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Article

Use of menopausal hormone therapy and ovarian cancer risk in a French cohort study

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Abstract

Background: Epidemiological studies have found that menopausal hormone therapy (MHT) use is associated with an increased ovarian cancer risk. However, whether different MHT types confer the same level of risk is unclear. We estimated the associations between different MHT types and the risk of ovarian cancer in a prospective cohort.

Methods: The study population included 75 606 postmenopausal women from the E3N cohort. Exposure to MHT was identified from self-reports in biennial questionnaires between 1992 and 2004 and from drug claim data matched to the cohort between 2004 and 2014. Hazard ratios and 95% confidence intervals (CIs) of ovarian cancer were estimated using multivariable Cox proportional hazards models with MHT as a time-varying exposure. Tests of statistical significance were 2-sided.

Results: Over an average 15.3 years follow-up, 416 ovarian cancers were diagnosed. Hazard ratios of ovarian cancer associated with ever use of estrogens combined with progesterone or dydrogesterone and ever use of estrogens combined with other progestagen were equal to 1.28 (95% CI = 1.04 to 1.57) and 0.81 (95% CI = 0.65 to 1.00), respectively ($P_{homogeneity} = .003$), compared with never use. The hazard ratio for unopposed estrogen use was 1.09 (95% CI = 0.82 to 1.46). We found no trend according to duration of use or time since last use except for estrogens combined with progesterone or dydrogesterone, which showed decreasing risk with increasing time since last use.

Conclusion: Different MHT types may impact ovarian cancer risk differentially. The possibility that MHT containing progestagens other than progesterone or dydrogesterone may confer some protection should be evaluated in other epidemiological studies.

Although the association between the use of menopausal hormone therapy (MHT) and the risk of breast (1,2) or endometrial (1,3) cancer is well established, the effect of MHT on the risk of ovarian cancer is less clear (1,4,5). This issue deserves attention because ovarian cancer is the eighth leading cause of cancer deaths in women worldwide and the fifth in Europe and the United States (6). Furthermore, MHT is still frequently prescribed, although to a lesser extent than before the publication of findings from the Women's Health Initiative clinical trial (2). Current guidelines from professional societies (7-11) generally recommend the use of systemic MHT for vasomotor symptom relief within 10 years after menopause onset and in women with premature or surgical menopause. They recommend against the use of MHT for the primary prevention of chronic conditions in the absence of vasomotor symptoms. Recommendations vary regarding MHT use to prevent osteoporosis. In 2015, MHT was used by approximatively 5 million women in the United States (2) and, in 2022, by 1.4 million women in England (12).

Whereas estrogens have long been implicated as etiologic factors of ovarian cancer (13-15), higher levels of progestagens may have a protective role (13,14,16,17). In combined estrogen-progestagen MHT (EP-MHT; prescribed to women with an intact uterus), progestagens may thus mitigate the ovarian carcinogenic effects of estrogens (18). Consistent with that hypothesis, the earliest meta-analyses examining the associations of estrogen-only MHT (E-only, given to hysterectomized women) and EP-MHT with ovarian cancer risk concluded that both were associated with an increased risk but in a more marked way for E-only (18-20). However, more recently, a pooled analysis of 52 epidemiological studies found a similar approximate 30% increased risk for both E-only and EP-MHT (21).

Regarding EP-MHT, different progestagens and/or number of days they are used per month have been shown to have a different impact on breast and endometrial cancer risks (2,22) and may also impact ovarian cancer differently (13). In particular, previous observations in the E3N cohort showed that EP-MHT containing progesterone or dydrogesterone were associated with different breast (23) and endometrial (24) cancer risks compared with EP-MHT containing other progestagens.

Postmenopausal women often take several MHT formulations over time, which makes the accurate assessment of any difference in risk between different MHT types difficult in the absence of

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lifetime exposure information. For example, some studies (21) considered only the last recorded MHT type, which may have masked any difference in ovarian cancer risk across different MHTs.

We therefore assessed the associations between MHT use and ovarian cancer risk in a large cohort of postmenopausal women with detailed information on exogenous hormone use assessed at multiple times during follow-up.

Methods

The E3N cohort

The E3N prospective cohort study includes 98 995 French women born between 1925 and 1950 insured by a national health scheme that covers people working within the national education system (25). Participants have been followed since 1990 through biennial self-administered questionnaires (11 waves of data collection available until 2014) with response rates around 80%-85%. Questionnaire data are linked to a database containing all outpatient health-care claims issued since January 1, 2004, for each E3N participant, including drug names and dates of purchase. Occurrences of deaths are identified from health scheme data and information from relatives and postal services. The French National Service on Causes of Death provided causes of death coded according to the Tenth Revision of the International Classification of Diseases.

