analyses because of the incompleteness of data in some countries, were confounders in the relation between MHT use and risk of breast cancer.

When 5% or more of the values of a covariate were missing in at least one country, a corresponding missing indicator was included in the models (age at menarche, age at first full-term pregnancy and alcohol consumption). Otherwise, missing values were replaced with the modal category observed among the subjects with complete data, in each country. The findings were virtually identical in an analysis where all individuals with missing values for covariates were excluded.

Wald χ^2 test of homogeneity of country-specific estimates obtained from a common Cox proportional hazard model was used to assess between-country heterogeneity of RRs. To estimate overall effects across countries, the method of DerSimonian and Laird,[29] based on the random effects model was used. The same method was used to estimate RRs associated with MHT use *vs*. MHT never-use and to compare different treatments: in the latter case, Cox models were also first used to estimate country-specific RRs (*e.g.*, for CEE *vs*. estradiol) and then the method of DerSimonian and Laird allowed calculating the overall estimate.

As sequential MHT regimens may be preferentially given to younger women than continuous combined regimens,[30] a sensitivity analysis investigated whether duration of MHT use ($\leq$1/[1–3]/[3–5]/[5–10] and >10 yr) or age at menopause (continuous, years) were confounders in the comparison of the two regimens regarding breast cancer risk.

Tests for trend in duration of use were computed in models restricted to current MHT users and evaluated the RR of breast cancer per year of MHT use. All tests of statistical significance were two sided, and significance was set at the 0.05 level. We performed all analyses using SAS software, version 9.1 (SAS Institute, Cary, NC) and Microsoft Excel.

Results

The characteristics of the 133,744 postmenopausal women included in the analysis are presented in Table 1. A total of 4,312 primary breast cancers were diagnosed during 1,153,747 person-years of follow-up (mean duration: 8.6 yr; standard deviation (SD): 2.3). The mean age at recruitment was 58.1 yr (ranging from 52.1 in Norway to 61.5 in the

Table 1. Distribution of baseline characteristics of the postmenopausal women in the cohort (the EPIC-study)

	All (n = 133,744)	Denmark (n = 21,794)	France (n = 33,125)	Germany (n = 11,575)	Italy (n = 14,074)	Norway (n = 10,578)	Spain (n = 9,360)	The Netherlands (n = 10,935)	United Kingdom (n = 22,303)
Recruitment period									
Median	1995	1996	1993	1996	1995	1998	1994	1995	1996
Range	1992–2000	1993–1997	1993–1997	1994–1998	1993–1998	1998–1998	1992–1996	1993–1997	1993–2000
Mean age recruitment (SD) (yr)	58.1 (6.0)	58.2 (4.0)	57.9 (5.4)	58.0 (4.8)	57.4 (5.1)	52.1 (2.8)	56.9 (5.1)	60.0 (5.4)	61.5 (8.4)
Mean length of follow-up (SD) (yr)	8.6 (2.3)	7.5 (1.5)	10.4 (2.4)	8.0 (1.8)	8.3 (1.7)	5.9 (0.8)	9.6 (2.0)	8.9 (2.0)	8.4 (2.0)
Person-years	1,153,747	163,519	344,343	93,044	116,364	62,723	89,563	97,358	186,834
No. incident breast cancer cases	4,312	674	1,644	288	346	162	154	364	680
Age at menarche (yr) (%)									
<12	14.0	8.4	16.2	8.1	21.3	8.3	16.9	9.1	18.5
[12–15]	76.5	76.2	79.6	80.0	74.6	84.5	72.7	77.2	69.9
>15	7.5	11.9	4.2	11.8	4.1	5.4	10.3	11.5	6.2
Missing	2.0	3.5	0.6	0.1	0.0	1.8	0.1	2.3	5.5
No. full-term pregnancies (%)									
None	11.9	11.9	10.2	13.4	13.3	8.4	11.2	12.8	14.0
One	14.5	14.7	14.7	24.1	20.4	12.1	7.5	7.7	13.0
Two	40.7	43.7	44.1	39.0	40.8	44.8	26.3	33.4	41.1
Three or more	32.9	29.7	31.0	23.5	25.6	34.7	55.1	46.0	31.9
Age at first full-term pregnancy (yr), (%)[1]									
<25	49.3	61.1	48.7	59.4	36.4	63.9	41.8	38.4	43.0
[25–30]	35.1	28.5	32.5	29.8	44.2	26.8	44.0	46.3	37.2
≥30	12.5	8.9	10.7	10.6	19.2	9.3	13.0	15.0	15.6
Unknown	3.1	1.6	8.1	0.2	0.1	0.1	1.2	0.2	4.2
Type of menopause (%)									
Artificial	6.7	6.3	5.6	7.5	8.6	1.4	13.5	5.9	7.1
Natural	93.3	93.7	94.4	92.5	91.4	98.6	86.5	94.1	92.9
Body Mass Index (kg/m^2) (%)									
<18.5	1.7	1.4	3.4	0.6	1.0	1.6	0.02	1.4	1.5
[18.5–25]	51.2	49.5	70.4	39.0	39.8	59.8	14.3	48.2	50.7
[25–30]	32.9	34.9	21.1	38.6	41.7	29.7	42.9	37.5	35.2