Participants gave written informed consent, and the E3N study was approved by the French National Commission for Data Protection and Privacy.

MHT exposure

The 1992 questionnaire requested information on lifetime MHT use, including, for each treatment episode, brand names, starting date, and duration of use. The information was updated in all subsequent questionnaires. From year 2004 onward, the use of MHT was identified from the drug claims database, using Anatomical Therapeutic Chemical codes G03C (estrogens) and G03F (progestagens and estrogens in combination). Coprescriptions of G03C and G03D (progestagens) were considered as EP-MHT. Self-reports up to year 2003 and drug claims data from 2004 onward allowed reconstructing of each participant's complete history of MHT exposure.

MHT included any nonvaginal use of estrogens (except estriol) or tibolone. Following our previous findings that associations with breast (23) and endometrial (24) cancer risks vary across different EP-MHT, exposure was classified as 1) E-only (mainly estradiol); 2) estrogen with progesterone or dydrogesterone; 3) estrogen with other progestagen; 4) other (ie, tibolone, MHT containing an androgen, or intramuscularly administered, or with no specified formulation).

Ovarian cancer cases

The endpoint was the diagnosis of a primary ovarian cancer, including epithelial invasive ovarian cancer (International Classification of Diseases for Oncology code: C569), fallopian tube (C570) or peritoneal (C482) cancers. Cancer occurrence was identified from the self-administered questionnaires, which systematically inquired about any cancer diagnosis (site and date of diagnosis), next-of-kin spontaneous reports, and the national cause-of-death registry. Medical confirmation (from pathology reports, other medical documents, or through contact with participants' physicians) was obtained for 94% and pathology reports for 80% of ovarian cancers. Owing to the high confirmation rate among self-reported ovarian cancers for which we could obtain medical information, medically confirmed ovarian cancers and those that could not be documented were considered as cases.

Covariates

Data on number of children, age at first birth, breastfeeding, age at menarche, use of infertility treatment, and tubal ligation were gathered from the questionnaires sent in 1990 and/or 1992. Family history of breast cancer was assessed in 1990 and 2000, family history of ovarian cancer in 2000 and educational level and level of physical activity as well as pap smear frequency (a proxy for gynecological surveillance) in 1990. Other data were updated regularly in follow-up questionnaires. In particular, the 1992 questionnaire requested information on lifetime ever use and duration of oral contraceptive use, and the information was updated in all subsequent questionnaires.

Population and follow-up

The study population was restricted to postmenopausal women (see Supplementary Methods, available online).

Follow-up started either at the date the 1992 questionnaire was returned for already postmenopausal women or at the date of the questionnaire when menopause was first reported. Follow-up ended at 1) the date of diagnosis of any cancer except nonmelanoma skin cancer or when occurrence of cancer was identified but no date of diagnosis could be retrieved, the date of the last questionnaire answered while the participant was free of cancer; 2) 3 years after the date of the last completed questionnaire (to include not only ovarian cancers self-reported in follow-up questionnaires but also those identified only through cause-of-death information); 3) date of death; 4) date of a bilateral (or second) oophorectomy; or 5) November 2014 (date when the last E3N questionnaire considered in the current study was sent to participants), whichever occurred first. Women were counted as cases if their date of end of follow-up corresponded to the date of diagnosis of an ovarian cancer and censored as noncases otherwise.

The study population included 75 606 postmenopausal women who were free of cancer at study entry (see Figure 1).

Statistical analysis

Hazard ratios (HRs) for risk of ovarian cancer and associated 95% confidence intervals (CIs) were estimated with Cox proportional hazards models for left-truncated and right-censored data, with age as the underlying time scale (26).

Exposure was time-varying in our models, with updates at the date of answer of each follow-up questionnaire up to the one sent out in 2002, and, from January 2004 onward, continuous updates based on the exact dates of MHT purchases. When using self-reported MHT information, the exposure reported in questionnaires n and earlier was used to categorize participants for the period between completion of questionnaires n and n + 1. For current users at a given questionnaire, duration of use increased with time elapsed since questionnaire completion, as we considered that MHT use did not stop until completion of the subsequent questionnaire. For past users at a given questionnaire, time since last use increased with time elapsed since its completion. If a woman took different types of MHT in different periods, she simultaneously contributed to each of the relevant categories (eg, recent use of E-only and past use of estrogen and progesterone or dydrogesterone) in the Cox models. MHT exposure was classified as unknown from the time when at least 3 years had elapsed since the last information on MHT use was collected and until the next updated information was available. Finally, MHT exposure was lagged by 2 years, which means that any exposure