Table 1. Distribution of baseline characteristics of the postmenopausal women in the cohort (the EPIC-study) (Continued)

	All (n = 133,744)	Denmark (n = 21,794)	France (n = 33,125)	Germany (n = 11,575)	Italy (n = 14,074)	Norway (n = 10,578)	Spain (n = 9,360)	The Netherlands (n = 10,935)	United Kingdom (n = 22,303)
≥30	14.2	14.3	5.0	21.8	17.5	8.9	42.7	12.9	12.7
Alcohol consumption (g/d) (%)									
0	16.4	3.1	14.9	5.7	24.1	23.0	56.9	18.9	10.8
[0–15]	63.5	65.5	59.9	76.3	56.9	75.8	33.7	61.4	72.2
[15–30]	11.7	15.3	16.8	12.3	13.3	1.1	6.9	12.6	5.8
≥30	7.1	16.1	8.4	5.7	5.6	0	2.5	6.8	3.6
Unknown	1.3	0.1	0	0	0.04	0.05	0	0.5	7.7
Previous use of oral contraceptives (%)									
Yes	45.5	54.4	44.0	65.2	25.5	56.5	21.7	57.4	40.1
No	54.5	45.6	56.0	34.8	74.5	43.5	78.3	42.6	59.9

[1]Among women with a first full-term pregnancy.

United Kingdom). Most women (93.3%) reported a natural menopause.

Overall, current use of MHT was reported by 30.9% of women (Table 2). Total duration of use at recruitment was 5 yr or less for 68.7% of current users with a known duration of use. Among current users, 65.0% used combined estrogen-progestin preparations, and 21.7% used estrogen-only preparations. There were wide variations across countries regarding MHT use, *e.g.*, 10.5% of Spanish women reported currently using MHT compared with 59.2% of Norwegian women; almost one fourth of Danish current users had been users for more than 10 yr, whereas the majority of Italian or Spanish women had used MHT for 3 yr or less. Among current users at recruitment, age at first use varied from 47.0 yr in Norway to 51.8 yr in France.

At recruitment, most current users of estrogen-only for whom we had information on the route of administration were using oral estrogens (57%), whereas 43% were using cutaneous estrogens (cream—excluding vaginal cream—or patch; Table 2). The most frequently used estrogen was estradiol, except for Germany and the United Kingdom, where CEE dominated. Among current users of combined MHT, sequential regimens were most frequently used. Testosterone derivatives were the predominant progestins in Denmark, Germany, Norway, the Netherlands and the United Kingdom, whereas progesterone derivatives were more used in France, Italy and Spain (Table 2). The most frequently used progestin in combined MHT was norethisterone acetate (NETA), followed by progesterone and norgestrel (data not shown).

Compared with never use of MHT, current use of estrogen-only MHT at recruitment was associated with an increased breast cancer risk [RR: 1.42 (95% CI: 1.23–1.64); Table 3]. The RR associated with use of combined MHT was 1.77 (95% CI: 1.40–2.24), but the RR estimates varied significantly across countries (p heterogeneity < 0.0001). Compared with estrogen only, current use of combined MHT was associated with a significant increase in risk ($p = 0.02$). Past use of MHT was associated with an overall RR of breast cancer of 1.16 (95% CI: 1.06–1.28), compared with MHT never use, with no significant heterogeneity across countries ($p = 0.73$) (data not shown).