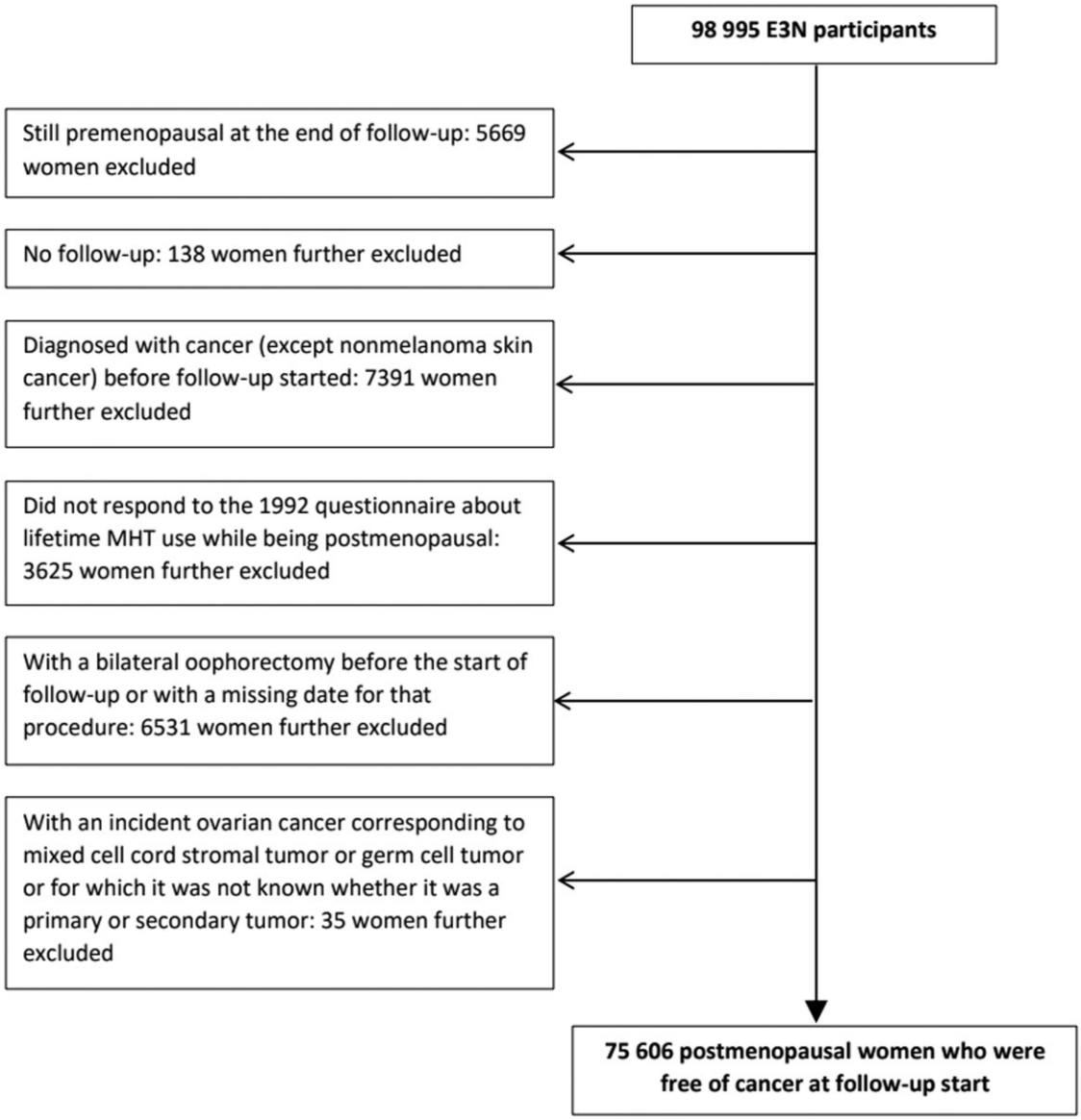

Figure 1. Flow chart. MHT = menopausal hormone therapy.

occurring in the 2-year period preceding the attained age was discarded and, as a consequence, that women were considered unexposed to MHT until 2 years had elapsed since the first MHT use. This was done to avoid reverse causation bias and, considering the rather late stage at ovarian cancer diagnosis, impose a reasonable time period for an effect of MHT on ovarian cancer diagnosis (27).

All analyses were adjusted for known ovarian cancer risk factors (family history of breast cancer in first degree relatives, family history of ovarian cancer in first degree relatives, number of children, duration of breastfeeding, personal history of endometriosis, tubal ligation, duration of oral contraceptive use, height, body mass index, smoking status, age at menarche, age at menopause, and previous hysterectomy) (5), and we verified that adding any other potential confounder listed in Table 1 in our model did not change the hazard ratio associated with MHT ever use by more than 0.05 point. Covariates that were updated during follow-up were included in the models as time-varying variables. Missing values for covariates were replaced by the modal or median value when data were missing for less than 5% of participants or by an "unknown" category. Because information on family history of ovarian cancer was available only from the questionnaire sent in 2000, the corresponding covariate was assigned an "unknown" category until the date of completion of that questionnaire.