The RR of breast cancer in current users of estrogen-only MHT increased with increasing duration of use before recruitment compared with MHT never users, from 1.01 (95% CI: 0.70–1.46) for use ≤1 yr to 1.40 (95% CI: 1.01–1.93) for 3–5 yr and 1.72 (95% CI: 1.15–2.57) for >10 yr [overall RR per year of use: 1.02 (95% CI: 0.99–1.06); Table 4]. The RR of breast cancer in current users of estrogen-progestin compared with MHT never users increased from 1.44 (95% CI: 1.09–1.89) for use ≤1 yr to 1.81 (95% CI: 1.44–2.29) for 3–5 yr and 1.98 (95% CI: 1.12–3.50) for >10 yr use [overall RR per year of use: 1.01 (95% CI: 0.99–1.03); Table 4].

Table 5 shows RR of breast cancer in current users relative to never users of MHT according to different hormones,

Table 2. Baseline use of MHT among postmenopausal women in the cohort (the EPIC-study)

	All (n = 133,744)	Denmark (n = 21,794)	France (n = 33,125)	Germany (n = 11,575)	Italy (n = 14,074)	Norway (n = 10,578)	Spain (n = 9,360)	The Netherlands (n = 10,935)	United Kingdom (n = 22,303)
Among all women									
MHT use (%)									
Never	53.9	49.5	42.4	39.8	74.7	30.6	81.0	73.7	59.5
Current	30.9	33.6	36.2	46.2	12.0	59.2	10.5	13.4	28.1
Past	13.9	16.6	18.2	13.2	12.9	9.7	8.5	12.8	10.8
Unknown	1.3	0.2	3.2	0.8	0.5	0.5	0.0	0.1	1.6
Among current users									
Type of MHT (%)									
Estrogen-only[1]	21.7	26.0	12.3	25.2	30.8	15.4	31.0	40.1	29.7
Estrogen-progestin[2]	65.0	57.1	87.1	59.4	32.6	79.6	46.0	19.8	50.9
Tibolone	2.5	4.4	0.0	0.1	6.2	0.0	0.0	6.8	7.9
Other/unknown	10.8	17.9	0.6	15.4	30.4	5.0	23.0	33.3	11.6
Mean age at first use[3] (SD)	49.7 (5.3)	48.6 (5.1)	51.8 (4.8)	49.9 (4.1)	49.7 (5.0)	47.0 (4.0)	49.0 (4.3)	48.8 (6.3)	49.7 (6.2)
Total duration of use (%)									
1 yr or less	16.5	9.7	20.7	5.3	25.0	20.3	40.9	15.9	16.1
1–3 yr	26.0	18.8	33.0	12.7	25.1	29.2	36.7	25.4	27.8
3–5 yr	17.1	15.4	16.1	11.9	15.4	23.1	11.1	17.4	20.7
5–10 yr	18.9	29.4	15.2	15.9	8.6	17.3	5.7	22.3	21.6
More than 10 yr	8.3	24.6	4.0	3.0	2.5	3.2	1.7	14.5	7.8
Unknown	13.3	2.0	11.0	51.0	23.4	7.0	3.9	4.4	6.1
Among current users of estrogen-only†									
Type of estrogens (%)									
Conjugated equine estrogens	21.4	1.0	3.5	54.9	8.5	0.0	7.2	27.6	47.5
Estradiol	61.8	82.3	61.4	37.5	71.0	89.3	50.3	61.2	43.8
Low-potency estrogens	11.3	4.8	33.5	6.2	20.5	10.2	0.0	8.0	4.7
Other/unknown	5.5	11.9	1.6	1.4	0.0	0.5	42.4	3.2	3.9
Route of administration (%)									
Oral	40.0	57.6	9.9	53.2	6.4	46.3	10.9	36.6	48.3
Cutaneous	30.0	16.0	55.9	21.7	14.1	36.3	64.1	35.9	23.4

Table 2. Baseline use of MHT among postmenopausal women in the cohort (the EPIC-study) (Continued)