In a sensitivity analysis aiming at assessing the association of exclusive use of a given MHT type with ovarian cancer risk, person-years of follow-up were censored from the time when at least 2 types of MHT had ever been used. We also reiterated our analyses without lagging MHT exposure. Finally, we limited the follow-up to the date of the last completed questionnaire, therefore excluding ovarian cancer cases identified only from cause-of-death information.

Model parameters were estimated and compared with likelihood-based methods and Wald tests. Tests of statistical significance were 2-sided, and significance was set at the 0.05 level.

Table 1. Characteristics of study participants at the end of follow-up, E3N cohort, 1990-2014 (n = 75 606)

Characteristics	All women (n = 75 606)	MHT never users[a] (n = 23 391)	MHT ever users[a] (n = 50 325)
Age, mean (SD) y	70.2 (7.4)	71.0 (8.4)	69.9 (6.9)
Year of birth, No. (%)			
1925-1929	5190 (6.9)	3370 (14.4)	1715 (3.4)
1930-1934	9027 (11.9)	4038 (17.3)	4776 (9.5)
1935-1939	14 021 (18.5)	3479 (14.9)	10 205 (20.3)
1940-1944	19 102 (25.3)	3715 (15.9)	14 939 (29.7)
1945-1950	28 266 (37.4)	8789 (37.6)	18 690 (37.1)
Years of schooling, No. (%)			
<13	9366 (12.4)	3674 (15.7)	5367 (10.7)
13-16	53 104 (70.2)	16 083 (68.8)	35 795 (71.1)
≥17	13 136 (17.4)	3634 (15.5)	9163 (18.2)
Smoking status, No. (%)			
Never smoked	40 060 (53.0)	13 237 (56.6)	25 809 (51.3)
Current smoker	6776 (9.0)	1952 (8.3)	4515 (9.0)
Past smoker	28 770 (38.1)	8202 (35.1)	20 001 (39.7)
Physical activity in 1990, quartiles, No. (%)			
≤27.3 METs h/wk	19 457 (25.7)	5777 (24.7)	13 167 (26.2)
27.4-38.5 METs h/wk	18 865 (25.0)	5548 (23.7)	12 877 (25.6)
38.6-55.1 METs h/wk	18 600 (24.6)	5566 (23.8)	12 554 (24.9)
>55.1 METs h/wk	18 684 (24.7)	6500 (27.8)	11 727 (23.3)
Body mass index, No. (%)			
<25.0 kg/m^2	50 123 (66.3)	14 150 (60.5)	34 786 (69.1)
25.0-29.9 kg/m^2	19 272 (25.5)	6523 (27.9)	12 249 (24.3)
≥30.0 kg/m^2	6211 (8.2)	2718 (11.6)	3290 (6.5)
Height, No. (%)			
≤158 cm	22 552 (29.8)	7473 (31.9)	14 516 (28.8)
159-161 cm	15 414 (20.4)	4627 (19.8)	10 391 (20.6)
162-165 cm	19 811 (26.2)	5982 (25.6)	13 346 (26.5)
>165 cm	17 829 (23.6)	5309 (22.7)	12 072 (24.0)
Parity, No. (%)			
Nulliparous	8724 (11.5)	3203 (13.7)	5279 (10.5)
1 child	11 803 (15.6)	3727 (15.9)	7772 (15.4)
2 children	32 390 (42.8)	8980 (38.4)	22 579 (44.9)
3 children	16 523 (21.9)	5034 (21.5)	11 113 (22.1)
≥4 children	6166 (8.2)	2447 (10.5)	3582 (7.1)
Breastfeeding, No. (%)			
Never	28 340 (37.5)	9002 (38.5)	18 630 (37.0)
Ever, <6 mo	28 577 (37.8)	7963 (34.0)	19 995 (39.7)
Ever, ≥6 mo	13 627 (18.0)	4847 (20.7)	8483 (16.9)
Ever, unknown duration	5062 (6.7)	1579 (6.8)	3217 (6.4)
Age at first birth, No. (%)			
Nulliparous	8724 (11.5)	3203 (13.7)	5279 (10.5)
Younger than 30	58 755 (77.7)	17 456 (74.6)	39 856 (79.2)
30 or older	8127 (10.7)	2732 (11.7)	5190 (10.3)
Age at menarche, No. (%)			
Younger than 13	33 859 (44.8)	10 399 (44.5)	22 554 (44.8)
13 or older	41 747 (55.2)	12 992 (55.5)	27 771 (55.2)
Age at menopause, No. (%)			
45 or younger	4110 (5.4)	1179 (5.0)	2802 (5.6)
45-52	46 648 (61.7)	12 119 (51.8)	33 177 (65.9)
Older than 52	24 848 (32.9)	10 093 (43.1)	14 346 (28.5)
Ever treated for infertility, No. (%)	5204 (6.9)	1483 (6.3)	3582 (7.1)
Duration of oral contraceptive use, No. (%)			
Never	28 887 (38.2)	11 725 (50.1)	16 400 (32.6)
Ever, <5 y	11 548 (15.3)	3150 (13.5)	8159 (16.2)
Ever, 5-10 y	7436 (9.8)	1838 (7.9)	5435 (10.8)
Ever, ≥10 y	9045 (12.0)	1968 (8.4)	6919 (13.7)
Ever, unknown duration	18 690 (24.7)	4710 (20.1)	13 412 (26.7)
Ever use of progestagens alone before menopause, No. (%)	36 931 (48.8)	7702 (32.9)	28 454 (56.5)
Ever use of vaginally administered estrogens, No. (%)	32 141 (42.5)	7659 (32.7)	23 868 (47.4)
Tubal ligation, No. (%)	7547 (10.0)	1989 (8.5)	5362 (10.7)
Hysterectomy, No. (%)	8314 (11.0)	2237 (9.6)	5879 (11.7)
Unilateral oophorectomy, No. (%)	3729 (4.9)	1030 (4.4)	2614 (5.2)
Personal history of endometriosis, No. (%)	4961 (6.6)	1225 (5.2)	3620 (7.2)
Personal history of ovarian cyst, No. (%)	11 950 (15.8)	3238 (13.8)	8441 (16.8)
Personal history of uterine polyp, No. (%)	16 007 (21.2)	4301 (18.4)	11 377 (22.6)
Personal history of uterine fibroma, No. (%)	21 316 (28.2)	5993 (25.6)	14 836 (29.5)