	All (n = 133,744)	Denmark (n = 21,794)	France (n = 33,125)	Germany (n = 11,575)	Italy (n = 14,074)	Norway (n = 10,578)	Spain (n = 9,360)	The Netherlands (n = 10,935)	United Kingdom (n = 22,303)
Other/unknown	30.0	26.4	34.2	25.1	79.5	17.4	25.0	27.5	28.3
Among current users of estrogen-progestin									
Type of progestin (%)									
Micronized progesterone	9.5	0.0	24.4	0.1	2.2	0.0	1.1	1.0	0.0
Progesterone derivative	35.8	19.2	68.6	19.5	83.9	0.7	78.9	30.2	35.3
Testosterone derivative	53.2	80.8	4.3	80.0	13.9	99.3	0.0	64.6	64.7
Other/unknown	1.5	0.0	2.7	0.5	0.0	0.0	20.0	4.1	0.0
Regimen (%)									
Sequential	44.2	71.6	7.1	69.2	18.2	61.3	2.9	67.4	89.6
Fixed continuous	15.3	24.4	2.2	24.5	0.7	38.1	0.0	5.8	8.5
Other/unknown	40.5	4.0	90.7	6.3	81.0	0.6	97.1	26.8	1.9

[1]Among women with available information. [2]Estradiol compounds, CEE and low-potency estrogens (estriol, estrone and promestriene).

regimens and routes of administration. The risk of breast cancer was not significantly different between women who currently used CEE-only compared with estradiol-only formulations (RR for CEE *vs.* estradiol: 1.15, 95% CI: 0.78–1.69; Table 5). Among women who only used estrogen-only MHT, the risks were not significantly different between those who used oral *vs.* those who used cutaneous preparations [excluding vaginal creams; RR: 1.13 (95% CI: 0.80–1.59)].

Comparison of a continuous *vs.* a sequential regimen of a given progestin was only possible for NETA and yielded a significant difference in risk, with a RR of 1.33 (95% CI: 1.08–1.65) (common estimate from France, United Kingdom, Germany, Denmark and Norway, data not shown).

We then examined the association of MHT containing different types of progestin (grouped according to whether they were progesterone or testosterone derivatives) with the risk of breast cancer, across homogeneous regimens. Progestins used in continuous regimens were predominantly testosterone derivatives; hence, we were unable to compare the effects of different types of progestins in continuous regimens. Among sequential regimens, there was no significant difference in the risk of breast cancer between testosterone- or progesterone-derived progestins [RR: 1.09 (95% CI: 0.81–1.48), overall estimate from France, United Kingdom, Germany and Denmark, Table 5].

We, therefore, examined again the risk of breast cancer associated with sequential *vs.* continuous regimens. Compared with a sequential MHT regimen with progestin added for 10–14 d to a month, a combined continuous regimen with progestin supplied daily was associated with a significant increase in risk (RR: 1.43, 95% CI: 1.19–1.72; Table 5).

Two-by-two comparisons of the risks associated with the different combined MHT most used in our cohort (*i.e.*, sequential combinations containing medrogestone, medroxyprogesterone acetate, norethisterone acetate, norgestrel and levonorgestrel and continuous combinations containing norethisterone acetate) showed significant differences between use of continuous NETA *vs.* sequential medroxyprogesterone acetate (RR: 1.66, 95% CI: 1.15–2.40, common estimate from France and Denmark) and continuous NETA *vs.* sequential NETA (RR: 1.33, 95% CI: 1.08–1.65, common estimate from France, United Kingdom, Germany, Denmark and Norway). None of the other 11 two-by-two comparisons yielded significant results (data not shown). In particular, the risk of breast cancer associated with use of estrogen plus sequential medroxyprogesterone acetate did not differ significantly from that of estrogen plus sequential NETA (overall estimate from France and Denmark; RR: 1.35, 95% CI: 0.93–1.95, for MHT containing sequential NETA *vs.* sequential medroxyprogesterone acetate).

A sensitivity analysis performed among women with a known age at menopause (n = 99,572) showed little difference in the risk estimates associated with MHT use after age at menopause was entered in the model (*e.g.*, overall RR estimates changed by less that 5% for MHT ever use, current

Table 3. Relative risk of breast cancer according to type of MHT currently used at baseline