(continued)

Table 1. (continued)

Characteristics	All women (n = 75 606)	MHT never users[a] (n = 23 391)	MHT ever users[a] (n = 50 325)
History of ovarian cancer in first-degree relatives, No. (%)			
No	64 150 (84.8)	19 243 (82.3)	44 176 (87.8)
Yes	834 (1.1)	231 (1.0)	592 (1.2)
Unknown	10 622 (14.0)	3917 (16.7)	5557 (11.0)
History of breast cancer in first-degree relatives, No. (%)	8524 (11.3)	2924 (12.5)	5400 (10.7)
Pap smear frequency at baseline, No. (%)			
Irregular	8450 (12.2)	4244 (20.7)	3962 (8.4)
Every year	38 496 (55.4)	8886 (43.4)	28 687 (60.7)
Every 2-3 y	19 970 (28.7)	6174 (30.1)	13 313 (28.2)
Every 4-5 y	2549 (3.7)	1184 (5.8)	1307 (2.8)
Unknown	6141 (8.1)	2903 (12.4)	3056 (6.1)

[a] There were 1890 women with an unknown MHT exposure status at the end of follow-up. MET = metabolic equivalent task; MHT = menopausal hormone therapy.

Table 2. Hazard ratios for ovarian cancer associated with exposure to MHTs, E3N cohort, 1990-2014 (n = 75 606)

Exposure characteristics	Any MHT		E-only		E + progesterone/ dydrogesterone		E + other progestagen[a]	
	No. cases	HR[b] (95% CI)	No. cases	HR[b,c] (95% CI)	No. cases	HR[b,c] (95% CI)	No. cases	HR[b,c] (95% CI)
Ever use[d]								
Never	140	1 (referent)	330	1 (referent)	230	1 (referent)	259	1 (referent)
Ever	253	1.02 (0.82 to 1.27)	63	1.09 (0.82 to 1.46)	163	1.28 (1.04 to 1.57)	134	0.81 (0.65 to 1.00)
Time since last use								
≤5 y	192	1.07 (0.85 to 1.35)	30	1.13 (0.76 to 1.68)	121	1.37 (1.09 to 1.72)	80	0.81 (0.63 to 1.06)
>5 to ≤10 y	40	0.91 (0.63 to 1.31)	17	1.42 (0.86 to 2.33)	31	1.16 (0.79 to 1.72)	33	0.81 (0.56 to 1.18)
>10 y	20	1.14 (0.70 to 1.84)	15	1.16 (0.68 to 1.98)	11	0.84 (0.45 to 1.56)	21	0.87 (0.54 to 1.38)
P_{trend}[e]		.30		.46		.049		.90
Duration of use								
≤5 y	105	0.98 (0.75 to 1.27)	48	1.09 (0.80 to 1.50)	95	1.25 (0.97 to 1.59)	82	0.80 (0.62 to 1.04)
>5 to ≤10 y	85	1.05 (0.79 to 1.39)	9	1.43 (0.70 to 2.91)	53	1.51 (1.10 to 2.06)	40	0.89 (0.63 to 1.26)
>10 y	56	1.29 (0.93 to 1.81)	2	1.32 (0.32 to 5.45)	15	1.20 (0.70 to 2.06)	10	0.73 (0.38 to 1.40)
P_{trend}[e]		.37		.55		.93		.74

[a] Other progestagens include chlormadinone acetate, cyproterone acetate, demegestone, dienogest, drospirenone, ethynodiol acetate, gestodene, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, and promegestone. CI = confidence interval; E = estrogen; HR = hazard ratio; MHT = menopausal hormone therapy.
[b] Adjusted for age (time scale), family history of breast cancer in first-degree relatives, family history of ovarian cancer in first-degree relatives, number of children, duration of breastfeeding, personal history of endometriosis, tubal ligation, duration of oral contraceptive use, height, body mass index, smoking status, age at menarche, age at menopause, and previous hysterectomy, using the categories shown in Table 1. Hazard ratios associated with the different exposure characteristics (ever use, time since last use, and duration of use) were obtained from separate models, including 1 characteristic of exposure at a time.
[c] For a given exposure characteristic, hazard ratios corresponding to E-only, E with progesterone or dydrogesterone, and E with other progestogen were obtained from 1 model where the corresponding variables for each MHT type were introduced simultaneously.
[d] There were 23 ovarian cancer cases among women with an unknown MHT exposure status (HR = 1.21, 95% CI = 0.77 to 1.90 compared with MHT never use).
[e] Among ever users, using an ordinal variable across categories of duration of use and time since last MHT use.

SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA) was used to perform the analyses.

Results

The characteristics of the study population, overall and according to MHT exposure at the end of follow-up, are displayed in Table 1 and Supplementary Table 1 (available online). Of the 75 606 women included, 23 391 (30.9%) never used MHT, 50 325 (66.6%) ever used MHT, and 1890 (2.5%) had an unknown exposure status at the end of follow-up. Among MHT ever users, 25.4% ever used E-only, 60.8% estrogen with progesterone or dydrogesterone, and 61.1% estrogen with other progestagen.

During a mean follow-up time of 15.3 (standard deviation, 6.3) years, 416 women were diagnosed with an incident primary ovarian cancer.

The age-adjusted hazard ratios of ovarian cancer associated with ever use of MHT, E-only, estrogen with progesterone or dydrogesterone, and estrogen with other progestagen were equal to 0.99 (95% CI = 0.80 to 1.21), 1.08 (95% CI = 0.82 to 1.41), 1.25 (95% CI = 1.02 to 1.53), and 0.79 (95% CI = 0.64 to 0.97), respectively, compared with never use. The corresponding multivariable hazard ratios were 1.02 (95% CI = 0.82 to 1.27), 1.09 (95% CI = 0.82 to 1.46), 1.28 (95% CI = 1.04 to 1.57), and 0.81 (95% CI = 0.65 to 1.00; $P = .053$), respectively, with a statistically significant ($P = .01$) overall heterogeneity between the hazard ratios for the 3 MHT types (Table 2). We also observed evidence of a difference in the hazard ratios between estrogen and progesterone or dydrogesterone and estrogen and other progestagen ($P_{homogeneity} = .003$) but not between E-only and estrogen with progesterone or dydrogesterone ($P = .42$) or between E-only and estrogen with other progestagen ($P = .12$).

There was no statistically significant trend according to duration of use or time since last use, for MHT overall as well as for the different MHT types, except for estrogen with progesterone or dydrogesterone, which showed a decreasing risk with increasing

Table 3. Hazard ratios for ovarian cancer associated with ever use of MHTs compared with never use in different population strata, E3N cohort, 1990-2014 (n = 75 606)