	Current use of estrogen-only[1]			Current use of estrogen-progestin		
	No. cases	RR[2]	95% CI	No. cases	RR[2]	95% CI
Denmark	68	1.56	1.17–2.09	207	2.71	2.23–3.28
France	80	1.32	1.04–1.67	635	1.48	1.31–1.67
Germany	50	2.07	1.42–3.00	110	2.20	1.60–3.01
Italy	12	1.09	0.61–1.97	17	1.60	0.96–2.66
Norway	17	1.61	0.90–2.88	90	1.65	1.10–2.46
Spain	6	1.25	0.52–3.00	4	0.51	0.18–1.41
The Netherlands	24	1.48	0.96–2.27	13	1.58	0.89–2.80
United Kingdom	49	1.11	0.80–1.54	143	1.88	1.50–2.37
p^3		0.12			<0.0001	
Overall		1.42	1.23–1.64		1.77	1.40–2.24

Reference: MHT never use. The EPIC-study.
[1]Estradiol compounds, CEE and low-potency estrogens (estriol, estrone and promestriene). [2]Adjusted for: age (continuous time scale), type of menopause (natural/artificial), body mass index (<18.5/[18.5–25]/[25–30]/30 or more kg/m^2), ever-use of oral contraceptives (yes/no), number of full-term pregnancies (0/1/2/3 or more), age at first full-term pregnancy (<25/[25–30]/30 or more yr old/unknown), age at menarche (<12/[12–16]/16 or more yr old/unknown), alcohol consumption (none/[0–15]/[15–30]/30 or more g/day/unknown). Further stratified by EPIC-participating centre. [3]p value for homogeneity across countries.

use and trends per year of use in current users of estrogen-only and combined MHT; data not shown). This was also the case (less than 5% change) for personal history of breast surgery (n = 111,288), familial history of breast cancer in first-degree relatives (n = 72,203) and physical activity (n = 122,529).

A sensitivity analysis performed among current users of combined MHT at recruitment with a known duration of use (n = 23,881) showed virtually no difference in the RR estimate comparing continuous combined and sequential regimens, after duration of use was entered in the model. It was also the case when age at menopause was entered in the model, together with duration of use (n = 8824) or alone (n = 10,228).

Tibolone was not extensively used; however, we found use to be associated with an increased breast cancer risk compared with MHT never use: the overall RR estimate (from United Kingdom, The Netherlands and Denmark) was 1.95 (95% CI: 1.43–2.65).

Discussion

In this large prospective cohort of 133,744 postmenopausal women from across Europe, compared with never users, current users of both estrogen-only and combined MHT had an increased risk of breast cancer, with the latter being associated with a higher risk than the former. In combined MHT, fixed continuous regimens were found to confer a significantly increased risk compared with sequential regimens. Among women who used sequential regimens, risk did not vary significantly between those who used testosterone-like or progesterone-like progestins. Among women who used estrogen-only MHT, risk did not vary significantly according to route of administration (oral *vs.* cutaneous) or estrogen component (estradiol compounds *vs.* CEE). Past use of MHT was associated with a small increase in risk.

User patterns at baseline

There is wide variation in user patterns of MHT across Europe, both with regard to the type and regimen of hormones, the inclination to start MHT and the duration of use. Medical opinion formers, the drug industry and the health authorities seem to have strongly influenced both women's perception of the menopause and treatment recommendations and use. Differences in national legislation and drug politics may also have an impact on the variety of MHT available in each country.

Age standardized incidence rates for breast cancer do not vary a great extent between the European countries included in this study,[31] although the lowest rate is found in Spain where the prevalence and duration of use of MHT is the lowest, which may have contributed to the relatively low incidence rates, although differences in screening practices and reproductive or other characteristics may also be important.

In contrast to the evidence to date, we did not find a significant trend of increasing risk with increasing duration of use of MHT, which may be due to insufficient statistical power in our study or a nonlinear relationship. We found that even a short duration of use (≤1 yr) of combined MHT was associated with a significant increase in risk. However, duration of use measured at baseline is an underestimation of the true duration of use in women continuing to use MHT during follow-up. On the other hand, if MHT acts as a promoter of preexisting tumors,[15,32] it is also possible that such short-term use increases breast cancer risk. This is

Table 4. Relative risk of breast cancer according to total duration of MHT use for current MHT users at baseline