Population characteristics	Any MHT		E-only		E + progesterone or dydrogesterone		E + other progestagen	
	No. exposed cases	HR[a] (95% CI)	No. exposed cases	HR[a,b] (95% CI)	No. exposed cases	HR[a,b] (95% CI)	No. exposed cases	HR[a,b] (95% CI)
Hysterectomy								
No	226	1.04 (0.83 to 1.31)	45	1.12 (0.81 to 1.55)	152	1.31 (1.06 to 1.64)	125	0.82 (0.66 to 1.04)
Yes	27	0.94 (0.46 to 1.91)	18	1.03 (0.53 to 2.00)	11	0.94 (0.46 to 1.93)	9	0.65 (0.30 to 1.38)
$P_{interaction}$[c]		.82		.82		.49		.71
Oral contraceptives								
Ever use	161	1.16 (0.84 to 1.59)	38	1.08 (0.74 to 1.58)	103	1.31 (0.99 to 1.72)	85	0.79 (0.59 to 1.04)
Never use	92	0.89 (0.66 to 1.20)	25	1.08 (0.69 to 1.69)	60	1.21 (0.88 to 1.68)	49	0.83 (0.59 to 1.16)
$P_{interaction}$[c]		.18		.50		.76		.74
Body mass index								
<25.0 kg/m^2	190	1.08 (0.83 to 1.40)	44	1.01 (0.72 to 1.43)	120	1.27 (1.00 to 1.63)	103	0.84 (0.65 to 1.08)
25.0-29.9 kg/m^2	52	0.98 (0.63 to 1.53)	15	1.19 (0.66 to 2.17)	37	1.46 (0.94 to 2.28)	29	0.87 (0.55 to 1.39)
≥30.0 kg/m^2	11	0.82 (0.36 to 1.86)	4	2.98 (0.88 to 10.1)	6	0.84 (0.32 to 2.19)	2	0.21 (0.05 to 0.93)
$P_{interaction}$[c]		.66		.71		.63		.21

[a] Adjusted for age (time scale), family history of breast cancer in first-degree relatives, family history of ovarian cancer in first-degree relatives, number of children, duration of breastfeeding, personal history of endometriosis, tubal ligation, duration of oral contraceptive use, height, body mass index (except in models stratified by body mass index), smoking status, age at menarche, age at menopause, and previous hysterectomy (except in models stratified by hysterectomy) using the categories shown in Table 1. CI = confidence interval; E = estrogen; HR = hazard ratio; MHT = menopausal hormone therapy.
[b] Hazard ratios corresponding to E-only, E with progesterone or dydrogesterone, and E with other progestogen were obtained from 1 model where variables corresponding to ever use of each MHT type were introduced simultaneously.
[c] We assessed interactions by adding cross-product interaction terms in the Cox models.

time since last use (Table 2). Cross-tabulating duration of use and time since last use did not reveal different trends in risk (Supplementary Table 2, available online).

We found no statistically significant effect modification of the associations by hysterectomy, previous use of oral contraceptives, or BMI (Table 3). The associations of MHT ever use compared with never use did not differ in a statistically significant manner by ovarian cancer histotype, but the number of women diagnosed with nonserous ovarian cancer was low (Supplementary Table 3, available online). Sensitivity analyses yielded results that were in line with those from our main analyses (Supplementary Results and Supplementary Tables 4-6, available online).

Discussion

In our study, we found no statistically significant association between ovarian cancer risk and the use of E-only MHT but a statistically significant higher risk associated with current or recent use of estrogens combined with progesterone or dydrogesterone and a lower (P = .053) risk associated with the use of estrogens combined with other progestagens compared with never use.

Although we found no statistically significant association between E-only use and ovarian cancer risk, the latest meta- or pooled analyses (4,21,28) showed approximately 30% increased risk. However, meta- or pooled analyses also showed evidence of an increase in risk with increasing duration of use (18,19,28) or that was limited to use of at least 10 years (28). In our study, exposure to E-only was 5 years or less for most women.

To our knowledge, the association of EP-MHT containing progesterone or its isomer dydrogesterone (the progestagen components of MHT most commonly used in France) with ovarian cancer risk has only been evaluated in 2 studies with only 10 or less women with ovarian cancer ever exposed to estrogen with progesterone or estrogen with dydrogesterone and thus imprecise estimates (29,30). Our results of different associations of EP-MHT with ovarian cancer depending on progestagen type are in line with our previous observations in the E3N cohort for other cancer sites where EP-MHT containing progesterone or dydrogesterone was less deleterious regarding the risk of breast cancer than EP-MHT containing other progestagens (23), and EP-MHT containing progesterone or dydrogesterone were the only EP-MHT types associated with duration-dependent increases in endometrial cancer risk (24). Of note, studies that compared the associations of ovarian cancer risk with the use of EP-MHT containing other progestagens yielded no difference between the progestagen types considered (29,31-35).