	≤1 yr		1–3 yr		3–5 yr		5–10 yr		>10 yr		Trend[1]
	No. cases	RR[2] (95% CI)	No. cases	RR[2] (95% CI)	No. cases	RR[2] (95% CI)	No. cases	RR[2] (95% CI)	No. cases	RR[2] (95% CI)	RR[2] (95% CI) for trend
Current use of estrogens only[3]											
Denmark	6	1.37 (0.61–3.10)	6	0.99 (0.44–2.25)	6	1.11 (0.49–2.51)	21	1.98 (1.25–3.13)	28	1.79 (1.18–2.71)	1.03 (0.98–1.08)
France	16	1.09 (0.66–1.79)	25	1.49 (0.99–2.22)	6	0.81 (0.36–1.81)	15	1.65 (0.99–2.76)	5	1.18 (0.49–2.85)	0.99 (0.93–1.07)
Germany	0	–	1	0.87 (0.12–6.37)	3	1.85 (0.57–5.98)	4	1.29 (0.46–3.59)	3	4.32 (1.32–14.1)	1.15 (0.95–1.39)
Italy	1	0.47 (0.07–3.37)	5	2.00 (0.82–4.90)	2	1.32 (0.33–5.37)	0	–	1	3.68 (0.50–27.2)	1.29 (0.90–1.84)
Norway	3	1.67 (0.51–5.47)	6	1.90 (0.79–4.52)	2	0.79 (0.19–3.28)	5	2.27 (0.89–5.84)	0	–	0.95 (0.78–1.15)
Spain	1	0.50 (0.07–3.68)	2	1.24 (0.29–5.26)	2	5.11 (1.15–22.6)	0	–	0	–	–
The Netherlands	1	0.48 (0.07–3.42)	7	1.84 (0.86–3.95)	3	1.04 (0.33–3.28)	6	1.40 (0.62–3.18)	6	2.21 (0.96–5.08)	1.10 (0.97–1.23)
United Kingdom	2	0.36 (0.09–1.48)	6	0.67 (0.30–1.53)	16	1.81 (1.07–3.06)	15	1.25 (0.73–2.13)	5	0.80 (0.33–1.95)	1.02 (0.95–1.09)
p^4		0.49		0.63		0.39		0.55		0.28	0.70
Overall		1.01 (0.70–1.46)		1.39 (1.07–1.81)		1.40 (1.01–1.93)		1.63 (1.26–2.09)		1.72 (1.15–2.57)	1.02 (0.99–1.06)
Current use of estrogen-progestin											
Denmark	14	2.70 (1.55–4.68)	35	2.46 (1.69–3.57)	34	2.73 (1.89–3.94)	62	2.36 (1.78–3.14)	57	3.25 (2.42–4.36)	1.01 (0.97–1.04)
France	104	1.27 (1.02–1.57)	221	1.54 (1.31–1.81)	112	1.54 (1.25–1.90)	107	1.57 (1.28–1.94)	16	1.04 (0.63–1.71)	1.00 (0.97–1.03)
Germany	1	0.43 (0.06–3.16)	14	2.03 (1.08–3.83)	10	1.42 (0.71–2.85)	12	1.46 (0.77–2.76)	2	1.58 (0.38–6.57)	1.08 (0.97–1.20)
Italy	3	1.45 (0.46–4.59)	4	1.17 (0.43–3.18)	7	3.06 (1.43–6.58)	1	0.99 (0.14–7.09)	0	–	0.96 (0.78–1.19)
Norway	15	1.25 (0.67–2.32)	30	1.77 (1.07–2.91)	20	1.51 (0.87–2.63)	19	1.92 (1.09–3.38)	6	3.88 (1.61–9.35)	1.04 (0.97–1.11)
Spain	2	0.71 (0.17–2.91)	2	0.56 (0.14–2.30)	0	–	0	–	0	–	–
The Netherlands	4	2.52 (0.93–6.87)	3	1.12 (0.35–3.54)	2	1.49 (0.37–6.04)	3	1.76 (0.56–5.55)	1	1.25 (0.18–8.98)	0.93 (0.78–1.11)
United Kingdom	16	1.23 (0.73–2.09)	45	1.88 (1.33–2.66)	28	1.60 (1.06–2.40)	39	2.46 (1.74–3.48)	6	1.58 (0.70–3.58)	1.02 (0.97–1.08)
p^4		0.19		0.25		0.11		0.21		0.02	0.69
Overall		1.44 (1.09–1.89)		1.73 (1.44–2.08)		1.81 (1.44–2.29)		1.93 (1.58–2.35)		1.98 (1.12–3.50)	1.01 (0.99–1.03)

Reference: MHT never use. The EPIC-study.
[1]Per year of use. [2]Adjusted for: age (continuous time scale), type of menopause (natural/artificial), body mass index (<18.5/[18.5–25]/[25–30]/30 or more kg/m^2), ever-use of oral contraceptives (yes/no), number of full-term pregnancies (0/1/2/3 or more), age at first full-term pregnancy (<25/[25–30]/30 or more yr old/unknown), age at menarche (<12/[12–16]/16 or more yr old/unknown), alcohol consumption (none/[0–15]/[15–30]/30 or more g/day/unknown). Further stratified by EPIC-participating centre. [3]Estradiol compounds, CEE and low-potency estrogens (estriol, estrone and promestriene). [4]p value for homogeneity across countries.

Table 5. Relative risk[1] (95% CI; no. cases) of breast cancer in current users of MHT according to the estrogen, progestin, administration route and regimen

	Denmark (n = 21,794)	France (n = 33,125)	Germany (n = 11,575)	Italy (n = 14,074)	Norway (n = 10,578)	The Netherlands (n = 10,935)	United Kingdom (n = 22,303)	p^2
Type of estrogen-only								
Estradiol compounds	1.61 (1.18–2.19) (58)	1.35 (1.00–1.81) (49)	1.81 (1.02–3.19) (15)	1.70 (0.94–3.08) (12)	1.48 (0.79–2.76) (14)	1.46 (084–2.54) (14)	1.08 (0.67–1.74) (20)	0.48
CEE			2.18 (1.41–3.37) (31)			1.76 (0.86–3.58) (8)	1.16 (0.76–1.78) (25)	0.09
Overall RR (CEE *vs*. estradiol): 1.15 (0.78–1.69)								
Administration route of estrogen-only								
Cutaneous		1.36 (1.00–1.85) (45)	2.04 (1.01–4.10) (9)		1.74 (0.77–3.94) (7)	1.17 (0.55–2.50) (7)	0.69 (0.32–1.47) (7)	0.25
Oral	1.70 (1.20–2.41) (43)	1.35 (0.67–2.72) (8)	1.88 (1.17–3.02) (24)		1.71 (0.79–3.69) (8)	1.66 (0.88–3.15) (10)	1.23 (0.82–1.86) (27)	0.55
Overall RR (oral *vs*. cutaneous): 1.13 (0.80–1.59)								
Progestin component in sequential regimen								
Progesterone derivatives	2.04 (1.32–3.15) (23)	1.41 (0.96–2.07) (28)	2.19 (1.30–3.68) (19)					0.25
Testosterone derivatives	2.46 (1.95–3.11) (108)	1.93 (1.17–3.18) (16)	1.74 (1.17–2.58) (46)		1.42 (0.90–2.24) (48)		1.88 (1.48–2.38) (126)	0.15
Overall RR (testosterone *vs*. progesterone derivatives, sequentially administered): 1.09 (0.81–1.48)								
Regimen of MHT								
Sequential	2.38 (1.91–2.96) (131)	1.56 (1.15–2.13) (44)	1.88 (1.31–2.69) (66)		1.42 (0.90–2.24) (48)	1.12 (0.49–2.56) (6)	1.91 (1.51–2.42) (131)	0.09
Fixed continuous	3.51 (2.66–4.62) (67)	2.25 (1.44–3.52) (20)	3.09 (2.08–4.60) (40)		1.98 (1.26–3.11) (42)		1.78 (0.97–3.29) (11)	0.07
Overall RR (fixed continuous *vs*. sequential): 1.43 (1.19–1.72)								

Reference: MHT never use. The EPIC study.
NB: Data are not presented where there are five or less cases in the considered category.
[1]Adjusted for: age (continuous time scale), type of menopause (natural/artificial), body mass index (<18.5/[18.5–25]/[25–30]/30 or more kg/m^2), ever-use of oral contraceptives (yes/no), number of full-term pregnancies (0/1/2/3 or more), age at first full-term pregnancy (<25/[25–30]/30 or more yr old/unknown), age at menarche (<12/[12–16]/16 or more yr old/unknown), alcohol consumption (none/[0–15]/[15–30]/30 or more g/day/unknown). Further stratified by EPIC-participating centre. [2]*p* value for homogeneity across countries.

supported by results from the Million Women Study, which also showed an increased risk with estrogen plus progestin use over the short-term.[16] Recent studies reporting a substantial reduction in the incidence of breast cancer almost concurrently with the sharp drop in the use of MHT[7,13,33,34] also support this hypothesis.