In our study, we observed that MHT comprising estrogens combined with progestagens other than progesterone or dydrogesterone [the predominant type of EP-MHT used outside France (2)] was associated with a lower (P = .053) ovarian cancer risk, whereas in previous meta-analyses, EP-MHT was associated with an increased risk (4,18-21). However, considering only studies with information on lifetime MHT use and appropriate methods to analyze MHT type-specific exposures (ie, mutual adjustment for the different MHT types considered or limiting analysis to women exposed only to a single type of MHT) (31,36-41), a higher ovarian cancer risk with E-only but not with EP-MHT was observed. The only exception was Riman et al. (31), who found that ever use of E-only or estrogens sequentially combined with progestins were associated with an increased risk, whereas estrogens combined with continuous progestins were not. More recently, a pooled analysis of primary data from 5 population-based, case-control studies in the Ovarian Cancer Association Consortium found that exclusive use of continuous EP-MHT by nonhysterectomized postmenopausal women was associated with decreased ovarian cancer risk (odds ratio = 0.85, 95% CI = 0.72 to 1.0; 346 exposed women with ovarian cancer), similar to our point estimate for estrogen with progestagen other than progesterone or dydrogesterone (HR = 0.81, 95% CI = 0.65 to 1.00), with no notable variation in risk according to duration or recency of use (42). Interestingly, the authors argue that in studies where the respective effects of E-only and EP-MHT are not assessed

carefully, the apparently deleterious effect of EP-MHT on ovarian cancer risk could be due to a confounding effect of E-only therapy.

The mechanisms underlying the associations between different MHT formulations and ovarian cancer risk are unknown, but hypotheses have been proposed regarding the opposing biological roles of estrogens and progesterone (43). Estrogen and progesterone receptors are present on the ovarian surface epithelium, and estrogens can stimulate the proliferation of the ovarian surface epithelium, however, progesterone could counteract this effect (13). After natural progesterone, its isomer dydrogesterone is the progestagen with the lowest bioavailability and potency of the progestogenic responses (44). Progestagens other than progesterone or dydrogesterone may therefore have a stronger protective role against ovarian tumor development. This hypothesis is supported by the consistent inverse association observed between the use of oral contraceptives (containing synthetic progestins) and ovarian cancer risk (22,45) and lends support to the higher risk of ovarian cancer observed in our study among users of estrogen with progesterone or dydrogesterone compared with estrogen with other progestagen.

The strengths of our study include its prospective design, its long-term follow-up, and the careful consideration of the entire history of MHT use, using self-reported information and drug claims data. We were also able to adjust our models for known ovarian cancer risk factors and consider a variety of other potential confounders, although residual confounding remains possible. Although the total number of women with ovarian cancer previously exposed to MHT (n = 253) was relatively high in our study, it remained limited in some exposure categories such as long-term use of E-only MHT, for nonserous ovarian cancers, or among hysterectomized or overweight women, which led to large confidence intervals surrounding some estimates. Until 2004, we used self-reported information to assess MHT exposure. However, recall bias is probably limited because MHT use information was updated every 2-3 years. Furthermore, previous studies have shown good agreement between self-reported MHT use and prescription data, especially for recent use (46,47). The use of cause-of-death data to identify ovarian cancers that could not have been self-reported because of particularly poor prognosis allowed us to minimize any selection bias that may arise if ovarian cancer prognosis was different in MHT users and nonusers. Finally, we must acknowledge the lack of information on EP-MHT regimens (ie, continuous or sequential) that could impact ovarian cancer risk. Indeed, in our cohort, most EP-MHT users used 2 distinct brands of estrogens and progestagen (eg, estrogen patch and progestagen pill) rather than single-pill combinations, and the number of days of hormone use was not recorded in the questionnaires.

In conclusion, consistent with what we previously observed for breast and endometrial cancers, E-only, EP-MHT containing progesterone or dydrogesterone, and EP-MHT containing other progestagens may impact ovarian cancer risk differentially. In particular, the possibility that progestagens other than progesterone or dydrogesterone confer some protection against ovarian cancer development should be evaluated in other epidemiological studies with accurate consideration of changes in MHT types used by women over time.

Data availability

Data underlying this article are made available under managed access owing to governance constraints and need to protect the privacy of study participants. Data on E3N cohort participants are available to bona fide researchers for all types of health related research, which is in the public interest. Raw data requests should be submitted through the E3N website (www.e3n.fr) or sent to contact@e3n.fr and will be reviewed by the E3N Access Committee. Further information is provided at https://www.e3n.fr/node/78.

Author contributions

Agnes Fournier, PhD (Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Writing—original draft; Writing—review & editing); Manon Cairat, PhD (Writing—original draft; Writing—review & editing); Gianluca Severi, PhD (Resources; Writing—review & editing); Marc J. Gunter, PhD (Supervision; Writing—review & editing); Sabina Rinaldi, PhD (Supervision; Writing—review & editing); and Laure Dossus, PhD (Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing—original draft; Writing—review & editing).

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Conflicts of interest

None exist.

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