Past use was found to be associated with a small but significant increased risk. Most studies show no increased risk for past users[15,16] although one study reported a small increased risk in past users who had used MHT within the last 5 yr.[35]

Types of hormones and regimen at baseline

In this study, the majority of women in most countries used a combination of estrogen plus progestin MHT. Fixed combinations with a continuous supply of progestin were associated with a greater risk of breast cancer than sequential combinations. This has also been reported by many others,[20,22,23,25,36–40] and only a few have reported no difference in risk between regimens.[21,41,42]

Campagnoli *et al.*[43] have suggested that combinations of estrogen plus a testosterone derivative may be associated with a greater risk than combinations with progesterone derivatives due to indirect effects of testosterone derivatives stimulating breast cancer cells in synergy with estrogens or increasing estrogen bioavailability. Particularly, high risks of breast cancer associated with the use of testosterone derivatives have indeed been observed in some countries.[20–23] However, others have suggested that continuous combinations that contain testosterone-derived progestins provide two to three times the monthly dose of progestin as do the corresponding sequential regimen, whereas combinations with progesterone-derived progestins generally provide about the same dose of progestins independent of type of regimen.[44] Hence, the particularly high risk with testosterone derivatives seen in some countries might reflect a dose-response relationship more than a real difference in progestinic effect between the progestins. Results from two other studies are consistent with this,[22,25] which supports our finding that there is no material difference in risk between progesterone and testosterone derivatives, once the type of regimen is taken into account.

For women who use estrogen-only preparations, we found no difference in breast cancer risk between use of estradiol or CEE constituents, which is consistent with other data.[16] An overall risk estimate from three countries in our study showed use of tibolone to be associated with an increased breast cancer risk. This is also consistent with other data,[16,22] although one case-control study found no association.[41]

Administration route of estrogens at baseline

The pharmacokinetics of estrogens is dependant on the route of administration.[45,46] There are only a few studies on the impact of different routes of administration on the risk of breast cancer, and we found no significant difference in risk between oral *vs.* cutaneous administration of estrogen-only MHT. This is consistent with most other studies,[16,38,47] but not with a recent case-control study,[41] and suggests that the route of administration does not modify the risk of breast cancer associated with MHT use.

Weakness and strength of the study

The main limitation of this study is the lack of information of MHT use after recruitment. MHT use is likely to have changed during follow-up, with some never users at recruitment becoming MHT users, some women switching from one type of MHT to another, and other ceasing use altogether, which will serve to dilute the associations found between MHT use and breast cancer risk. However, in an analysis where follow-up was censored 4 yr after recruitment (*i.e.*, where follow-up was limited to a period of time during which the percentage of women changing their exposure status should be reasonable), we did not find any other significant differences in risk estimates between different MHTs than those found in the main analysis (data not shown).

Our models were not adjusted for age at menopause, personal history of benign breast disease, physical activity or history of breast cancer in first-degree relatives because of the incompleteness of data for many of these variables. However, sensitivity analyses showed these factors are only likely to be weak (if any) confounders of the relation between use of MHT and risk of breast cancer. In the analyses, we have conducted multiple comparisons, and we cannot exclude the possibility that some significant results are observed by chance.

The main strength of this cohort study is the large number of incident cases of breast cancer and the variety of MHT preparations used. Information on use of MHT was self-reported, however, the reliability of self-reported use of MHT is believed to be high.[48–51]

Conclusion

This large cohort study is the first to examine patterns of MHT use and subsequent breast cancer risk across Europe. Use of MHT was associated with a significant increase in risk of breast cancer, with the highest risk among current users of combined MHT, particularly among those using continuous regimens.

This study adds to the increasing evidence that breast cancer risk may vary according to the characteristics of the progestin component of combined MHT, especially the number of days it is administered each month. The impact of the progestin component of MHT must, therefore, remain an active area of research to identify a treatment with the least potential for exerting adverse effects, notably on the breast, whilst assuring adequate protection against endometrial proliferation. Future studies should be designed to disentangle the effects of various progestin-related parameters such as substance, dosage and regimen to encourage a discussion in the medical profession and the national drug authorities on which hormones to recommend to women with disabling menopausal complaints.

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